Rare endocrine tumour guidelines

Children's Cancer and Leukaemia Group | the EXPERTS in CHILDHOOD CANCER

Guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence

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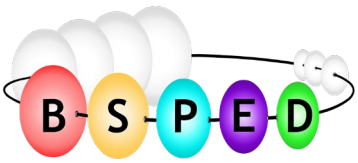

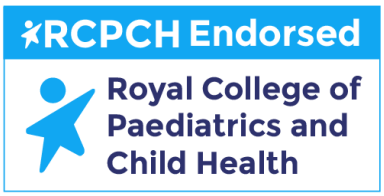

Guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence

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Summary of guideline

Tumours of the anterior part of the pituitary gland represent just 1% of all childhood (aged <15 years) intracranial neoplasms; yet they can confer high morbidity and little evidence and guidance is in place for their management.

Between 2014 and 2022, a multidisciplinary expert group systematically developed the first comprehensive clinical practice guideline for children and young people under the age of 19 years (hereafter referred to as CYP) presenting with a suspected pituitary adenoma to inform specialist care and improve health outcomes.

Through robust literature searches and a Delphi consensus exercise with an international Delphi consensus panel of experts, the available scientific evidence and expert opinions were consolidated into 74 recommendations.

While in many aspects the care for CYP is similar to that of adults, key differences exist, particularly in aetiology and presentation. CYP with suspected pituitary adenomas require careful clinical examination, appropriate hormonal workup, dedicated pituitary imaging and visual assessment. Consideration should be given to the potential for syndromic disease and genetic assessment. Multidisciplinary discussion at the local and national level can be key for management. Pituitary surgery should be performed in specialist centres. The collection of outcome data on novel modalities of medical treatment, surgical intervention and radiotherapy is essential for optimal future treatment.

Contents

Summary of general and specific recommendations

Recommen-dation (R) number	Recommendations	Strength of Recommendation
General statements		
Management statements		
General: R1	Offer CYP with suspected or confirmed pituitary adenoma management in a specialist age-appropriate endocrine and neuro-oncology centre by an MDT working collaboratively with appropriate local healthcare professionals.	strong recommendation, low quality evidence, Delphi 100%
General: R2	Offer all CYP with a pituitary mass a growth and pubertal assessment and baseline pituitary hormone measurements.	strong recommendation, high quality evidence
General: R3	Clinicians treating CYP with pituitary adenomas should have access to a national paediatric pituitary-specific advisory panel in order to discuss the management of complex patients.	strong recommendation, low quality evidence, Delphi 90%
General: R4.1	Report CYP with a confirmed pituitary adenoma to an appropriate national registry.	strong recommendation, low quality evidence, Delphi 90%
General: R4.2	Offer transfer to adult pituitary services for continued surveillance at completion of growth and puberty.	strong recommendation, low quality evidence, Delphi 89%
Neuroimaging		
General: R5	Offer pre-contrast (T1 and T2) and post-contrast-enhanced (T1) thin-sliced pituitary MRI, including post-contrast volumetric (gradient (recalled) echo) sequences for increased sensitivity, to CYP presenting with a visual field defect or with signs and symptoms of pituitary hypersecretion or hyposecretion.	strong recommendation, low quality evidence, Delphi 92%
General: R6	Consider 3-Tesla MRI for surgical planning or intraoperative MRI, as it enhances anatomical definition and might improve completeness of resection without altering complication rates.	moderate recommendation, low quality evidence, Delphi 92%
Visual Assessment		
General: R7	In CYP with suspected or confirmed pituitary adenoma, offer assessment of visual acuity (ideally logarithm of the minimum angle of resolution measurement), visual fields (ideally Goldmann perimetry) and fundoscopy, with or without colour vision.	strong recommendation, low quality evidence, Delphi 94%
General: R8	In CYP with confirmed pituitary adenoma with potentially severe acuity or field deficits, consider baseline optical coherence tomography.	weak recommendation, low quality evidence, GDG consensus
General: R9.1	Consider visual assessment (including acuity and fields if age-appropriate) in all CYP with a pituitary macroadenoma within 3 months of first-line therapy.	moderate recommendation, low quality evidence, Delphi 94% and GDG consensus
General: R9.2	Ongoing visual follow-up should be based on individual indications.	moderate recommendation, low quality evidence, Delphi 81% and GDG consensus

Recommen-dation (R) number	Recommendations	Strength of Recommendation
Histopathology		
General: R10	Offer histopathological assessment of the operated pituitary adenoma tissue, including immunostaining for pituitary hormones and Ki-67, and additional immunoprofiling when relevant, to accurately classify the pituitary neoplasm.	strong recommendation, moderate quality evidence, Delphi 100%
Genetics		
General: R11.1	Offer genetic assessment to all CYP with a pituitary adenoma to inform management and family surveillance.	strong recommendation, high quality evidence
General: R11.2	Given the high prevalence of genetic abnormalities in somatotroph and lactotroph tumours, offer genetic testing to all CYP with growth hormone (GH) and prolactin excess.	strong recommendation, high quality evidence
Pituitary Surgery		
General: R12	If surgery is indicated in CYP with pituitary adenoma, offer transsphenoidal surgery as the technique of choice, even in patients with incompletely pneumatised sphenoid sinuses.	strong recommendation, low quality evidence, Delphi 100% and GDG consensus
General: R13	In CYP with pituitary adenoma, consider endoscopic rather than microscopic transsphenoidal surgery, for its potentially superior efficacy in preserving pituitary function.	weak recommendation, low quality evidence, Delphi 86%
General: R14	In all CYP with pituitary adenoma who undergo surgery, offer strict fluid and electrolyte balance monitoring peri-operatively and post-operatively	strong recommendation, moderate quality evidence, Delphi 100%
Radiotherapy		
General: R15	In CYP with pituitary adenoma, offer radiotherapy when the tumour is symptomatic, growing, resistant to medical therapy and surgically inaccessible.	strong recommendation, low quality evidence, Delphi 94%
General: R16	Consider clinical radiation treatment protocols for CYP according to adult guidelines or paediatric regimens for similarly located tumours.	moderate recommendation, low quality evidence, Delphi 94%
General: R17	Consider external beam fractionated radiotherapy at a total dose of 45–50.4 Gy in 1.8 Gy daily fractions to CYP with pituitary adenomas indicated for radiotherapy; offer fractionated radiotherapy as proton beam therapy, where available, or as highly conformal photon therapy; single fraction radiosurgery might be appropriate in older patients in individual circumstances.	moderate recommendation, low quality evidence, Delphi 100% and GDG consensus
Specific recommendations		
Prolactinoma		
Specific: R1	Offer serum prolactin measurement in CYP presenting with one or more of the following signs and symptoms: delayed puberty; galactorrhoea; visual field loss; growth or pubertal arrest; girls with menstrual disturbance.	strong recommendation, moderate quality evidence
Specific: R2	In CYP with signs or symptoms of hyperprolactinaemia, offer prolactin measurement in a single blood sample collected at any time of day.	strong recommendation, high quality evidence
Specific: R3	Consider investigating modestly elevated serum prolactin levels by serial measurements over time to exclude the effect of stress and prolactin pulsatility.	moderate recommendation, low quality evidence, Delphi 87%

Recommen-dation (R) number	Recommendations	Strength of Recommendation
Specific: R4	The diagnosis of hyperprolactinaemia in CYP requires age-specific and sex-specific prolactin reference ranges and the exclusion of confounding conditions, such as hypothyroidism, renal and/or hepatic impairment and use of medications that cause hyperprolactinaemia.	strong recommendation, moderate quality evidence
Specific: R5	Assess baseline macroprolactin levels where serum prolactin is found to be mildly or incidentally elevated.	strong recommendation, low quality evidence, GDG consensus
Specific: R6	Perform serial dilutions of serum for prolactin measurement in CYP with large pituitary lesions and normal or mildly elevated prolactin levels.	strong recommendation, moderate quality evidence
Specific: R7	In CYP with prolactinoma, offer a dopamine agonist as first-line therapy to reduce serum prolactin concentrations and induce tumour shrinkage; cabergoline is the dopamine agonist of choice given its superior effectiveness and lower adverse effect profile.	strong recommendation, moderate quality evidence
Specific: R8	In CYP with prolactinoma, offer cabergoline as first-line therapy, even in the presence of visual disturbance and pituitary apoplexy, while carefully monitoring for any deterioration in vision, pituitary function or general status.	strong recommendation, low quality evidence, Delphi 100%
Specific: R9	For CYP resistant to standard doses of cabergoline, offer graduated dose increments up to 3.5mg per week, or up to 7mg per week in exceptional cases.	strong recommendation, moderate quality evidence, Delphi 100%
Specific: R10.1	Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient is unable to tolerate, or is resistant to high dose cabergoline.	strong recommendation, low quality evidence, Delphi 95%
Specific: R10.2	Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient develops deteriorating vision on cabergoline.	strong recommendation, low quality evidence, Delphi 90%
Specific: R10.3	Following multidisciplinary discussion, for CYP with prolactinomas offer radiotherapy if surgery is not an option.	strong recommendation, low quality evidence, Delphi 100%
Specific: R11	In CYP with prolactinoma, offer echocardiogram at the start of treatment with a dopamine agonist; offer yearly surveillance echocardiography for patients receiving >2mg per week cabergoline and every 5-years if on ≤2mg per week.	moderate recommendation, moderate quality evidence
Specific: R12	Temozolomide treatment might need consideration for CYP with aggressive pituitary tumours resistant to medical, surgical and radiation therapy.	weak recommendation, low quality evidence, Delphi 88%
Specific: R13	If the serum level of prolactin has been normalised for at least 2 years on medical therapy and there is no visible residual on MRI, consider gradual cabergoline dose reduction to maintain normoprolactinaemia and eventual treatment discontinuation, with continued serum prolactin monitoring for at least 2 more years.	moderate recommendation, low quality evidence, Delphi 100%
Cushing's disease		
Specific: R14	Offer screening for Cushing's syndrome in CYP with obesity, but only if weight gain is inexplicable and combined with either a decrement in height SD score (SDS) or height velocity.	strong recommendation, moderate quality evidence
Specific: R15	In CYP with suspected Cushing's syndrome, offer investigations using established algorithms, first to determine the diagnosis of Cushing's	strong recommendation, moderate quality evidence

Recommen-dation (R) number	Recommendations	Strength of Recommendation
	syndrome (the presence of hypercortisolaemia), followed by investigations to ascertain its aetiology.	
Specific: R16	Suspected Cushing's syndrome in CYP is effectively excluded by: either two normal 24 hour urinary free cortisol (UFC) measurements and a normal low-dose dexamethasone suppression test (LDDST, 0.5mg 6 hourly for 48 hours or if patient's weight is <40kg, 30µg/kg per day for 48 hours); or a midnight sleeping serum cortisol concentration <50nmol/l.	strong recommendation, high quality evidence
Specific: R17	Two late-night salivary cortisol tests could be a useful alternative for the midnight serum cortisol test as a means of excluding Cushing's syndrome, but age-specific and assay-specific normal ranges are not currently available and need to be carefully characterised.	moderate recommendation, moderate quality evidence
Specific: R18.1	In CYP with confirmed Cushing's syndrome, Cushing's disease can be confirmed by its ACTH dependency, which is supported by a normal or elevated 09:00h plasma ACTH.	strong recommendation, moderate quality evidence
Specific: R18.2	In CYP with confirmed Cushing's syndrome, the diagnosis of pituitary-origin ACTH excess is supported by >20% increase in cortisol from baseline during a corticotrophin releasing hormone (CRH) or desmopressin test.	moderate recommendation, low quality evidence, Delphi 92%
Specific: R19.1	Offer BSIPSS to CYP with confirmed ACTH-dependent Cushing's syndrome and no identified adenoma on pituitary MRI, to confirm a central source of ACTH excess.	strong recommendation, low quality evidence, Delphi 83%
Specific: R19.2	Offer BSIPSS only in a specialist centre with expertise in such testing and by an experienced interventional radiologist who regularly undertakes this procedure in adults.	strong recommendation, moderate quality evidence
Specific: R19.3	Consider confirming hypercortisolaemia immediately prior to BSIPSS to ensure the patient is in an active disease phase.	moderate recommendation, moderate quality evidence
Specific: R19.4	During BSIPSS, a pituitary source of ACTH excess is confirmed by a ≥2:1 ratio of central:peripheral ACTH before CRH or desmopressin and ≥3:1 ratio after CRH or desmopressin stimulation.	strong recommendation, low quality evidence, Delphi 100%
Specific: R19.5	BSIPSS could provide some information on tumour lateralisation, if the inter-petrosal sinus ACTH gradient after CRH or desmopressin stimulation is ≥1.4 between the two sides.	moderate recommendation, moderate quality evidence, Delphi 67% and GDG consensus
Specific: R20.1	Offer selective adenomectomy as first-line treatment of choice for CYP with Cushing's disease.	strong recommendation, moderate quality evidence
Specific: R20.2	Consider repeat surgery for CYP with persistent or recurrent disease.	moderate recommendation, low quality evidence, Delphi 100%
Specific: R21	Offer radiotherapy to CYP with recurrent Cushing's disease not amenable to curative surgery.	strong recommendation, moderate quality evidence, Delphi 93%
Specific: R22.1	Offer oral medical therapies such as metyrapone or ketoconazole to reduce the cortisol burden in CYP with Cushing's disease awaiting definitive surgery or the effect of pituitary radiotherapy.	strong recommendation, low quality evidence, Delphi 100%
Specific: R22.2	Due to their adverse effects, metyrapone and ketoconazole have a limited role in the long-term treatment of Cushing's disease in CYP.	strong recommendation, low quality evidence, Delphi 60% and GDG consensus

Recommen-dation (R) number	Recommendations	Strength of Recommendation
Specific: R23	Offer intravenous etomidate treatment in CYP with Cushing's disease in an intensive care setting only for the emergency control of severe cortisol excess.	strong recommendation, moderate quality evidence, Delphi 100%
Specific: R24	Reserve bilateral adrenalectomy only for CYP with severe refractory Cushing's disease or for life-threatening emergencies.	strong recommendation, low quality evidence, Delphi 80% and GDG consensus
Specific: R25	Consider dynamic testing for GH deficiency soon after definitive therapy in all CYP in remission from Cushing's disease who have not completed linear growth, and closely monitor pubertal progression to identify hypogonadotrophic hypogonadism.	moderate recommendation, moderate quality evidence
Specific: R26	Offer prompt initiation of GH replacement to CYP in remission from Cushing's disease who are proven GH deficient or fail to show catch-up growth (strong recommendation, moderate quality evidence, GDG consensus).	strong recommendation, moderate quality evidence, GDG consensus
Specific: R27	Consider BMD assessment prior to adult transition in patients at high risk for bone fragility.	weak recommendation, low quality evidence, Delphi 86%
Specific: R28	To assess possible recurrence, offer to all CYP in remission from Cushing's disease: 6-monthly clinical examination, 24h UFC, electrolytes and morning serum cortisol for at least 2 years and life-long annual clinical assessment.	strong recommendation, low quality evidence, Delphi 100%
Specific: R29	In addition to life-long follow-up for endocrinopathies, consider long-term monitoring for psychiatric and neurocognitive co-morbidities following remission of Cushing's disease in CYP.	moderate recommendation, moderate quality evidence
Specific: R30	In suspected recurrence of Cushing's disease in CYP, offer the same stepwise investigations as at first presentation.	strong recommendation, low quality evidence, GDG consensus
GH excess – gigantism and acromegaly		
Specific: R31	Offer testing for GH excess to CYP with excess height (more than 2 SDS) or consistently elevated height velocity and acromegalic features, with or without delayed or arrested puberty or family history of pituitary adenoma.	strong recommendation, moderate quality evidence, Delphi 100%
Specific: R32	A diagnosis of GH excess is supported by an elevated serum IGF-1 level in relation to the age-adjusted, sex-adjusted and Tanner stage-matched normal range (strong recommendation, moderate quality evidence).	strong recommendation, moderate-quality evidence
Specific: R33	Consider the diagnosis of GH excess in CYP whose serum GH levels fail to suppress below 1µg/l in response to an oral glucose load (cut-off based on adult population); however, complete suppression of GH can be difficult to achieve in normal adolescence.	moderate recommendation, moderate quality evidence, Delphi 100%
Specific: R34	In CYP with GH excess, offer dynamic pituitary assessment of possible hypofunction and hyperfunction of other anterior pituitary hormones.	strong recommendation, high quality evidence
Specific: R35.1	Pituitary adenomas can be associated with syndromic diseases; offer clinical evaluation for associated syndromic causes of somatotrophinomas to CYP with GH excess.	strong recommendation, low quality evidence, Delphi 93%
Specific: R35.2	Offer biochemical screening for pituitary hormone excess to all CYP with Carney complex, McCune–Albright syndrome and patients with MEN1 or MEN1-like disease.	strong recommendation, high quality evidence, Delphi 100%

Recommen-dation (R) number	Recommendations	Strength of Recommendation
Specific: R36	Offer surgery to reduce GH burden as the treatment of choice in the majority of CYP with GH-secreting adenomas, even where surgical cure is unlikely.	strong recommendation, moderate quality evidence, Delphi 93%
Specific: R37.1	Consider preoperative medical therapy with somatostatin analogues and/or GH receptor antagonists to rapidly control signs and symptoms and support perioperative airway management.	weak recommendation, low quality evidence, Delphi 75%, GDG consensus
Specific: R37.2	Consider preoperative medical therapy with somatostatin analogues and/or GH receptor antagonists to reduce height velocity, particularly if pituitary surgery is delayed.	weak recommendation, low quality evidence, Delphi 100%
Specific: R38	Offer monotherapy or combination medical therapy in CYP with GH excess and post-operative residual disease.	strong recommendation, moderate quality evidence, Delphi 100%
Specific: R39	Assess efficacy of medical treatment in CYP with GH excess by both auxological measurements and serum levels of GH and IGF-1.	strong recommendation, moderate quality evidence, Delphi 100%
Specific: R40.1	Offer pituitary radiotherapy to CYP with GH-secreting adenoma and uncontrolled tumour growth and incomplete surgical and medical response, except for patients with skull base fibrous dysplasia.	strong recommendation, low quality evidence, Delphi 75%
Specific: R40.2	After radiotherapy in CYP with GH-secreting adenoma, offer intermittent dose reduction or withdrawal of medical therapy to assess radiation efficacy on GH hypersecretion.	strong recommendation, low quality evidence, Delphi 100%
Specific: R41	There is no evidence to suggest that CYP with GH excess require routine screening for colonic polyps during childhood.	strong recommendation, low quality evidence, Delphi 92%
Specific: R42	Consider avoiding corrective surgery for jaw, spine and joint abnormalities in CYP with gigantism or acromegaly until GH and IGF-1 is at safe level.	weak recommendation, low quality evidence, GDG consensus
TSHomas		
Specific: R43	Consider assessment for TSHoma in CYP with hyperthyroxinaemia and an unsuppressed TSH, particularly in the presence of clinical thyrotoxicosis, neurological or visual deterioration.	moderate recommendation, moderate quality evidence
Specific: R44	Consider assessment for thyroid hormone resistance and euthyroid hyperthyroxinaemia in the differential diagnosis of TSHoma in CYP.	moderate recommendation, low quality evidence, Delphi 100%
Specific: R45	Consider preoperative somatostatin analogue treatment to normalise thyroid function in CYP with confirmed TSHoma.	moderate recommendation, low quality evidence, Delphi 73% and GDG consensus
Specific: R46	Offer transsphenoidal surgery as the treatment of choice in CYP with TSHomas.	moderate recommendation, low quality evidence, Delphi 93%
Specific: R47	Disease monitoring with regular thyroid function tests and regular MRI surveillance, similar to the protocol described for NFPA, is suggested in CYP with confirmed TSHomas.	weak recommendation, low quality evidence, GDG consensus
Specific: R48	Consider pituitary radiotherapy in CYP with post-operative tumour remnant and resistance to medical therapy or relapsing TSHomas if reoperation is not an option.	moderate recommendation, low quality evidence, Delphi 92% and GDG consensus
Incidentalomas and non-functioning pituitary adenomas		

Recommen-dation (R) number	Recommendations	Strength of Recommendation
Specific: R49	Identification of a pituitary incidentaloma or NFPA requires exclusion of clinical or laboratory evidence of pituitary hormone hypersecretion (except mild hyperprolactinaemia from pituitary stalk disruption); exclusion of elevation of serum level of alpha-fetoprotein (AFP) and β-human chorionic gonadotropin (βHCG) and the absence of other suprasellar and intracranial lesions	strong recommendation, low quality evidence, Delphi 100%
Specific: R50	Offer baseline and dynamic evaluation of pituitary function to assess hypopituitarism and exclude hormone excess in all CYP with suspected NFPA.	strong recommendation, low quality evidence, Delphi 100%
Specific: R51	There is no evidence to suggest a benefit of routine diagnostic biopsy in CYP of incidental pituitary masses whose radiological features are typical of a pituitary adenoma and there are no other intracranial abnormalities.	strong recommendation, low quality evidence, GDG consensus
Specific: R52	Offer treatment to CYP with NFPA only if the patient is symptomatic (hypopituitarism), the visual pathway is threatened or there is interval tumour growth on MRI.	strong recommendation, low quality evidence, Delphi 94%
Specific: R53	Offer transsphenoidal surgery as the treatment of choice in CYP with NFPA needing surgical intervention.	strong recommendation, high quality evidence, Delphi 100%
Specific: R54	There is insufficient evidence to recommend medical therapy, including cabergoline, in CYP with NFPA.	moderate recommendation, low quality evidence, Delphi 80%
Specific: R55	Consider second surgery or radiotherapy for CYP with recurrent or symptomatic NFPAs.	moderate recommendation, low quality evidence, Delphi 94% and GDG consensus
Specific: R56	Following NFPA surgery in CYP, offer post-operative MRI surveillance at a minimum of 3 and 6 months, and 1, 2, 3 and 5 years after surgery.	strong recommendation, low quality evidence, Delphi 89%
Specific: R57	In CYP with incidental NFPAs, offer MRI surveillance: for microincidentalomas: at 12 months and, if stable, at 1–2 year intervals for 3 years with gradual reduction thereafter; for macroincidentalomas: at 6 months and, if stable, annually for 3 years with gradual reduction thereafter.	strong recommendation, low quality evidence, Delphi 100%

Introduction

The diagnosis and management of pituitary adenomas in children and young people under 19 years of age (hereafter referred to as CYP) is challenging, owing to the rarity of these tumours in this age group, their potential to disrupt maturation, their more aggressive nature and the increased potential for familial or genetic aetiology in this age group compared with adults[1-3]. Pituitary adenomas increase in incidence during late adolescence, rising from 1% of all intracranial neoplasms before 15 years of age to 18% for patients aged 15-24 years[4]. These patients can present, often late, to a range of different paediatric or adult specialists: endocrinologists, ophthalmologists, neuro-oncologists, medical oncologists or neurosurgeons.

Pituitary adenomas are neoplasms (usually non-malignant) arising from the hormone-secreting cells of the anterior pituitary. In CYP, they often secrete hormones in excess, but the resulting characteristic signs and symptoms, such as pubertal delay, amenorrhoea, features of Cushing's disease or rapid growth velocity might be occult or missed during development, leading to late diagnoses[5,6]. Pituitary adenomas are defined as macroadenomas if they measure ≥1 cm and microadenomas if they measure <1 cm, whereas neoplasms of >4 cm in size are referred to as giant adenomas. Large pituitary adenomas are more prevalent in CYP than in adults[6]. Mass effects are more common at presentation in CYP than in adults and cause deficits of pituitary hormones, visual field defects, hypothalamic dysfunction and even raised intracranial pressure or oculo-motor nerve palsy. Of note, the 2022 edition of the WHO Classification of Endocrine Tumours and of Central Nervous System Tumours proposed a pathology-based classification of pituitary adenomas as pituitary neuroendocrine tumours (abbreviated to PitNETs), a term that is currently being debated in the field[7-13].

Pituitary adenomas have a high survival rate but might confer potentially serious, life-changing and life-limiting sequelae. They increase in incidence with increasing age over childhood and represent 78% of pituitary fossa lesions in CYP[14]. Between 1997 and 2016 in the UK, 5 children with pituitary adenoma were diagnosed aged 0–4 years, 14 children aged 5–9 years, 78 young people aged 10–14 years and 282 young people aged 15–19[15]. As children with pituitary adenomas can, on average, expect to live for a further 6–7 decades, their health-related quality of life is paramount. Managing CYP with pituitary adenomas is challenging due to the lack of high-quality evidence for treatment recommendations for this age group.

In order to achieve optimal care, to improve quality of life and reduce secondary and long-term health-related morbidity, CYP with pituitary adenomas should be managed within a pituitary-specific multidisciplinary team (MDT), with experts from both paediatric and adult practice. Such a level of care could also improve and expedite diagnosis (including complex endocrine and genetic screening of patients with suspected familial aetiology), acute decision-making, perioperative care and long-term surveillance. In contrast to oncology care for CYP, which is usually well-organised with centralised units, a less well-developed management provision exists for CYP with pituitary neoplasms. The UK and many other countries lack a dedicated pituitary MDT for CYP.

Having recognised these challenges, a Guideline Development Group (GDG) and an international Delphi panel was formed to develop consensus on diagnostic and management recommendations for CYP with pituitary adenomas according to rigorous methodology approved by the UK National Institute for Health and Care Excellence (NICE). The GDG made 74 recommendations that are included in this guideline, 17 general recommendations regarding neuroimaging, visual assessment, histopathology, genetics, pituitary surgery and radiotherapy as well as 57 recommendations for each

of the individual pituitary adenoma types in CYP: prolactinomas, Cushing's disease, growth hormone (GH) excess causing gigantism and acromegaly, clinically non-functioning pituitary adenomas (NFPAs) and thyroid stimulating hormone (TSH) secreting adenomas (TSHomas) and we also mention the rare functioning gonadotroph adenomas. This guideline is intended to provide an evidence-based and eminence-based document for clinicians in several disciplines to whom CYP present to optimise the management of suspected pituitary adenomas in CYP in order to improve the quality of clinical care and thus health outcomes. This guideline in a slightly abbreviated form has been published in two parts by Nature Reviews Endocrinology[16,17].

Methodology

This guideline was commissioned by the British Society for Paediatric Endocrinology and Diabetes (BSPED) and the Children's Cancer and Leukaemia Group (CCLG), and was developed in accordance with Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II)[18] criteria and the CCLG guideline development standard operating procedure[19]. Members of the Project Board, GDG and Delphi consensus panel (**Supplementary Table 1**) were selected based on clinical and academic experience in pituitary tumour diagnosis and management. The methodology is summarised in **Figure 1**. All stages of the development process were appraised and endorsed by the Quality Improvement Committee of the UK Royal College of Paediatrics and Child Health (RCPCH).

Developing the clinical questions

The GDG identified its objectives and summarised these as a series of 155 Population, Intervention, Comparison, Outcome (PICO) clinical questions[20] (**Supplementary Table 2**) that were circulated to stakeholder organisations (listed later and in the Acknowledgements) for comments, and then finalised by the GDG. The clinical questions guided the systematic literature search (**Supplementary Table 3**), critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG.

Identifying, reviewing and synthesising evidence

The GDG screened titles and abstracts published in English since January 1990, and identified by three systematic literature searches conducted on the core databases, Ovid MEDLINE, PubMed, EMBASE and Cochrane Library, in October 2014, February 2021 and April 2022 (**Figure 2**). Relevant publications were further monitored and collected via regular automated alerts from PubMed until September 2023. Full text articles relevant to development of this guideline were reviewed and appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria[21]. For inclusion and exclusion criteria, search terms and strategies, see **Supplementary Table 3**. For detailed evidence tables for recommendations for the general sections see **Supplementary Table 4 and for the disease sections see Supplementary Table 5**. Given the rarity of pituitary adenomas in CYP, especially in the youngest developing children aged <15 years, most paediatric evidence was of low quality and the authors have often drawn on evidence from the adult literature, which is noted where relevant. Supplementary data for this guideline can be found on the CCLG website. (Rare endocrine tumour guidelines).

Developing recommendations

Where there was sufficient moderate quality evidence to answer the PICO questions, the GDG originally made 54 recommendations, whose strength was determined using the GRADE criteria[21] by a trade-off between benefits and harms, given the quality of the underpinning evidence. Where the evidence base was lacking, low quality, conflicting or largely extrapolated from adult experiences, the GDG formulated consensus recommendations and submitted these to experts outside the GDG (the international Delphi consensus panel, **Supplementary Table 1**) in three rounds of a Delphi consensus process (first round, 74 recommendations; second round 41 recommendations; third limited round for one question, see **Supplementary Table 6** for full details of the voting for each recommendation). In some cases, a strong recommendation is paired with moderate quality evidence: these recommendations are based on adult data and strong recommendations in adult

guidelines that are applicable to CYP. High quality evidence is unlikely to be prospectively generated in the CYP age group in the future due to the rarity of these conditions.

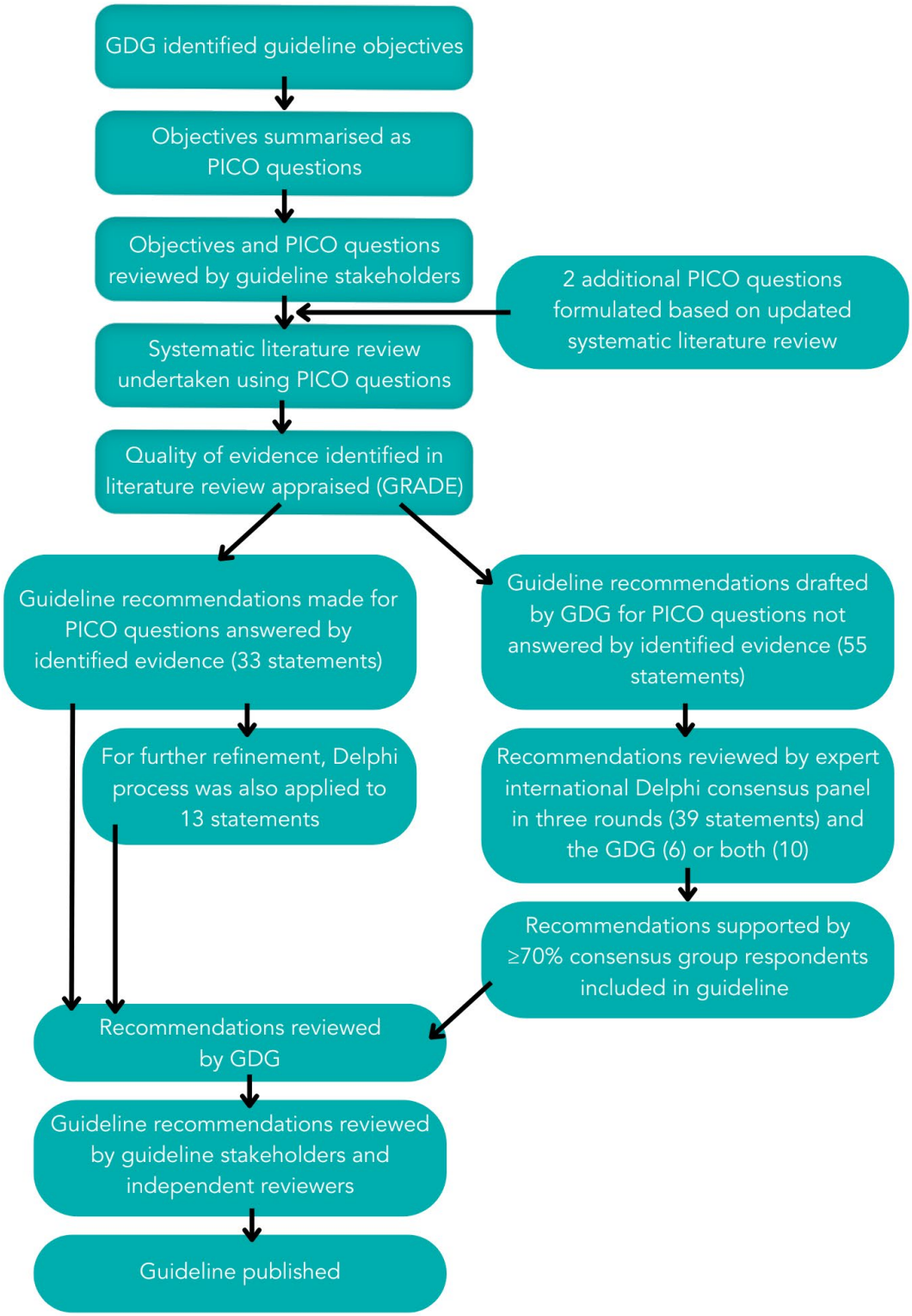
Following a revised literature review in 2021, the GDG finalised a total of 74 main recommendations with a total of 89 statements, as some of the recommendations included two or more interrelated statements. Of 89 statements, 34 were evidence-based (with 13 of these also having Delphi-consensus), and 55 are eminence-based (49 based on Delphi-consensus, 10 of these with additional GDG-consensus, and 6 based on GDG-consensus alone). We followed a consistent NICE terminology, using the verbs 'should' and 'offer' to indicate strong recommendations, whereas 'consider' was used to indicate moderate or weak recommendations. The evidence levels are shown as strong, moderate or low quality using GRADE criteria together with any Delphi or GDG consensus. Recommendations supported by ≥70% consensus group respondents are included in these guidelines. Areas where the GDG felt that further research was required have been proposed as research recommendations.

As part of the guideline development process, the draft article was submitted to two paediatric endocrinology international experts for external peer review between August and November 2018. A second round of external peer review took place before submission for publication in February 2022 by four national and four international experts (three adult endocrinologists, four paediatric endocrinologists and one histopathologist).

Stakeholder, patient and public involvement

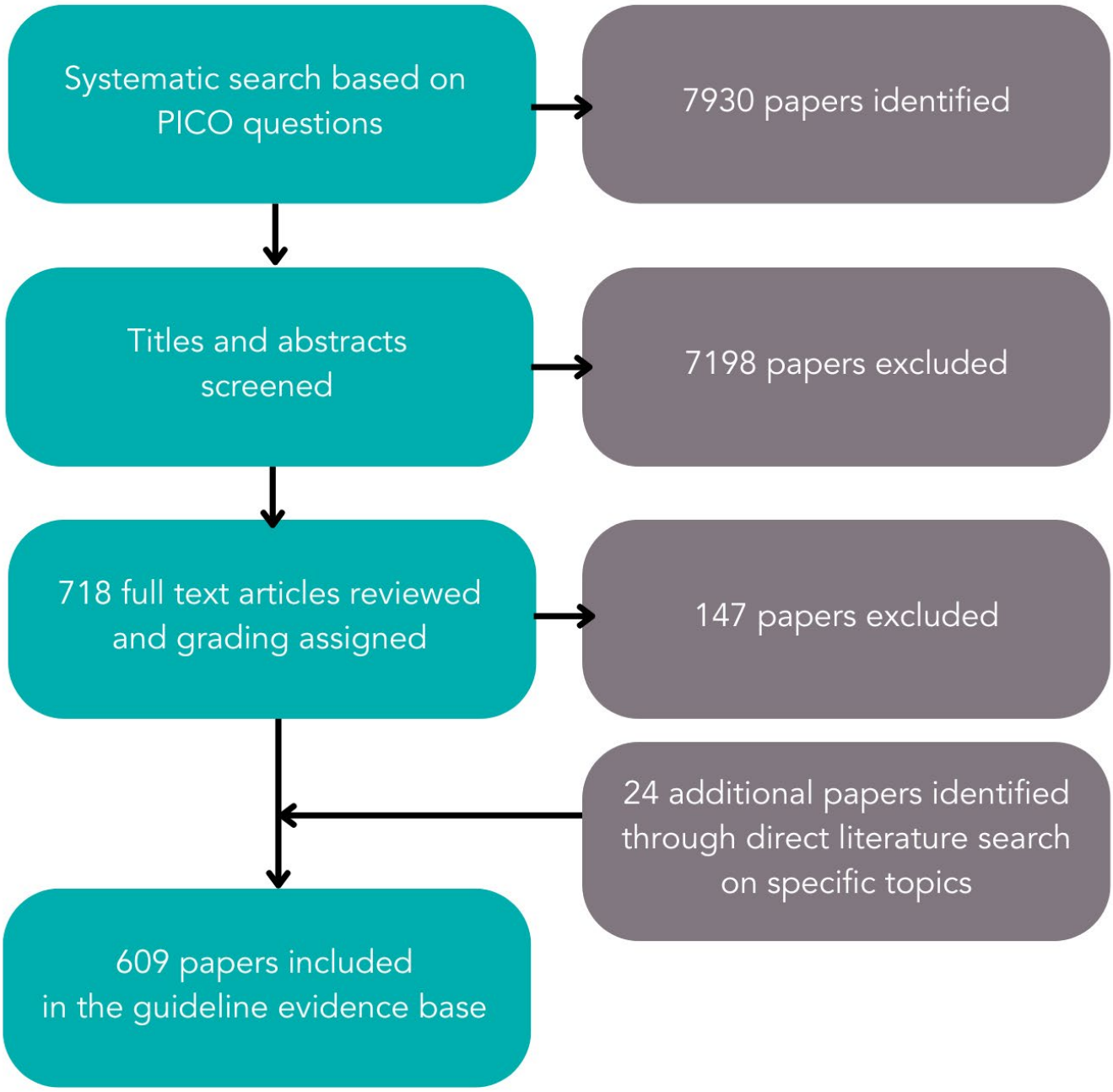
This guideline received scientific comments and endorsement from various stakeholders, listed here and in the Acknowledgements. Stakeholders were given the opportunity to comment on the PICO questions, on the first draft of the recommendations (September and December 2016) and on the final draft (November 2021–January 2022). The following learned societies endorsed this guideline: Society for Endocrinology, Society of British Neurological Surgeons, British Paediatric Neurosurgical Group, Royal College of Physicians, BSPED, British Society of Paediatric Radiology, RCPCH, British Neuropathology Society and the Association for Clinical Biochemistry and Laboratory Medicine. In addition, views from patients with pituitary adenoma, survivors and their families were sought through various patient organisations in October and November 2021, including: Association of Multiple Endocrine Neoplastic Disorders (AMEND), Success Charity and the Pituitary Foundation. All feedback was considered by the GDG before the guideline was finalised and submitted for publication.

Figure 1: Guideline development process



Flowchart of the guideline development process for recommendations for the diagnosis and management of pituitary adenomas in children and young people under 19 years of age. The Guideline Development Group (GDG) established the objectives and identified and refined recommendations using Population, Intervention, Comparison, Outcome (PICO) clinical questions[20] to undertake systematic literature reviews. Evidence was graded using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria[21]. Recommendations supported by insufficient, low quality or conflicting evidence, or evidence that was largely extrapolated from adult experiences, were reviewed by a Delphi consensus process. Recommendations that achieved consensus, alongside those with sufficient evidence not to require a consensus process, were reviewed and this guideline was published following the National Institute for Health and Care Excellence (NICE)-approved Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II)[18].

Figure 2: Literature review



Flowchart showing the literature review showing the number of publications identified and included in the guideline evidence base. Details of the literature search, inclusion and exclusion criteria and the search terms used during PubMed, Cochrane and Embase libraries searches are detailed in Supplementary Table 3.

General recommendations

Management statements

- **General: R1. Offer CYP with suspected or confirmed pituitary adenoma management in a specialist age-appropriate endocrine and neuro-oncology centre by an MDT working collaboratively with appropriate local healthcare professionals** (strong recommendation, low quality evidence, Delphi 100%).
- **General: R2. Offer all CYP with a pituitary mass a growth and pubertal assessment and baseline pituitary hormone measurements** (strong recommendation, high quality evidence).
- **General: R3. Clinicians treating CYP with pituitary adenomas should have access to a national paediatric pituitary-specific advisory panel in order to discuss the management of complex patients** (strong recommendation, low quality evidence, Delphi 90%).
- **General: R4.1. Report CYP with a confirmed pituitary adenoma to an appropriate national registry** (strong recommendation, low quality evidence, Delphi 90%)
- **General: R4.2. Offer transfer to adult pituitary services for continued surveillance at completion of growth and puberty** (strong recommendation, low quality evidence, Delphi 89%).

No published evidence is available to guide the organisation of age-specific services for the management of pituitary and other rare endocrine tumours in CYP. All CYP with a suspected pituitary adenoma or any radiological abnormality in the region of the pituitary fossa and stalk require a clinical assessment of growth and puberty and its age-appropriate timing. Baseline assessment for pituitary hormone deficiencies and specific investigations for hormone excess[22] should be performed, coordinated and interpreted by a paediatric endocrinologist with expertise in pituitary disorders at a specialist centre. The availability of paediatric pituitary-specific advisory panels is scarce in various countries and setting these up would benefit management of pituitary adenomas in CYP[23]. Consultation with an adult endocrinologist specialising in pituitary adenomas for the interpretation of results is key for care in the majority of patients. Close interaction between paediatric and adult endocrine services is required to coordinate long-term medical care and the transition to adult services. The timing of this transition depends on local guidelines but could be variable for patients with pituitary adenoma due to potential developmental delays. Patient support groups for pituitary patients (for example, the Pituitary Foundation, Child Growth Foundation, AMEND, Success Charity, Pituitary Network Association and World Alliance of Pituitary Organizations) offer educational resources and support communities that highlight the unique challenges affecting this developmental age group and could provide help for people living with pituitary disease.

Neuroimaging

- **General: R5. Offer pre-contrast (T1 and T2) and post-contrast-enhanced (T1) thin-sliced pituitary MRI, including post-contrast volumetric (gradient (recalled) echo) sequences for increased sensitivity, to CYP presenting with a visual field defect or with signs and symptoms of pituitary hypersecretion or hyposecretion** (strong recommendation, low quality evidence, Delphi 92%).
- **General: R6. Consider 3-Tesla MRI for surgical planning or intraoperative MRI, as it enhances anatomical definition and might improve completeness of resection without altering complication rates** (moderate recommendation, low quality evidence, Delphi 92%).

In CYP undergoing investigation for suspected pituitary adenoma, a dedicated pituitary MRI before (T1 and T2) and after gadolinium contrast enhancement (T1) is the imaging investigation of choice and should be reported by a neuroradiologist. The standard pituitary protocol (2mm slice, spin echo T1-weighted sequences performed before and after contrast, and fast or turbo spin echo T2-weighted sequences pre-contrast) can be supplemented by a volumetric (gradient (recalled) echo) acquisition after contrast, and some evidence suggests this strategy could improve the sensitivity for adenoma detection[24-29]. The differential diagnosis of pituitary fossa lesions in CYP (for example, Rathke cleft cysts or craniopharyngioma) is beyond the scope of this guideline, but these entities have separate guidelines[30,31].

In patients with suspected pituitary adenoma where MRI is negative or equivocal, molecular (functional) imaging might aid neoplasm localisation[32]. Specifically, hybrid imaging techniques (for example, PET–CT co-registered with MRI or PET–MRI) using ligands such as ^{11}C-methionine or ^{18}F-fluoroethyltyrosine have shown promising results in both *de novo* and recurrent functioning pituitary adenomas ; however, the successful use of these imaging modalities has only been reported in a small number of CYP to date[32,33] and currently these techniques are in the research stage.

The better resolution of a 3-Tesla MRI can improve anatomical delineation of pituitary adenomas and might enhance surgical planning but, as yet is without evidence of an increased sensitivity for adenoma detection[34]. Intraoperative MRI might improve complete resection rates of adenomas without increasing complication rates[35-41]. Low-level gadolinium deposits in the dentate nucleus and globus pallidus, have unknown long-term neurological impact. Therefore, unenhanced T1-weighted and T2-weighted MRI sequences should be considered during follow-up in CYP[42-44], especially if good quality enhanced images have been obtained at diagnosis. Macrocyclic or newer linear gadolinium-containing contrast agents should be used in weight-adapted doses. In patients with estimated glomerular filtration rate <30 ml/min/1.73 m^2 or on dialysis, administration of gadolinium-containing contrast should be considered individually, and alternative imaging modalities utilized whenever possible. If gadolinium-containing contrast agents are necessary, macrocyclic or newer linear gadolinium-containing contrast agents could be administered with patient or parental consent citing an exceedingly low risk (much less than 1%) of developing nephrogenic systemic fibrosis[45].

Visual assessment

- **General: R7. In CYP with suspected or confirmed pituitary adenoma, offer assessment of visual acuity (ideally logarithm of the minimum angle of resolution measurement), visual fields (ideally Goldmann perimetry) and fundoscopy, with or without colour vision** (strong recommendation, low quality evidence, Delphi 94%)
- **General: R8. In CYP with confirmed pituitary adenoma with potentially severe acuity or field deficits, consider baseline optical coherence tomography** (weak recommendation, low quality evidence, GDG consensus).
- **General: R9.1. Consider visual assessment (including acuity and fields if age-appropriate) in all CYP with a pituitary macroadenoma within 3 months of first-line therapy** (moderate recommendation, low quality evidence, Delphi 94% and GDG consensus).
- **General: R9.2. Ongoing visual follow-up should be based on individual indications** (moderate recommendation, low quality evidence, Delphi 81% and GDG consensus).

Pituitary macroadenomas can impinge on the optic chiasm and optic nerves. Visual disturbances are more often encountered in CYP with pituitary adenoma than in adult patients. Data on visual

function testing in patients with paediatric pituitary adenomas are scarce. Yet, studies of children with other lesions of the sellar or suprasellar region that affect vision and various other causes of visual impairment suggest that visual acuity, visual field testing and assessment of optical nerve integrity, as well as fundoscopy, can detect abnormalities at diagnosis[46-50]. Visual acuity is a psychophysical measure that relies on a patient's cooperation and attention. Qualitative measures of visual acuity are insufficient, and subtle and even large changes in visual acuity might not be adequately detected by these methods. Instead, visual acuity should be measured with age-specific tests and recorded as the internationally-recognised logarithm of the minimum angle of resolution measurement[51].

Age-appropriate visual field testing is of key importance in patients with pituitary macroadenomas and also in those with microadenomas after surgery. No data are available on optical coherence tomography in paediatric patients with pituitary adenomas, but optical coherence tomography can be a surrogate for visual field loss and visual dysfunction, as a thinner retinal nerve fibre layer is present in patients with visual field loss, reduced visual acuity or evidence of optic neuropathy[52]. Although the use of optical coherence tomography is limited by cooperation of the patient, this cooperation is required to a lesser extent than in visual field testing. Despite variability in cooperation among children aged under 6 years, reliable optical coherence tomography imaging was obtained in children from as young as 3 years of age[53]. No data are available for visual evoked potentials (a measure of the electrical signal generated at the visual cortex in response to visual stimulation) in CYP with pituitary adenomas. Visual evoked potentials have been used for non-verbal or disabled children, where standard visual assessment is difficult, but should not be used for long-term surveillance[30,54].

If CYP with pituitary adenomas treated with surgery, further recovery of visual field deficits is unlikely after the first post-operative month[55,56], with age <6 years and the presence of visual symptoms at diagnosis indicating an increased risk of poor visual outcomes[57,58]. Monitoring of CYP with pituitary adenomas should be determined on an individual patient basis, depending on baseline visual assessment and MRI appearances. Given the data from adults with pituitary adenoma[59] and from paediatric patients with craniopharyngioma (a neoplasm of the sellar or suprasellar region that can also affect vision)[30], the GDG strengthened the visual assessment recommendations (General: R8 and R9).

Histopathology

- **General: R10. Offer histopathological assessment of the operated pituitary adenoma tissue, including immunostaining for pituitary hormones and Ki-67, and additional immunoprofiling when relevant, to accurately classify the pituitary neoplasm** (strong recommendation, moderate quality evidence, Delphi 100%).

Data from adult patients with pituitary adenoma who undergo surgery and the recent WHO guidelines[12,60] suggest that Ki-67 staining and mitotic activity might help predict clinical outcomes in adults[61-63]. While available data on the prognostic value of Ki-67 is controversial, the 2022 WHO guideline encourages accurate quantification (positive staining per 500–1000 neoplastic cells in two hotspots). Therefore, prospective evaluation is recommended in CYP to identify correlates with outcome.

A paediatric pituitary adenoma surgical series found that 55% (28 out of 51 patients) had Ki-67 of ≥3%[5]. Furthermore, data on 42 paediatric pituitary tumours suggested that the combination of ≥3%

Ki-67 and local invasion on imaging predicts a 25% recurrence rate after surgery[64]. Recommendations from the *European Pituitary Pathology Group* for standardised reporting of paediatric and adult pituitary neoplasms suggest a multilevel approach, with pituitary hormones, cytokeratin and Ki-67 as the most basic report[65]. Transcription factors should be added if the sample is immunonegative or has scanty hormonal staining, or there is plurihormonal or unusual combination of hormone staining. In selected cases, chromogranin, somatostatin receptor and p53 staining can be added based on further clinical information[65]. O6-methylguanine-DNA methyltransferase immunohistochemistry can be useful if considering temozolomide therapy for aggressively growing tumours[66], as strong staining might predict lack of response. Electron microscopy is not routinely used in molecular pathology of pituitary neoplasms from CYP but might assist in selected patients. Several studies have provided data on the molecular pathology of pituitary neoplasms, which might have a role in their future classification[62,67]. Given data from adult pituitary adenoma guidelines[66] and the recent WHO classifications[12,60], the GDG strengthened **R10**.

Genetics

- **General: 11.1. Offer genetic assessment to all CYP with a pituitary adenoma to inform management and family surveillance** (strong recommendation, high quality evidence).
- **General: 11.2. Given the high prevalence of genetic abnormalities in somatotroph and lactotroph tumours, offer genetic testing to all CYP with growth hormone (GH) and prolactin excess** (strong recommendation, high quality evidence).

Several genes have been identified in association with pituitary adenomas in CYP, occurring as isolated pituitary adenomas (familial isolated pituitary adenoma or FIPA) or as part of a syndromic disease[68-72]. Although these conditions are rare, the number of identified germline (and somatic) genetic alterations are expected to increase in the future with the implementation of wider genetic testing. This knowledge could inform prognosis, treatment and screening for other manifestations in the proband, while family members could benefit from genetic testing and clinical screening[73-77]. Genetic testing is available in several laboratories that also support testing for international patients.

Genetic assessment of potential mutation carriers of known mutations should be performed prior to the typical age at onset of symptoms (variable for different diseases). Some advocate genetic screening from the age of the youngest known patient (for example, aged 4 years for *AIP* mutations[78]), whereas others suggest genetic screening at the point where biochemical screening is advised if the patient is a carrier (for example, aged 5–10 years for multiple endocrine neoplasia type 1 syndrome (MEN1)[79]). Follow-up of gene mutation carriers might include yearly clinical and biochemical follow-up. Timing of pituitary MRI screening and assessment of other potentially associated features depend on the genetic disease in question. Treatment of pituitary neoplasms of genetic origin, in general, is similar, but might require more treatment modalities compared with patients without genetic aetiology[73,75].

If mutations in known genes have been ruled out in a proband with young-onset or familial disease, no clinical assessment is recommended for family members, as genetic background is uncertain, penetrance is probably incomplete and regular long-term screening could lead to anxiety and increased health expenses[78].

GH excess in CYP

Among all pituitary adenomas, childhood-onset GH-secreting adenomas (with or without prolactin co-secretion) are most likely to have an identifiable genetic cause[80]; for example, almost 50% of

patients with gigantism have an identifiable genetic alteration[80,81]. Germline genetic abnormalities in CYP with GH-secreting pituitary adenomas have been identified in patients with FIPA (*AIP, GPR101* (female predominance, causing X-linked acrogigantism, X-LAG)) or with syndromic disease (*MEN1, CDKN1B, PRKAR1A, PRKACB, SDHx* and *MAX)*. In X-LAG, duplications in the Xq26.3 region lead to enhanced *GPR101* gene expression via disruption of the topologically associating domain (TAD) surrounding the gene, so X-LAG represents a TADopathy[82]. Mosaic mutations have been seen in *GNAS* (McCune-Albright syndrome) and *GPR101* (in boys), whereas somatic *GNAS* mutations restricted to the pituitary are rare in CYP, unlike in adults where they have been identified in 20–40% of tumour samples[83-85]. In CYP with GH-secreting adenoma, *AIP* mutations (29% of gigantism patients) and duplication in *GPR101* (10%) occur most frequently, followed by McCune-Albright syndrome (5%), Carney complex (1%), MEN1 (1%)[80] and rarely MEN1-like disease or phaeochromocytoma–paraganglioma-related gene alterations.

Prolactinomas in CYP

MEN1 and *AIP* germline abnormalities occur in both familial and apparently sporadic forms of prolactinoma[74,75,86,87], while MEN1-like (MEN4 or the recently suggested MEN5[88] due to *MAX* variants) or phaeochromocytoma–paraganglioma gene-related pituitary disease (also known as the three P Association or 3PA due to *SDH*x variants) is rare. In patients with a macroprolactinoma diagnosed before their 20th birthday, 14% have a genetic aetiology (5% *MEN1* and 9% *AIP*)[87], while 34% of patients with MEN1 under 21 years of age have a pituitary adenoma, 70% of these being prolactinomas[74]. In an *AIP* mutation-positive patient cohort, 10% had a prolactinoma, and a third of these had childhood-onset disease[75]. Of note, patients with microprolactinomas and *AIP* mutation have been described in a familial setting, but only extremely rarely in a sporadic setting[75]. Some patients with hyperprolactinaemia, but no detectable pituitary mass and variable phenotype, have been reported to have prolactin receptor mutations; however, none manifested symptoms in childhood[89,90]. No other gene has been reliably identified in familial or sporadic childhood-onset prolactinomas. For follow-up of patients with *MEN1* mutations, we refer to the MEN1 guidelines[79].

Corticotroph pituitary tumours in CYP

Germline mutations are rare in CYP with corticotroph adenomas[86,91]. *MEN1* mutations have occasionally been identified in both microadenomas and macroadenomas (2 of 55 patients with MEN1 aged <21 years)[74,92,93]. Variants in *CABLES1* (2 of 146 paediatric patients with corticotrophinomas) and *CDKN1B* (3 of 190 paediatric patients with or without additional MEN1-like manifestations) have also been identified[91,94]. A unique form of Cushing's disease due to infant-onset pituitary blastoma has been associated with DICER1 syndrome, with a very low penetrance (<1%); pituitary blastoma is pathognomic for *DICER1* mutations, based on the 18 patients published[95,96]. One patient has also been identified with DICER1 syndrome-related pituitary blastoma, who was diagnosed later in childhood[97,98].

Somatic mutations of the *USP8* deubiquitinase gene have been implicated in over a third of childhood[99] and adult-onset[100-102] corticotrophinomas, most typically in female patients with corticotroph microadenomas. In one case report, developmental delay was associated with a germline *USP8* mutation and Cushing's disease[103]. Large somatic genomic aberrations in the DNA of paediatric corticotrophinomas might indicate a more aggressive neoplasm compared to tumours without large genomic aberrations[104].

TSHomas

TSHomas have not been associated with germline genetic alterations in CYP, except one patient with resistance to thyroid hormone due to *THRB* mutation and a TSHoma[105]. TSHomas have rarely

been described in adult patients with *MEN1* and *AIP* variants[72].

Non-functioning pituitary adenomas in CYP

Non-functioning pituitary adenomas (NFPAs) occur in 25% of CYP with MEN1 syndrome. Non-functioning microadenomas, not dissimilar to incidentalomas, have been identified as part of clinical screening in *MEN1* and *AIP* mutation-positive CYP[73-75,84]. In a few *AIP* mutation-positive CYP, clinically non-functioning but GH and prolactin immunostaining positive macroadenomas have been identified[75,86]. Functioning gonadotroph adenoma in childhood has not been described with a germline mutation.

Pituitary surgery

- **General: R12. If surgery is indicated in CYP with pituitary adenoma, offer transsphenoidal surgery as the technique of choice, even in patients with incompletely pneumatised sphenoid sinuses** (strong recommendation, low quality evidence, Delphi 100% and GDG consensus).
- **General: R13. In CYP with pituitary adenoma, consider endoscopic rather than microscopic transsphenoidal surgery, for its potentially superior efficacy in preserving pituitary function** (weak recommendation, low quality evidence, Delphi 86%).
- **General: R14. In all CYP with pituitary adenoma who undergo surgery, offer strict fluid and electrolyte balance monitoring peri-operatively and post-operatively** (strong recommendation, moderate quality evidence, Delphi 100%).

In patients with pituitary adenoma, surgery is often a necessary primary or secondary intervention. In CYP with pituitary adenoma, transsphenoidal resection by pituitary surgeons in age-appropriate neurosurgical units with extensive experience (at least 50 pituitary operations per year per unit[106-108]), including in children, is a safe and effective procedure[109-117].

In CYP, transsphenoidal surgery by an experienced pituitary surgeon is the definitive treatment of choice for most pituitary adenomas, even in children with incompletely pneumatised sinuses; intraoperative image guidance might be additionally helpful. In a study of 66 children with pituitary adenomas[110], 17% of patients required drilling of incompletely pneumatised sphenoid sinuses, but anatomical differences related to patient age or size was not a limiting factor to the surgical procedure or its outcome. Likewise, further transsphenoidal surgery, if necessary, was performed with minimal difficulty and with results approaching those in adults undergoing debulking or removal of recurrent or residual lesions[110].

Changes in water metabolism and regulation of arginine vasopressin (AVP) are common complications of pituitary surgery[118,119]. Several patterns have been observed, for example: transient or permanent AVP deficiency; biphasic response with signs of AVP deficiency followed by inappropriate antidiuresis (SIADH); and triphasic pattern with usually permanent AVP deficiency after the two phases of the biphasic pattern. Patients must be managed in a setting where close observations (including careful monitoring of fluid input and output) can occur, so that any concerns can be flagged and raised with an expert endocrinologist at an early stage[120,121]. In a retrospective study of 160 children undergoing transsphenoidal surgery for pituitary neoplasms, the post-operative incidence of AVP deficiency (diabetes insipidus) and SIADH was 26% and 14%, respectively[118]. Risk factors for AVP deficiency or SIADH were female sex, cerebrospinal fluid leak,

drain after surgery, invasion of the posterior pituitary by the tumour or manipulation of the posterior pituitary during surgery.

In CYP with pituitary apoplexy, the GDG suggests adopting the recommendations of available adult guidelines[122], given the limited case reports and case series in CYP[119,123-129]. However, paediatric pituitary apoplexy can be more severe than in adults and selected patients might benefit from early surgery[128].

Endoscopic over microscopic transsphenoidal techniques are increasingly used in pituitary surgery, and are perceived as providing better operative visualisation and fewer perioperative complications and hormone deficiencies[130]. While further data are needed to show the clear advantage of endoscopic surgery, most adult guidelines agree that the surgeon's experience is more important to outcome than surgical technique (microscopic or endoscopic)[131]. Endoscopic transsphenoidal pituitary surgery in CYP with Cushing's disease show an excellent efficacy outcome[130] and improved safety, reducing surgical trauma, pain perception, paediatric intensive care unit admissions, blood transfusions, anterior pituitary deficiencies and incidence of AVP deficiency[130,132,133]. Over time, this strategy could become the standard surgical approach in children, as is current practice in adults. Postoperative high-quality outpatient support for CYP for biochemical assessment can shorten the hospital stay[134].

Indications for repeat pituitary surgery in recurrent or progressive disease are detailed for each individual pituitary adenoma type in the appropriate part of the guideline.

Radiotherapy

- **General: R15. In CYP with pituitary adenoma, offer radiotherapy when the tumour is symptomatic, growing, resistant to medical therapy and surgically inaccessible** (strong recommendation, low quality evidence, Delphi 94%).
- **General: R16. Consider clinical radiation treatment protocols for CYP according to adult guidelines or paediatric regimens for similarly located tumours** (moderate recommendation, low quality evidence, Delphi 94%).
- **General: R17. Consider external beam fractionated radiotherapy at a total dose of 45–50.4 Gy in 1.8 Gy daily fractions to CYP with pituitary adenomas indicated for radiotherapy; offer fractionated radiotherapy as proton beam therapy, where available, or as highly conformal photon therapy; single fraction radiosurgery might be appropriate in older patients in individual circumstances** (moderate recommendation, low quality evidence, Delphi 100% and GDG consensus).

The evidence for radiotherapy in CYP with pituitary adenomas is both limited and inconsistently reported. Some studies consider all adenomas[113,135-138], while others report on specific tumour types separately[115,139-144]. While focal radiotherapy (photon or proton beam therapy) is consistently administered to salvage those CYP with pituitary adenomas who have relapsed following surgery, no standardised timing of treatment indication has been developed (for example, number of surgeries offered prior to radiotherapy)[145]. Moreover, there is lack of data on dose fractionation or radiation modality comparisons that assess effectiveness or risk–benefit outcomes. Thus, few data are available on which to base recommendations regarding conventional photon radiation versus high energy proton beam therapy, or stereotactic radiosurgery. Even fewer toxicity data exist, particularly regarding cognitive outcomes, vasculopathies, secondary tumours and wider endocrinopathies, especially relevant to CYP.

If radiotherapy is needed, highly conformal radiotherapeutic techniques should be used, according to availability. Options include: high energy photon-based therapy (delivered as intensity modulated radiotherapy or conventionally fractionated stereotactic radiotherapy); proton beam fractionated radiotherapy; or hypo-fractionated stereotactic radiosurgery.

In CYP with pituitary adenomas, the largest clinical experience comes from conventionally fractionated external beam photons. Intensity-modulated radiation therapy (IMRT, including volumetric modulated and tomotherapy arc techniques) and stereotactic radiotherapy with photons have more conformal coverage than older 3D-conformal radiotherapy techniques, thereby reducing high radiation doses to organs at risk outside the treated volume[146-151]. However, IMRT still exposes surrounding normal tissue to a low dose of radiation.

In adults with pituitary adenomas, the total radiation dose recommendation is usually 45 to 50.4 Gy, 1.8 Gy per fractionation, once a day, 5 days per week over 25 or 30 days[139,151-155]. This regimen has been demonstrated to cure children with Cushing's disease[156]. All regimens should limit radiation delivery to no more than 1.8 Gy per fraction in keeping with modern paediatric cranial radiation schedules.

Despite the restrictions of cost and availability, modern fractionated external beam therapy with protons is increasingly applied to paediatric neoplasms, driven by the expected decrease in late effects[157-160]. Prospective data collection for long-term endocrine, vascular, second malignancy and cognitive outcomes for proton beam therapy in CYP is ongoing already in the UK and represents one of our research recommendations.

Stereotactic radiosurgery delivers a single large radiotherapeutic fraction to a limited volume with a restricted margin. This technique is routinely used for irradiating pituitary neoplasms in adults. Single fraction radiosurgery lacks long-term safety data in CYP and concerns have been raised regarding late toxicity, with younger children, especially under 5 years, possibly being at increased risk of vasculopathy and cognitive impairment.

In CYP with NFPA, radiotherapy might be considered as an adjuvant therapy after subtotal resection or where surgery is contraindicated. Radiotherapy might also be considered as second-line therapy for radiological progression or recurrence. In CYP with hormone-secreting pituitary adenomas, radiotherapy should be considered in patients with biochemical progression despite maximal surgery and medical therapy[156], although no clear risk–benefit analysis has been performed to identify the number of times surgery should be attempted before proceeding to radiotherapy. An age-appropriate pituitary MDT should determine radiation treatment options on an individual patient basis[30,161].

Risk–benefit outcome data is insufficient to support one radiotherapy treatment modality over another[144,162,163]. However, where the planning target volume includes the optic chiasm or optic nerves, stereotactic radiosurgery should be avoided and fractionated radiotherapy employed instead, as the stereotactic radiosurgery dose typically exceeds tissue tolerance. On the two Delphi consensus rounds performed, individual experts held particularly strong positions and disagreements occurred, with those who expressed a preference for stereotactic radiosurgery[144] against those who have concerns about the late effects of high doses per fraction in children. Both sides agreed that fairly few data exist on important long-term health, well-being and cognitive function following single fraction radiation in CYP.

Radiotherapy: outcomes

Adjuvant radiotherapy after transsphenoidal surgery achieves long-term tumour control in over 90% of adult patients with NFPA[139,164,165]. Endocrinological criteria determining biochemical remission vary across reported series, making it difficult to compare tumour control in functioning pituitary adenomas. Specific data for Cushing's disease can be found in the Cushing's disease section of this guideline. Of note, 4 out of 12 CYP with GH excess achieved remission after radiosurgery[144].

Radiotherapy: adverse effects

Hypopituitarism

Hypopituitarism is one of the most common adverse effects in CYP with pituitary adenomas who undergo radiotherapy. GH deficiency could be present at diagnosis due to tumour location, and it is universally present by 5 years after radiotherapy. Hypopituitarism with multiple hormone deficiencies evolves over time to an incidence of ~20% at 5 years after radiotherapy, and 80% at 10–15 years[165,166], although late effects of surgery or the evolving tumour also have a role. In CYP who undergo radiotherapy, follow-up for hypopituitarism needs to be lifelong, with planned transition to specialist adult services.

Effect on the brain

The young brain, although more plastic than the adult brain, is also more vulnerable to injury; for example, stereotactic radiosurgery might carry a higher risk of radionecrosis in CYP than standard fractionated external beam radiotherapy[167]. Other late effects of concern, particularly in children, include neurocognitive sequelae[142], cerebrovascular events and second malignancies[168]. In a group of 462 patients with pituitary adenoma (age range 10-83 years) Sattler *et al.*[169] reported no increased incidence of secondary tumours or mortality in patients receiving adjuvant post-operative radiotherapy compared with those treated with surgery alone. By contrast, Minniti *et al.*[170] reported a 2.4% risk of secondary brain tumours at 20 years after surgery and radiotherapy for pituitary adenoma in adults. However, long-term mortality from second brain tumours was minimal and mortality predominantly arose from cerebrovascular events of complex multifactorial aetiology. Thus, these authors concluded that the low incidence of second brain tumours should not preclude the use of radiotherapy as an effective treatment modality in patients with otherwise uncontrolled pituitary adenomas.

Second tumours

In a large cohort of adult patients with GH deficiency from a GH treatment database, secondary tumour incidence rate ratios for those who underwent radiotherapy to treat their primary pituitary tumour (pituitary adenoma or craniopharyngioma) versus no radiotherapy was 3.34 for malignant brain tumours and 4.06 for meningiomas. With every 10 years of younger age at radiotherapy, the risk of developing a malignant brain tumour increased by 2.4-fold and the risk of meningioma increased by 1.6-fold[171]. Incidence rates were similar in patients treated with conventional and stereotactic radiotherapy. The authors concluded there was a statistically significant increased risk of developing a malignant brain tumour and a meningioma after radiotherapy for pituitary tumours, especially when given at age <30 years, and emphasised the need for caution in balancing the risk–benefit ratio of radiotherapy in young patients[171]. A very high meningioma risk (standardized incidence ratio 658) was also found after cranial radiotherapy in the *Safety and Appropriateness of Growth Hormone Treatments in Europe* cohort (10,403 children treated with GH), but GH in replacement doses to children with GH deficiency was not implicated in the risk of secondary malignancies[172,173].

Fertility of CYP with pituitary adenomas

The issue regarding future fertility of CYP with pituitary adenomas was not a question explored by the guideline process. However, the GDG feels that this is an important question; therefore, we hope to provide some useful relevant information in this added section. As the vast majority of CYP with pituitary adenomas will not receive adjuvant systemic chemotherapy, any risk of damage to the gonads is not a significant problem. Both males and females with sellar/suprasellar tumours are at risk, however, of gonadotropin deficiency. This can be due to the mass effects of the tumour itself, due to elevated prolactin levels which cannot be fully controlled, due to extensive or repeated surgery or due to the effect of radiotherapy. There are then two options for fertility intervention: (i) treatment with gonadotrophins at the time of required fertility and (ii) collection of oocytes or sperm before surgery or radiotherapy if the patient is at the appropriate pubertal development stage and the gonadal axis is thus functionally able to allow this intervention.

i. Ovulation and spermatogenesis induction with gonadotrophins (FSH and HCG injections) are available for patient requiring fertility, while in vitro fertilisation procedures are also options.
   - **Females** – Women with hypopituitarism often need assisted reproductive treatment[174]. Pregnancy rates in hypopituitary women, according to a 2020 systematic review[175], range between 47% and 100% in various studies. In patients achieving pregnancy, live birth rate ranges from 61% to 100%.
   - **Males** –Spermatogenesis induction is usually successful in males with pituitary tumours occurring after puberty[176]. Male CYP with pituitary tumours may present with pubertal arrest or delay, but successful spermatogenesis induction has been seen in this patient group as well[177].

ii. Collection of oocytes or sperm before intervention of surgery or radiotherapy
   - **Females** – The potential role of fertility preservation with egg collection, which requires a fully functional menstrual rhythm, gonadotrophin injection and surgical procedure, would not be usually indicated for a CYP with pituitary adenoma.
   - **Males** – Boys with adequate virilisation, with a minimum pubertal Tanner stage 3 and testicular volumes ≥ 8ml have successfully banked sperm before gonadotoxic therapy[178]. In suitable patients, in the case of a minor, this will require judgement as to the patient's competency to consent. The process of counselling and informed consent to sperm banking is governed in the UK by the Human Fertilisation and Embryology Authority. Therefore, following pubertal staging, adolescent males with a pituitary tumour and a potential for development of gonadotrophin deficiency due to surgical or radiotherapy treatment of the pituitary lesion, could be offered the opportunity to cryopreserve sperm, following an individual [not proxy] consent process.

The issue of fertility choices and potential preimplantation genetics of patients with inherited genetic alterations related to pituitary tumours is beyond the scope of this guideline.

Specific recommendations

Prolactinomas

Epidemiology and aetiology

Prolactinomas are the most common adenoma type in CYP, occurring in approximately 0.1 million children every year[179]. However, prolactinomas are exceptionally rare before puberty, when corticotrophinomas are more common. In a series of 136 CYP presenting with pituitary adenomas before 20 years of age, 53% had prolactinomas, but 93% of these presented after 12 years of age. Pituitary adenomas were 3 times[180-182] to 4.5 times[183] more common in female patients than in male patients. Although patients can present with prolactinomas within the first decade of life[179-181,184], an adolescent presentation is more typical[87,180,182-185]. Median duration of symptom history before diagnosis is 12 months[179,186]. Of note, macroprolactinomas or giant prolactinomas, which can exert secondary mass effects that compromise growth, puberty and vision, also occur more frequently in CYP than in adults[182,187]. In a study of CYP with macroprolactinomas, 46% had overweight or obesity at diagnosis, and of these, 23% cited weight gain as one of the reasons for seeking medical advice[87].

A small percentage of paediatric prolactinomas are related to familial isolated pituitary adenoma or syndromic disease (multiple endocrine neoplasia type 1 syndrome (MEN1), MEN1-like or phaeochromocytoma–paraganglioma-related pituitary disease), even without a known family history[72]. Therefore, genetic testing should be considered (see R11).
In addition, some patients with hyperprolactinaemia without a detectable pituitary tumour and variable phenotype have been reported to have prolactin receptor mutations; none manifested symptoms in childhood [89,90].

Diagnosis: clinical features

- **Specific: R1. Offer serum prolactin measurement in CYP presenting with one or more of the following signs and symptoms: delayed puberty; galactorrhoea; visual field loss; growth or pubertal arrest; girls with menstrual disturbance** (strong recommendation, moderate quality evidence).

High serum levels of prolactin inhibit gonadotrophin secretion via inhibition of the hypothalamic hormone kisspeptin[188]. Paediatric patients with hyperprolactinaemia might therefore present with delayed (>2 standard deviation (SD) later than the mean population age for sex) or arrested puberty, growth failure or short stature, primary amenorrhoea, galactorrhoea, menstrual disturbance or secondary amenorrhoea (in post-menarcheal girls)[179,182]. Boys might present with gynaecomastia as a result of hypogonadism. Mass effects, occurring more commonly in boys than girls, include headache and visual field loss[189]. Obesity, gynaecomastia, constitutional delay in growth and puberty in boys, and menstrual disturbance in girls are common physiological variations that are very rarely caused by a prolactinoma. However, the cost of measuring prolactin is offset by the benefits of an early diagnosis and timely treatment.

Diagnosis: biochemical evaluation

- **Specific: R2. In CYP with signs or symptoms of hyperprolactinaemia, offer prolactin measurement in a single blood sample collected at any time of day** (strong recommendation, high quality evidence).

- **Specific: R3. Consider investigating modestly elevated serum prolactin levels by serial measurements over time to exclude the effect of stress and prolactin pulsatility** (moderate recommendation, low quality evidence, Delphi 87%).

A single prolactin measurement taken at any time of the day is sufficient to assess hyperprolactinaemia[190-192]. As prolactin secretion also rises in response to stress, in patients with elevated baseline prolactin (up to five times of the upper limit of normal[193]), sampling can be repeated on a different day with two or three samples at 20–60 min intervals using an indwelling cannula, to differentiate stress-related hyperprolactinaemia from organic disease[190,193-195].

- **Specific: R4. The diagnosis of hyperprolactinaemia in CYP requires age-specific and sex-specific prolactin reference ranges and the exclusion of confounding conditions, such as hypothyroidism, renal and/or hepatic impairment and use of medications that cause hyperprolactinaemia** (strong recommendation, moderate quality evidence).

Serum prolactin concentrations vary with age and sex. They are highest in the first 2 years of life and fall to a nadir in mid-childhood, to rise again in adolescence when they are higher in girls than in boys [196]. Paediatric cohort studies of prolactinomas report diagnostic serum prolactin concentrations usually above 4,000 mU/l (188 µg/l)[87,180,184], although lower levels can be seen in patients with microprolactinomas[179]. To rule out mixed prolactin and GH hypersecretion, age-dependent and sex-dependent insulin-like growth factor 1 (IGF-1) evaluation should always accompany prolactin assessment in CYP with prolactinomas.

Unexplained, persistently mildly or moderately elevated prolactin in blood samples taken after rest, could be due to a stalk effect (disconnection hyperprolactinaemia, pituitary stalk compression from mass lesions disrupting the dopaminergic inhibition of lactotroph cells)[197]. In adult patients with stalk effect, prolactin levels are reported above the normal range but not higher than 2,000 mU/l; 94 µg/l[198,199] or six times above the upper limit of normal[193]. Even if no corresponding symptoms of hyperprolactinaemia, hypopituitarism or a pituitary mass are observed, pituitary imaging should be considered. If hyperprolactinaemia is due to a pituitary mass, baseline and dynamic pituitary assessment can identify a potential lack or excess of other anterior pituitary hormones.

Severe primary hypothyroidism can be accompanied by hyperprolactinaemia, probably due to compensatory thyrotropin-releasing hormone hypersecretion and pituitary hyperplasia; care should be taken to distinguish such pituitary enlargement from a true prolactinoma[200-204]. Severe and prolonged primary hypothyroidism in children can disrupt kidney and liver function as well as delay growth and puberty. In a large cohort of 2,848 adults, hyperprolactinaemia was reported in 43% of women and 40% of men presenting with frank primary hypothyroidism, 36% of women and 32% of men with subclinical hypothyroidism, and only in around 2% of euthyroid individuals[201]. Hyperprolactinaemia is reported in 30–65% of adult patients with chronic kidney disease due to increased prolactin secretion and reduced renal clearance[205-209]. Severe liver disease is also associated with hyperprolactinaemia in adults[193]. Intracranial hypotension can cause hyperprolactinaemia[193]. Although we could find no parallel data describing the prevalence of hyperprolactinaemia in these clinical scenarios in CYP, the Guideline Development Group (GDG)[16] recommends the exclusion of confounding diseases. Tetrahydrobiopterin deficiencies, a group of rare neurometabolic disorders characterized by insufficient synthesis of monoamine neurotransmitters including dopamine, can be associated with hyperprolactinaemia (10-30 fold elevation of prolactin) in up to 80% of the patients, usually from the teenage years; development of

a microprolactinoma has been also described in case reports[210,211]. While less likely in the CYP population, pregnancy should not be overlooked as a cause of hyperprolactinaemia[193].

Medications are one of the most common causes of hyperprolactinaemia in adults through direct prolactin stimulatory pathways or by antagonising inhibitory dopaminergic tone[212-216]. Medication-induced hyperprolactinaemia is also well-described in CYP (**Table 1**). The role of synthetic oral oestrogens (for example, contraceptive pills) in causing mild elevation of prolactin is controversial.

- **Specific: R5. Assess baseline macroprolactin levels where serum prolactin is found to be mildly or incidentally elevated** (strong recommendation, low quality evidence, GDG consensus).

In addition to monomeric prolactin (23 kDa), dimeric (48–56 KDa) and polymeric (>100 KDa) forms (usually associated with an antibody) can circulate ('macroprolactin', which has low biological activity), with or without excess monomeric prolactin. No routine assays distinguish between monomeric prolactin and macroprolactin, so prompt and appropriate secondary analysis should be undertaken to detect the possible presence of macroprolactin in the initial investigation of asymptomatic CYP with hyperprolactinaemia[195,217-222]. In large retrospective cohorts of adults with hyperprolactinaemia, macroprolactinaemia was present in 10–40% of individuals with hyperprolactinaemia[191,217,218], 20% of whom had galactorrhoea, 45% oligo-amenorrhoea and 20% pituitary adenomas. Few patients with macroprolactinaemia are reported in the paediatric literature. In a cohort of five patients aged 11–18 years with an incidental finding of hyperprolactinaemia due to macroprolactinaemia, none developed clinical features of prolactin excess during an observation period ranging from 3 months to 8 years[223]. In another report, one of six CYP with macroprolactinaemia was asymptomatic, the other five had either headache, menstrual disturbance, short stature, increased hair growth or early puberty. Four of those with symptoms underwent pituitary MRI and a microadenoma was identified in two (one with headache and one with oligomenorrhoea)[224]. Given these data and the current widespread clinical practice[182], the GDG strengthened **R5**.

- **Specific: R6. Perform serial dilutions of serum for prolactin measurement in CYP with large pituitary lesions and normal or mildly elevated prolactin levels** (strong recommendation, moderate quality evidence).

Serum prolactin levels directly correlate with prolactinoma size and are important markers of treatment response. Based on adult data, approximately 5% of patients with macroprolactinomas and a paradoxically modest serum concentration of hyperprolactinaemia, have grossly elevated prolactin concentrations following serum dilution[225]. When prolactin is measured in two-site immunoradiometric assays, very high concentrations of prolactin could saturate the signalling antibody, making it less available for binding to the coupling antibody, resulting in artificially low measurements[190,226-228]. This phenomenon has been described as the 'high dose hook effect'[225] and is well recognised. Some prolactin assay manufacturers have put specific mitigating factors in place, such as large linear ranges or automatic dilution steps, in many modern assays. However, potential remains for this effect to be a source of anomalous results[229]. Thus, contact with the clinical biochemist to request manual dilution is advised, when a discrepancy exists between a large pituitary adenoma on imaging and only modestly elevated prolactin concentrations on initial biochemistry. Of note, inconsistent symptoms and laboratory results can occasionally arise due to biotin exposure or heterophilic anti-animal antibodies[193].

Table 1: Drugs reported inducing hyperprolactinaemia in CYP[511]

We restricted this table to drugs which have been reported to cause hyperprolactinaemia in CYP.
*Aripriprazole is a partial agonist at the type 2 dopamine receptor and display partial agonist activity at the type 1A serotonin receptor (5HT1A) and antagonist at 5HT2A receptor. It can be used in combination with other psychotropic medications to reduce prolactin levels. Aripriprazole itself can sometimes cause mild hyperprolactinaemia[524].

Medication class	High >50 percent of patients	Moderate 25-50 percent of patients	Low <25 percent of patients	Case reports
Antipsychotics, first-generation 'typical'	Fluphenazine[512] Haloperidol[513,514]	Chlorpromazine[515] Loxapine[516] Pimozide[517,518]		
Antipsychotics, second-generation 'atypical'	Paliperidone[519,520] Risperidone[514,521-524]	Asenapine[525] Molindone[526] Olanzapine[513,524] Lurasidone[527,528]	Ziprasidone[529] Quetiapine[523,524]	Clozapine[513] Aripriprazole*[524,530] Amisulpride[531] Brexpiprazole[532]
Antidepressants	Clomipramine[533]		Desipramine[534]	Bupropione[535] Citalopram[536] Escitalopram[537] Fluoxetine[538] Sertraline[539] Duloxetine[537] Paroxetine[540] Venlafaxine[541]
Anti-emetics and gastrointestinal medications	Metoclopramide[542-544] Domperidone[545,546]			Omeprazol[547] Lansoprazol[547] Cisapride[541]
Others	Fenfluramine[548]		Oestrogens[549]	Clonidine[550] Methylphenidate[541] Guanfacine[541] Valproic acid[541] Penicillamine[541]

Treatment

- **Specific: R7. In CYP with prolactinoma, offer a dopamine agonist as first-line therapy to reduce serum prolactin concentrations and induce tumour shrinkage; cabergoline is the dopamine agonist of choice given its superior effectiveness and lower adverse effect profile** (strong recommendation, moderate quality evidence).
- **Specific: R8. In CYP with prolactinoma, offer cabergoline as first-line therapy, even in the presence of visual disturbance and pituitary apoplexy, while carefully monitoring for any deterioration in vision, pituitary function or general status** (strong recommendation, low quality evidence, Delphi 100%).

Dopamine agonists reduce pituitary origin hyperprolactinaemia of any cause[193]. In adults with prolactinoma, dopamine agonists induce normalisation of the prolactin level (median: 68% of patients; range: 40–100%), tumour shrinkage (62%; 20–100%), resolution of visual field defects (67%; 33–100%), normalisation of menses (78%; 40–100%), fertility (53%; 10–100%) and sexual function (67%; 6–100%), and resolution of galactorrhoea (86%; 33–100%)[186,230-232]. In both adults and CYP with prolactinoma, cabergoline is the dopamine-agonist of choice[179,186,187]. Cabergoline has a longer half-life and greater affinity for the dopamine receptor than other dopamine agonists. In a randomised controlled trial of adult women with prolactinoma, cabergoline was superior to bromocriptine in normalising prolactin (83% versus 59%), resuming ovulatory cycles or achieving pregnancy. Adverse events were more commonly reported with bromocriptine than cabergoline (72% versus 52%)[233].

In studies of CYP with prolactinomas, dopamine agonists lower prolactin concentrations in 60–70% of patients[87,179,180,184,186,234], reduce tumour size by 80–88%[179,186], improve visual deficits[235], resolve pubertal delay and eliminate headache[186]. In an observational study of 28 paediatric patients, CYP with prolactinomas smaller than 13.5 mm in diameter (13 patients) achieved normalisation of prolactin levels without surgery, using conventional cabergoline doses (up to 2 mg/week)[187]. Moreover, another series of 22 CYP with prolactinomas reported all tumours >20 mm diameter required surgery[182]. Although successful dopamine agonist discontinuation has been achieved in CYP, younger patients and those with high serum prolactin concentrations at diagnosis (a marker of adenoma size) are less likely to achieve complete remission and euprolactinaemia[179,186,236]. Medication-induced shrinkage of prolactinomas that have invaded sphenoid bone can cause rhinorrhoea after a few months of drug administration (mean 3.3 months, range 3 days – 17 months) due to a cerebrospinal fluid leak[237], but this adverse effect can also occur during long-term treatment. Detection of β2-transferrin or β-trace protein (specific to cerebrospinal fluid) in nasal secretions confirms a cerebrospinal fluid leak[238]. Cerebrospinal fluid leak can require urgent intervention (for example lumbar drain or surgical repair), with or without a temporary cessation in dopamine agonist therapy[239]. Apoplexy has been described during cabergoline therapy both in adults and CYP[182].

- **Specific: R9. For CYP resistant to standard doses of cabergoline, offer graduated dose increments up to 3.5 mg per week, or up to 7 mg per week in exceptional cases** (strong recommendation, moderate quality evidence, Delphi 100%).

Evidence indicates that adult patients with prolactinoma who are unresponsive to standard dopamine agonist doses (up to cabergoline 1.5–2 mg per week) might respond to higher doses (3.5–7 mg per week), whilst even higher doses (up to 12 mg per week[240,241], but below the 21 mg per week dose used for Parkinson disease) have been tried. High dose cabergoline is reportedly well tolerated and doses up to 7 mg per week have been used to successfully treat CYP with prolactinoma[19,87,186,242]. However, others report little benefit of cabergoline doses above 3.5 mg per

week in adults[240]. Patients with cabergoline resistance or intolerance will require adjuvant therapy with surgery or radiotherapy[241,243,244].

- **Specific: R10.1. Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient is unable to tolerate, or is resistant to high dose cabergoline** (strong recommendation, low quality evidence, Delphi 95%)
- **Specific: R10.2. Following multidisciplinary discussion, for CYP with prolactinomas offer surgery when the patient develops deteriorating vision on cabergoline** (strong recommendation, low quality evidence, Delphi 90%).
- **Specific: R10.3. Following multidisciplinary discussion, for CYP with prolactinomas offer radiotherapy if surgery is not an option** (strong recommendation, low quality evidence, Delphi 100%).

Small nocturnal dose increments of cabergoline can effectively diminish the adverse effects of gastrointestinal intolerance and postural hypotension, thereby avoiding trials of less effective dopamine agonists (bromocriptine or quinagolide). Dose-independent psychological intolerance (mood changes, depression, aggression, hypersexuality and impulse control disorder) is similar between agents and described in adults as well as CYP[236,245], but the frequency of these adverse events might be higher in CYP than adults[186,246]. Dopamine agonist resistance is usually defined in adults and CYP as failure to achieve normoprolactinaemia (biochemical resistance), and less than 50% reduction in tumour area in the coronal plane and/or less than 30% reduction of the longest diameter of the tumour (tumour size resistance, assessed by response evaluation criteria in solid tumours (RECIST) criteria))[247] after 3–6 months of maximally tolerated dopamine agonist doses (at least 2 mg per week)[193,240,244,248,249]. In a paediatric macroprolactinoma cohort who were unresponsive to 3 months of 15mg per day bromocriptine, 600µg per day quinagolide or 3.5mg per week cabergoline, 26% were biochemically resistant and 24% tumour-shrinkage resistant[87]. This resistance directly correlated with tumour size and prolactin levels (which in turn were closely correlated) but was independent of *MEN1* mutation status[87].

In CYP with prolactinoma, neurosurgical intervention should be considered if vision deteriorates or does not improve on medical therapy, or if dopamine agonist resistance, escape or intolerance occurs. Careful multidisciplinary discussion is needed if the patient expresses preference for surgery rather than long-term medication or is non-adherent to the latter.

Transsphenoidal surgery induced remission in 30–50% of adults with prolactinomas and any residual post-operative hyperprolactinaemia was subsequently more responsive to dopamine agonists than pre-operatively[250-253]. Tumour size negatively predicted surgical remission rates, with smaller adenomas being more often cured by surgery alone than larger ones[254,255]. Paediatric series report lower surgical remission rates than in adults, most likely due to the higher incidence of proportionately larger prolactinomas in CYP, as well as a possible higher frequency of new and permanent pituitary hormone deficiencies after surgery[22,245,256-258]. In adults with microprolactinomas or intrasellar macroprolactinomas, surgery is a viable option with an excellent cure rate (83% in microprolactinomas and 60% in macroprolactinomas), especially in high volume surgical centres and is certainly an alternative to long-term cabergoline therapy[193,259].

Radiotherapy should be reserved for exceptional patients with a growing prolactinoma and where other treatment modalities are not available or have been exhausted; the main indication for radiotherapy is control of tumour growth; normalisation of prolactin levels is a secondary objective[16]. After radiotherapy, initially 6-monthly and later 12-monthly follow-up should monitor for the

development of hypopituitarism or recurrence. The detailed assessment and treatment of hypopituitarism in CYP is beyond the scope of these guidelines.

- Specific: R11. In CYP with prolactinoma, offer echocardiogram at the start of treatment with a dopamine agonist; offer yearly surveillance echocardiography for patients receiving >2 mg per week cabergoline and every 5-years if on ≤2 mg per week (moderate recommendation, moderate quality evidence).

High dose and long-term use of dopamine agonists in Parkinson disease pose a recognised risk of cardiac valve regurgitation[260]; however, the doses used in treating prolactinomas are notably lower. A meta-analysis that identified an increased prevalence of echocardiographic tricuspid regurgitation in adults was heavily influenced by a single study, with no reports of increased clinical valvular disease[261]. A subsequent population-based, matched control cohort study in adults failed to identify an excess in hard clinical cardiac endpoints[262]. Nevertheless, the long-term cardiac safety of ergot-based dopamine agonists in CYP requires a balanced judgement against the increasing background rate of cardiac valvulopathy that occurs with age, and the often more aggressive nature of prolactinomas in the paediatric age group, who require longer treatment durations and higher cumulative doses than adults. The relative contributions of peak versus cumulative doses of dopamine agonists in the aetiology of valvulopathy are unknown. In adults with Parkinson disease and moderate to severe valvulopathy, the mean cumulative cabergoline dose was 4,015 mg, with one SD below the mean being 720 mg[263-265], yet a critical cumulative dose threshold could not be established[265]. Similar respective cumulative doses in CYP with prolactinoma would require 39 years (4,015 mg) or 7 years (720 mg) of 2 mg per week cabergoline treatment. To date, valvulopathy in CYP treated with dopamine agonists for hyperprolactinaemia has not been reported. A 2019 position statement for adults with prolactinomas treated with dopamine agonists recommends pre-treatment baseline and annual echocardiography with cardiac auscultation for those on >2 mg per week of cabergoline, reduced to 5-yearly echocardiographic surveillance if the cabergoline dose is ≤2 mg per week[266]. Until data specific to CYP emerge, following these recommendations (endorsed by three relevant UK professional societies[265]) seems prudent.

- Specific: R12. Temozolomide treatment might need consideration for CYP with aggressive pituitary tumours resistant to medical, surgical and radiation therapy (weak recommendation, low quality evidence, Delphi 88%).

Temozolomide treatment for aggressive pituitary tumours and pituitary carcinomas is well described in the adult pituitary literature[267-276]. These entities are extremely rare in CYP: four patients with pituitary carcinomas are reported to have had disease commencing in childhood[277-280]. The 2017 *European Society of Endocrinology* guideline recommends first-line temozolomide monotherapy for aggressive pituitary tumours and pituitary carcinomas unresponsive to standard therapies, with evaluation of responders and non-responders after three cycles of 150 mg/m^2 per day for 5 days in every 28, with dose increases to 200 mg/m^2 per day in patients with good tolerance[66,281]. A minimum of 6 months treatment is recommended for responding patients. Five paediatric patients receiving temozolomide treatment for pituitary tumours were identified in the literature, with two more paediatric-onset patients receiving temozolomide as adults (**Table 2**).

Table 2: Paediatric-onset pituitary adenomas treated with temozolomide

Sex	Age at diagnosis (years)	Age at temozolomide treatment (years)	Dose and response to temozolomide	Anterior pituitary hormone staining	Reference
Male	13	16	200 mg/m^2 per day, 5 days per month; good prolactin and size response	Prolactin	Whitelaw, et al. [551]; patient also mentioned in Arya, et al. [182]
Female	8	8	200 mg/m^2 per day, 5 days per month	Prolactin	Felker, et al. [552]
Male	14	18	200 mg/m^2 per day, 5 days per month, 40% shrinkage after 6 cycles	GH and prolactin	Lasolle, et al. [553]
Male	4 (*AIP* positive)	4	180 mg per day, 5 days per month	GH	Dutta, et al. [461]
Female	9	9	200 mg/m^2 per day, 5 days per month	Hormone-negative	Guzel, et al. [278]
Female	13	25	75-200 mg/m^2 per day, 5 days per months, 50% shrinkage after 12 cycles	ACTH	Lasolle, et al. [553]
Female	17	27	5 mg per day, 5 days per month	Prolactin	Chentli, et al. [554]
Male	18	19.75	200 mg/m^2 per day, 5 days per month, partial biochemical response, poor tumour size response	Prolactin	Arya, et al. [182]

Follow-up and surveillance

- **Specific: R13. If the serum level of prolactin has been normalised for at least 2 years on medical therapy and there is no visible residual prolactinoma on MRI, consider gradual cabergoline dose reduction to maintain normoprolactinaemia and eventual treatment discontinuation, with continued serum prolactin monitoring for at least 2 more years** (moderate recommendation, low quality evidence, Delphi 100%).

The relapse rates of prolactinomas in CYP treated with dopamine agonists is not reported. The *Endocrine Society* guideline for treating hyperprolactinaemia in adults recommends a trial of therapy discontinuation in those patients with no tumour remnant on MRI and normoprolactinaemia after 2 or more years of medical treatment[193,195]. Studies report variable (26–89%) hyperprolactinaemia recurrence rates under these conditions, largely within the first 2 years of treatment withdrawal[193,282,283]. Discontinuation might also be attempted with normoprolactinaemia and a small tumour remnant[257].

Two meta-analyses have examined factors associated with relapse following treatment withdrawal in patients with prolactinoma treated with dopamine agonists. The first (19 studies, 743 patients) concluded that both the use of cabergoline and treatment for more than 2 years, were associated with a decreased relapse rate[284]. The second (11 studies, 637 patients) found that tapering doses

prior to withdrawal reduced the risk of relapse, but treatment beyond 2 years had no further beneficial effect[285].

CYP with prolactinomas should be monitored clinically (including assessment of growth, puberty, galactorrhoea, menstrual history, gynaecomastia or loss of libido in puberty) and biochemically by measurement of serum prolactin. For macroprolactinomas, MRI should be repeated 3–6 months after starting cabergoline treatment; for microprolactinomas, reimaging depends on clinical and biochemical follow-up, imaging is suggested before considering cabergoline withdrawal[193]. Longer term imaging frequency depends on symptoms, biochemical control and on the closeness of the pituitary mass to the optic chiasm[193]. One observational study (including 11 CYP) reported low bone mineral density (BMD) at diagnosis with modest degrees of recovery after 2 years of dopamine agonist therapy. Assessment of BMD 2 years after diagnosis might be important in patients with prolactinoma[286]; but the inevitable negative impact of delayed growth and puberty on peak bone mineral accrual will confound definitions of 'osteopaenia' in CYP. Thus, repeated longitudinal assessments require interpretation not only alongside cure rates, but also with clinical pubertal staging, additional sex and adrenal hormone replacement, and at growth completion (epiphyseal fusion) and full pubertal maturation (age 25 years).

The optimal frequency of MRI imaging following cessation of treatment is unknown. Prolactin levels, assessed at 3–6 monthly intervals initially, can be used as markers of tumour relapse, although biochemical relapse is not always accompanied by radiological MRI change[282].

Cushing's disease

Epidemiology and aetiology

Cushing's disease is caused by an adrenocorticotropin (ACTH)-secreting pituitary adenoma and is the most common form of ACTH-dependent Cushing's syndrome, yet it is rare in CYP. The incidence is approximately 10% of that in adults, ~0.5 new patients per million individuals per year[287]. Cushing's disease accounts for 75–80% of CYP with Cushing's syndrome, compared with 49–71% of adults[288,289]. In fact, corticotroph adenomas are the most common pituitary adenoma diagnosed in early childhood (55% of pituitary adenomas aged 0–11 years; 30% 12–17 years)[183], with mean age at presentation of 12.3±3.5 years (mean±SD; range 5.7–17.8)[290]. An overall male predominance exists in CYP, with 63% of patients in paediatric Cushing's disease being boys, compared with 79% of patients being female in adult series. This discrepancy is driven by prepubertal male predominance (71%)[291-293]. Boys with Cushing's disease tend to have more aggressive disease with elevated BMI, shorter height and higher plasma ACTH levels than girls[294,295]. At all ages, microadenomas are the most common cause of Cushing's disease, accounting for 98% of cases in CYP, with the adenoma diameter frequently being ≤2 mm[183,287,291,296,297]. Macroadenomas, often showing invasion of the cavernous sinus, are rare in CYP (2–5% CYP versus 10% of adults with Cushing's disease)[298-300]. Genetic associations are described in the Genetics section.

Diagnosis: clinical features

- **Specific: R14. Offer screening for Cushing's syndrome in CYP with obesity, but only if weight gain is inexplicable and combined with either a decrement in height SD score (SDS) or height velocity** (strong recommendation, moderate quality evidence).

The clinical features of Cushing's disease in CYP are well documented[288,294,296,301-303] and demonstrate interesting differences compared with adult patients[291]. CYP might show growth failure (subnormal growth velocity), with respective short stature and weight gain (height SDS below and BMI SDS

above the mean for age and sex)[288,291,296,303,304]. Yet not all CYP with Cushing's syndrome have obesity and few patients with obesity prove to have Cushing's syndrome[305]. Consensus Statements advise that only CYP with unexplained weight gain and either growth rate deceleration or decrement in height centile over time require investigation, as this combination of features has a high sensitivity and specificity for Cushing's syndrome in CYP[306,307]. The presence of growth failure sensitively discriminates simple obesity from Cushing's syndrome in prepubertal CYP[308], but is an unreliable indicator in post-pubertal CYP, who require assessment according to adult guidelines[307].

Diagnosis: biochemical investigations

- **Specific: R15. In CYP with suspected Cushing's syndrome, offer investigations using established algorithms, first to determine the diagnosis of Cushing's syndrome (the presence of hypercortisolaemia), followed by investigations to ascertain its aetiology** (strong recommendation, moderate quality evidence).

The biochemical investigation of children with suspected Cushing's syndrome has been extensively reviewed[288,301,306,309-314]. The algorithms for testing consist initially of confirmation or exclusion of the diagnosis of hypercortisolaemia and then investigations to determine its aetiology[306,309].

- **Specific: R16. Suspected Cushing's syndrome in CYP is effectively excluded by: either two normal 24 hour urinary free cortisol (UFC) measurements and a normal low-dose dexamethasone suppression test (LDDST, 0.5 mg 6 hourly for 48 hours or if patient's weight is <40 kg, 30 µg/kg per day for 48 hours); or a midnight sleeping serum cortisol concentration <50 nmol/l** (strong recommendation, high quality evidence).
- **Specific: R17. Two late-night salivary cortisol tests could be a useful alternative for the midnight serum cortisol test as a means of excluding Cushing's syndrome, but age-specific and assay-specific normal ranges are not currently available and need to be carefully characterised** (moderate recommendation, moderate quality evidence).

Diagnosis of hypercortisolism usually includes three tests: dexamethasone-suppression testing, 24-hour UFC and late-night salivary or sleeping midnight serum cortisol level (**Table 3**). None of these tests has 100% diagnostic accuracy and each test has some limitations[315-320]. It is important to eliminate the effect of exogenous glucocorticoids before biochemical testing.

Table 3: Recommended protocol for diagnosis of Cushing's disease in CYP[a].

Type of test	Diagnostic cut-off	Sensitivity[b]	Specificity[b]
Confirmation of Cushing's syndrome			
1: UFC excretion (24 hr urine collection) for 3 days	>193 nmol/24hr[c] (>70 µg/m^2)	89%	100%
2: Serum cortisol circadian rhythm study (09:00h, 18:00h, midnight (sleeping))	≥50 nmol/l[d] (≥1.8 µg/dl)	100%[d]	60%[d]
3: Late-night salivary cortisol	Based on local assay cut-off	95%	100%
4: LDDST. Dose 0.5 mg 6 hourly (09:00, 15:00, 21:00, 03:00h) for 48 h; the dose for patients weighing <40 kg is 30 µg/kg per day; serum cortisol level is measured at 0, 24 and 4 8h.	≥50 nmol/l (≥1.8 µg/dl)	95%	80%
5: Overnight dexamethasone test. Dose 25 µg/kg at 23:00 p.m. or midnight (maximum dose 1 mg); serum cortisol measured at 09.00	≥50 nmol/l (≥1.8 µg/dl)	11% (based on 9 patients[555]); 75% (based on 4 patients[305])	Not applicable
Confirmation of Cushing's disease			
1: Plasma ACTH (09:00h)	>1.1 pmol/l (>5 ng/l)	68%	100%
2: CRH test (1.0 µg/kg intravenously)	Cortisol increase ≥20%[e]	74–100%	Not applicable
4: Pituitary MRI scan	Adenoma detection	63%	92%
5. Bilateral inferior petrosal sinus sampling for ACTH (with intravenous CRH or desmopressin)	Central:peripheral ACTH ratio ≥3 (after intravenous CRH or desmopressin)	100%	Not applicable

[a]The protocol in this table was originally presented in[70,301].
[b]Data from references[70,303-305,315,316,327,328,555,556]. [c]Urinary cortisol values are assay dependent, this value refers to radioimmunoassay data. [d]Diagnostic cut-offs refer to midnight serum cortisol values. [e]≥35% increase in ACTH during CRH testing has also been used as a diagnostic cut-off[305,311]. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; LDDST, low-dose dexamethasone suppression test; UFC, urinary free cortisol

Dexamethasone-suppression testing can be either standard 48-hour LDDST, or overnight dexamethasone test (25 µg/kg at 11 p.m. or midnight, maximum dose 1 mg). The 1mg overnight dexamethasone suppression test is now routine in adults[307], but considerably less data are available in children, where this test has lower sensitivity[315,321,322]. Both the 48-hour and the overnight dexamethasone tests can be influenced by diarrhoea or coeliac disease, or by medications that increase cortisol binding globulin levels or influence CYP3A4 activity. Measurements of serum dexamethasone can be used to ensure appropriate blood levels, but data for children are lacking and dexamethasone assays are not widely available. Repeated 24h UFC measurements in the

normal range (corrected for body surface area, µg/m^2 per 24 hours) can support the lack of hypercortisolism. Physiological increases in UFC excretion can occur in girls in the peri-menarcheal phase. Limitations of the UFC test include difficulties in accurately and repeatedly collecting urinary samples in young children, lower sensitivity in milder cases of hypercortisolism and in severe kidney dysfunction. A sleeping midnight serum cortisol measurement has high sensitivity (94–100%) and specificity (100%) for Cushing's disease. The test needs an overnight stay in the hospital and the patient needs to be asleep at the initiation of sampling. By contrast, a late-night salivary cortisol test is easy and cost-efficient, with high sensitivity (93–100%) and specificity (95–100%), but lacks age-specific and assay-specific normal ranges.

Clinical suspicion of Cushing's syndrome, but normal biochemical test results could rarely be due to periodic Cushing's syndrome. In these patients, multiple, periodic, sequential late-night salivary cortisol tests can be helpful for detecting episodes of cortisol excess longitudinally[306,307,309,323].

- **Specific: R18.1. In CYP with confirmed Cushing's syndrome, Cushing's disease can be confirmed by its ACTH dependency, which is supported by a normal or elevated 09:00h plasma ACTH** (strong recommendation, moderate quality evidence).
- **Specific: R18.2. In CYP with confirmed Cushing's syndrome, the diagnosis of pituitary-origin ACTH excess is supported by >20% increase in cortisol from baseline during a corticotrophin releasing hormone (CRH) or desmopressin test** (moderate recommendation, low quality evidence, Delphi 92%).

Following confirmation of hypercortisolism, the priority is to determine its cause. Cushing's disease is most easily confirmed by determination of basal (morning, 08:00–09:00h) plasma ACTH. In all patients with Cushing's disease, ACTH is detectable (>5 ng/l (>1.1 pmol/l), **Table 3**). In the presence of confirmed hypercortisolism, using a cut-off value of 29 ng/l (6.4 pmol/l), ACTH has a 70% sensitivity and 100% specificity for diagnosing Cushing's disease[311]. Based on adult data and guidelines, in ACTH-independent Cushing's syndrome ACTH is always low and usually undetectable.

High-dose dexamethasone suppression tests (HDDST, 80–120 µg/kg, maximum 8 mg) are no longer necessary in the routine investigation of Cushing's disease, given that in CYP (as in adults), >30% cortisol suppression during LDDST (but still above 50 nmol/l) correlates with HDDST results and strongly supports the diagnosis of Cushing's disease. Furthermore, CYP with ectopic ACTH-secreting tumours might show cortisol suppression on HDDST, while the HDDST itself can induce transient hypertension and hyperglycaemia in CYP[301,315,324-326]. Therefore, many centres have abandoned HDDST. A CRH test using human sequence CRH (1 µg/kg intravenously) is recommended to support the suspected diagnosis of Cushing's disease; in 92% of paediatric patients with Cushing's disease (36 of 39 patients), serum cortisol level increased by >20% (range 2%–454%) in response to CRH[291]. Ectopic ACTH syndrome is so rare in children that the need for a CRH test is questionable, although a cortisol increase of >20% to CRH has a 97.5% sensitivity and 100% specificity for Cushing's disease and can contribute to the diagnosis[311]. As availability of CRH is not universal, desmopressin (10 µg intravenous) has been used in CYP for bilateral simultaneous inferior petrosal sinus sampling (BSIPPS), with similar cut-off ratios to the CRH test[327,328]. A recommended protocol for the diagnosis of Cushing's disease in CYP is shown in **Table 3**. All tests need to be interpreted in the light of the pre-test probability of the disease being present.

Diagnosis: Neuroimaging and BSIPSS

In CYP with suspected Cushing's disease, pre-operative MRI to localise the pituitary adenoma is

strongly recommended, although only 50–63% of corticotroph adenomas were identified on post-contrast images in several large paediatric series[291,311,329]. This poor visualisation rate in children could be explained by the limited spatial resolution of MRI making small lesions within a small pituitary gland inconspicuous. Therefore, pituitary MRI imaging alone cannot reliably predict the adenoma position or confirm the diagnosis of Cushing's disease in CYP.

- **Specific: R19.1. Offer BSIPSS to CYP with confirmed ACTH-dependent Cushing's syndrome and no identified adenoma on pituitary MRI, to confirm a central source of ACTH excess** (strong recommendation, low quality evidence, Delphi 83%).
- **Specific: R19.2. Offer BSIPSS only in a specialist centre with expertise in such testing and by an experienced interventional radiologist who regularly undertakes this procedure in adults** (strong recommendation, moderate quality evidence).
- **Specific: R19.3. Consider confirming hypercortisolaemia immediately prior to BSIPSS to ensure the patient is in an active disease phase** (moderate recommendation, moderate quality evidence).
- **Specific: R19.4. During BSIPSS, a pituitary source of ACTH excess is confirmed by a ≥2:1 ratio of central:peripheral ACTH before CRH or desmopressin and ≥3:1 ratio after CRH or desmopressin stimulation** (strong recommendation, low quality evidence, Delphi 100%).
- **Specific: R19.5 BSIPSS could provide some information on tumour lateralisation, if the inter-petrosal sinus ACTH gradient after CRH or desmopressin stimulation is ≥1.4 between the two sides** (moderate recommendation, moderate quality evidence, Delphi 67% and GDG consensus).

BSIPSS was initially piloted in adults at the National Institute of Health (NIH)[330] to enable distinction between Cushing's disease and ectopic ACTH syndrome. In adult practice, BSIPSS has become routine unless the MRI unequivocally shows a pituitary adenoma that is unlikely to be an incidentaloma. A pituitary source of ACTH excess confirmed during BSIPSS has a high sensitivity for Cushing's disease in experienced centres[291,310,329-331]. Hypercortisolaemia can be confirmed on the morning of the BSIPSS procedure to ensure the rare patients with cyclical Cushing's disease[305] are in an active phase. BSIPSS using desmopressin as the stimulant has been reported in five paediatric series, with similar accuracy to CRH stimulation[327,328,332,333]. The reliability of the results of BSIPSS and the incidence of adverse events are related to the experience of the radiology team[310]. To enable the accurate interpretation of the results, medical therapy for Cushing's disease (steroidogenesis inhibitors) must be stopped before undertaking BSIPSS; the length of time of treatment discontinuation depends on the half-life of the agent used).

BSIPSS might also help to lateralise pituitary ACTH secretion, where no lesion is visible on MRI[306,309]. If on BSIPSS, the ACTH gradient between the two sides is greater than or equal to 1.4 after CRH (or desmopressin) stimulation, this finding might indicate lateralisation of the tumour[310,329,330,334-336] with possibly greater accuracy in CYP than in adults with Cushing's disease[298,334]. The first paediatric data were reported in a large NIH series, where the predictive value for lateralisation was 75–80%[288,293]. Similar values have been reported in other smaller series, with surgical concordance of adenoma site in 87–91% of patients[298,334]. Another NIH study of BSIPSS in 94 paediatric patients reported only 58% concurrence of ACTH lateralisation with site of adenoma at surgery, which increased to 70% (51 out of 73) after exclusion of 18 centrally located and 4 bilateral lesions[336]. Data from 2021 and 2022 confirm similar[331] or higher (87.5%) percentages[329]. Based on these data, the GDG strengthened **R19.5**. Theoretically, false lateralisation could occur due to altered pituitary blood flow[330,337], but in adult patients with Cushing's disease, despite asymmetric internal petrosal sinuses in 11 of 38 patients (39%), both symmetric (100%) and asymmetric (93%) petrosal sinuses gave good

lateralisation[338]. Prolactin measurements during BSIPSS have been reported to be a useful marker of accurate catheterisation, but two studies in adult Cushing's disease suggested that prolactin-corrected ACTH concentrations did not substantially increase the accuracy of lateralisation[339,340] and this protocol has not been studied in CYP. Thus, no robust data exist to demonstrate, unequivocally, that lateralisation of the tumour on BSIPSS improves surgical outcomes or preservation of residual pituitary function. However, observational studies of CYP suggest that improvements in rates of surgical cure might be related to the introduction of BSIPSS[298,334].

Treatment: pituitary surgery

- **Specific: R20.1. Offer selective adenomectomy as first-line treatment of choice for CYP with Cushing's disease** (strong recommendation, moderate quality evidence).
- **Specific: R20.2. Consider repeat surgery for CYP with persistent or recurrent disease** (moderate recommendation, low quality evidence, Delphi 100%).

Optimal treatment for CYP with Cushing's disease is surgical resection by selective removal of the adenoma, performed by a surgeon experienced in paediatric transsphenoidal surgery[323]. Selective removal of the adenoma is now considered first-line therapy, maximising the potential for normal pituitary tissue to remain *in situ*[183,296,323]. Low rates of post-operative hypopituitarism have been reported in several large studies in CYP[111,341]. However, selective microadenomectomy can be technically very difficult in children and the surgeon's experience is a predictor of success[323,342].

Early post-operative remission in children was associated with identification of the adenoma at surgery, whilst long-term remission correlated with a younger age, a smaller adenoma, the absence of cavernous sinus or dural invasion and a morning serum cortisol level of <1µg/dl (<28nmol/l) after surgery[296]. Repeat surgery for paediatric Cushing's disease resulted in early biochemical remission in 93% of 27 patients[296]. However, recurrence of Cushing's disease in adults has been reported up to 15 years after apparent surgical cure, even in individuals who had very low or undetectable post-operative cortisol levels[142,343]. Therefore, lifelong follow-up for children treated for Cushing's disease is essential.

Treatment: pituitary radiotherapy

- **Specific: R21. Offer radiotherapy to CYP with recurrent Cushing's disease not amenable to curative surgery** (strong recommendation, moderate quality evidence, Delphi 93%).

A proportion of paediatric patients who undergo transsphenoidal surgery for Cushing's disease do not achieve post-operative cure or remission[156,321,344]. The options for second-line therapy are repeat transsphenoidal surgery, radiotherapy, long-term medical therapy to control hypercortisolaemia and bilateral adrenalectomy. Focal external beam radiotherapy is more rapidly effective in children with Cushing's disease than in adults[141,156,344,345], and often initiated 2–4 weeks after unsuccessful transsphenoidal surgery, when it is clear from circulating cortisol levels that a complete cure has not been achieved[323].

Stereotactic radiotherapy, fractionated proton beam and gamma knife approaches have been proposed and utilised in adult Cushing's disease. By contrast, over the past decade, fractionated proton beam radiotherapy with ongoing safety data monitoring has become the standard for focal cranial radiation in CYP with brain tumours generally[30]; however, experience is limited, particularly in children[162,346]. For fractionated treatment, a total radiation dose of 45 Gy in 25 fractions over 35 days seems effective[151,156]. A gamma knife stereotactic radiosurgery study in CYP with Cushing's disease used maximum dose of 50 Gy (range, 33–80) and a margin dose of 25 Gy (range, 12.90–27.1)[144].The

rapid effectiveness of these treatments are shown in **Table 4**; however, long-term data on adverse late effects are needed.

Table 4: Radiotherapy in CYP with Cushing's disease

Reference	Type of radiotherapy	Number of children included	Number of children cured	Time scale for cure
Jennings et al. 1977, ref[141]	Conventional	15	12	18 months (10 children within 9 months)
Thoren et al. 1986, ref[557]	Gamma knife	8	7	12 months
Storr et al. 2003, ref[156]	Conventional	7	7	0.94 years (range 0.25–2.86)
Acharya et al. 2010, ref[344]	Conventional	8	4	9-18 months
Shrivastava et al. 2019, ref[144]	Gamma knife	24	19	12 months (range, 2-42 months)

Treatment: medical therapies

- **Specific: R22.1.** Offer oral medical therapies such as metyrapone or ketoconazole to reduce the cortisol burden in CYP with Cushing's disease awaiting definitive surgery or the effect of pituitary radiotherapy (strong recommendation, low quality evidence, Delphi 100%).
- **Specific: R22.2.** Due to their adverse effects, metyrapone and ketoconazole have a limited role in the long-term treatment of Cushing's disease in CYP (strong recommendation, low quality evidence, Delphi 60% and GDG consensus).

Adrenal steroidogenesis inhibitors, such as metyrapone and ketoconazole, are well tolerated and can be highly effective at reducing cortisol levels, either alone or in combination[323]. In CYP, these drugs should be prescribed by experienced clinical teams with careful titration (metyrapone: 15 mg/kg every 4 hours for 6 doses, alternatively 300 mg/m^2 every 4 hours, usual dose 250–750 mg every 4 hours; ketoconazole for patients over 12 years: initially 400–600 mg per day in 2–3 divided doses, increased to 800–1200 mg per day until cortisol levels normalise and then reaching maintenance dose of 400–800 mg per day in 2–3 divided doses). However, hypercortisolaemia control can be lost due to the hypersecretion of ACTH and treatment might not be effective long-term. Common adverse effects of metyrapone include hirsutism, dizziness, arthralgia, fatigue, hypokalaemia and nausea[307]. Prolonged usage can lead to hyperandrogenism and advanced bone age in children. Ketoconazole is associated with hepatotoxicity and liver function should be monitored on therapy. Gastrointestinal disturbance and adrenal insufficiency are recognised adverse effects of both therapies.

The GDG refined **R22.2** after three rounds of an international Delphi consensus, in which only four individuals had the expertise to respond (voting details are in[16]). Definitive treatments, which allow rapid normalisation of subsequent growth and puberty, such as surgery and/or radiotherapy, are currently recommended for the management of paediatric Cushing's disease, whilst medical therapies are currently limited[321] and not well studied. Nevertheless, given the rarity of this condition in CYP, the effect of these medical agents on growth, and the importance of normalising childhood growth and puberty, the GDG felt that, by contrast to adults where long-term medical therapy might have a place after other treatments have failed[307], their use in CYP should be confined to normalising cortisol levels in preparation for surgery or while awaiting a biochemical response to radiotherapy.

The effects and safety of osilodrostat, an inhibitor of 11β-hydroxylase (CYP11B1), are currently being evaluated in a small phase II trial in CYP (NCT03708900)[347], while the effects of cabergoline[348], mifepristone and pasireotide in children are very limited or unknown. Temozolomide treatment has been used in an adult patient with childhood-onset Cushing's disease (**Table 2**).

- **Specific: R23. Offer intravenous etomidate treatment in CYP with Cushing's disease in an intensive care setting only for the emergency control of severe cortisol excess** (strong recommendation, moderate quality evidence, Delphi 100%).

Intravenous administration of etomidate has successfully controlled hypercortisolaemia in children with severe Cushing's disease, who were either too unwell for transsphenoidal surgery or presented with acute unmanageable symptoms, for example, respiratory failure or severe psychosis[349,350]. To enable the accurate assessment of surgical response, oral therapies, if feasible, should be stopped before surgery, depending on the half-life of the treatment; for example, for metyrapone, 48h discontinuation should be sufficient.

Treatment: bilateral adrenalectomy

- **Specific: R24. Reserve bilateral adrenalectomy only for CYP with severe refractory Cushing's disease or for life-threatening emergencies** (strong recommendation, low quality evidence, Delphi 80% and GDG consensus).

Bilateral adrenalectomy remains a therapeutic option for Cushing's disease in life-threatening situations or where transsphenoidal surgery is not possible or not available[351]. However, corticotroph tumour progression after bilateral adrenalectomy (Nelson syndrome, a potentially life-threatening secondary consequence of bilateral adrenalectomy, in which the pituitary adenoma continues to grow and secrete ACTH) seems to be more frequent in children than in adults and often requires pituitary surgery or radiotherapy[352-354].

Follow-up and surveillance

- **Specific: R25. Consider dynamic testing for GH deficiency soon after definitive therapy in all CYP in remission from Cushing's disease who have not completed linear growth, and closely monitor pubertal progression to identify hypogonadotrophic hypogonadism** (moderate recommendation, moderate quality evidence).
- **Specific: R26. Offer prompt initiation of GH replacement to CYP in remission from Cushing's disease who are proven GH deficient or fail to show catch-up growth (strong recommendation, moderate quality evidence, GDG consensus).**
- **Specific: R27. Consider BMD assessment prior to adult transition in patients at high risk for bone fragility** (weak recommendation, low quality evidence, Delphi 86%).

Growth failure and resultant short stature are almost always present at diagnosis in paediatric patients with Cushing's disease[288,355]. Virilisation from adrenal androgens can lead to pubarche and gonadotropin-independent pubertal development, accelerating skeletal maturity and further compromising adult height potential[356,357]. After normalisation of cortisol, CYP with growth retardation should be evaluated for GH deficiency with appropriate dynamic testing and receive early GH replacement therapy, given the limited window of opportunity to normalise lean to adipose mass ratio, promote catch-up growth and attain their normal adult height[310,355,358-362]. Given these data and the current clinical practice[315], a randomised controlled trial of early GH treatment in CYP in remission from Cushing's disease is unlikely, and the GDG therefore strengthened **R26**. GH

deficiency is well recognised following transsphenoidal surgery[359,363] and pituitary irradiation[142,156,344,363]. The challenge is to reverse these adverse effects and maximise growth potential to achieve normal adult height and body composition. One approach is to routinely assess for the possibility of GH deficiency soon (up to 3 months)[315] after surgery or radiotherapy and substitute GH at conventional replacement doses (0.025 mg/kg per day), if deficient. Gonadotrophin-releasing hormone analogue therapy can be added to delay puberty and epiphyseal closure. Results demonstrate that this regimen usually enables adequate catch-up growth and adult height within the range of target height for the majority of patients[142,364]. Combined treatment with GH and aromatase inhibitors to reduce bone maturation induced by oestradiol could also be a therapeutic alternative in pubertal patients[365]. Normal body composition and BMD is more difficult to achieve[364,366]. Many CYP with Cushing's disease have disturbed timing or progression through puberty and require sex steroid replacement to enhance growth velocity and reverse the suppressant effect of cortisol excess on gonadotrophins[356].

Pituitary function following remission

- **Specific: R28. To assess possible recurrence, offer to all CYP in remission from Cushing's disease: 6-monthly clinical examination, 24h UFC, electrolytes and morning serum cortisol for at least 2 years and life-long annual clinical assessment** (strong recommendation, low quality evidence, Delphi 100%).

Pituitary hormone deficiencies are common after surgical or radiotherapeutic cure of Cushing's disease[142,344,363,367]. GH deficiency is the most frequent pituitary deficit (see previous section), although recovery in adult life has been reported[142,368]. During long-term follow-up of patients in remission, gonadotrophin secretion is generally preserved, with normal or true gonadotrophin-dependent early puberty occurring, the latter being well-recognised after cranial radiotherapy[369]. After radiotherapy, additional anterior pituitary deficiencies (TSH and permanent ACTH deficits) can rarely develop, typically occurring in combination[142,368], with the risk of anterior pituitary hormone deficiencies potentially increasing over time[310].

Psychiatric and neurocognitive effects

- **Specific: R29. In addition to life-long follow-up for endocrinopathies, consider long-term monitoring for psychiatric and neurocognitive co-morbidities following remission of Cushing's disease in CYP** (moderate recommendation, moderate quality evidence).

Studies of adult patients with Cushing's syndrome have reported brain atrophy, cognitive impairment and psychological disease, most commonly depression, associated with excess endogenous circulating glucocorticoids[370,371]. A study in 11 patients[372] also found considerable cerebral atrophy in children with Cushing's disease at diagnosis, but without IQ differences between patients and control individuals. Interestingly, an almost complete reversal occurred of the cerebral atrophy 1 year after cure with transsphenoidal surgery, but with a paradoxical decline in cognitive function. Another study shows notable improvements in severe psychiatric and behavioural symptoms after cure; however, long-term cognitive and memory problems were identified in ~25% patients[142] and this observation is consistent with similar cognitive and memory deterioration in adults[373]. Furthermore, the grey matter volume loss of active Cushing's disease reverses 3 months after remission, except in the frontal and temporal lobes, strongly associated with cognition and memory[374]. Children with Cushing's disease experience impaired health-related quality of life, which is not fully resolved 1 year post-treatment[375].

Relapse of Cushing's disease

- **Specific: R30. In suspected recurrence of Cushing's disease in CYP, offer the same stepwise investigations as at first presentation** (strong recommendation, low quality evidence, GDG consensus).

Reported recurrence rates after remission of Cushing's disease in CYP vary considerably from 6% to 40%[142,296,304,376,377] and usually occur within 5 years following definitive treatment. However, relapse can occur later[142], and the percentage of patients who relapse increases with time[343], suggesting that life-long follow-up is required. This observation is consistent with data from long-term follow-up in adult patients with Cushing's disease[343,352], therefore the GDG strengthened **R30**.

GH excess: gigantism and acromegaly

Epidemiology and aetiology

A GH-secreting pituitary adenoma arising from somatotroph cells (somatotrophinoma) is the most common cause of acromegaly in CYP and is usually detectable on a contrast-enhanced pituitary MRI. Rarely, CYP with somatotroph hyperplasia due to McCune-Albright syndrome[76], Carney complex[378], X-linked acrogigantism[69] or GH-releasing hormone-secreting adenomas (usually associated with MEN1 syndrome in CYP[379,380]) have been described. GH excess is rare in CYP. Annual incidence rates of GH excess are estimated as 3–8 cases per million person-years among children aged 0–17 years old, while annual prevalence rates are estimated as 29–37 patients per million children aged 0–17 years[381-389]. Among surgically-treated paediatric pituitary adenomas, 8.8%[390] to 21%[113] are associated with GH excess, with an age-related increase (6.4% 0–11 years, 9.1% 12–17 years and 11.8% 18–19 years). While there are more male patients with gigantism overall[81,390,391], more girls (62%) than boys are diagnosed with gigantism in the CYP age group[80].

If GH excess occurs before epiphyseal fusion, the patient develops tall stature or gigantism. The definition of pituitary gigantism is arbitrary[84,392]. The following definitions have been used in various studies:

Definitions of pituitary gigantism in CYP

GH–IGF-1 excess associated with:

- Accelerated growth velocity > +2 SDS *or*
- Abnormally tall stature defined as:
  - +2 or +3 SDS above the country-specific, age-appropriate and sex-appropriate mean height *or*
  - +2 SDS above the mid-parental height

Gigantism can be exacerbated by delayed puberty due to gonadotrophin inhibition by co-secretion of prolactin from the adenoma, hyperprolactinaemia from stalk compression or mass effects causing gonadotrophin deficiency. Gigantism has an identifiable genetic basis in almost 50% of patients currently, so genetic assessment and testing is particularly important in CYP (see Genetics section).

Diagnosis: clinical features

- **Specific: R31. Offer testing for GH excess to CYP with excess height (more than 2 SDS) or consistently elevated height velocity and acromegalic features, with or without delayed or arrested puberty or family history of pituitary adenoma** (strong recommendation, moderate quality evidence, Delphi 100%).

The most prominent clinical feature of GH excess in CYP before epiphyseal closure is increased growth velocity. Serial heights and photographs are useful for timing the onset of disease[393].

Ethnicity-adjusted height >2 SDS above age-adjusted and sex-adjusted normal values or +2 SDS above mid-parental target height, persistently elevated growth velocity (>2 SDS), acral enlargement, headache, visual field defects, pubertal delay, delayed bone age and joint pain are common signs of GH excess in CYP. Other features, typical of adult-onset GH excess, can also develop, including: coarsened facial features, prognathism, dental malocclusion, teeth separation, frontal bossing, sweating, kyphosis, insulin resistance and occasionally secondary diabetes mellitus, hypertension, sleep disturbance, sleep apnoea, carpal tunnel syndrome, galactorrhoea, pituitary apoplexy, left ventricular hypertrophy and diastolic dysfunction[80,342,390,394-409], while joint hypermobility has occasionally been observed[410].

X-linked acrogigantism is characterised by tall stature onset before 5 years (usually before 2 years), in all patients[69,77,81,391,411-413] and disproportionally enlarged hands, feet, teeth separation, acanthosis nigricans, increased BMI and increased appetite[69,411]. In McCune-Albright syndrome[76] early-onset (3 years onwards) GH excess, café-au-lait pigmentation, fibrous dysplasia and precocious puberty (or other hormone excess conditions) are prominent clinical features, while in Carney complex[378] typical skin pigmentation, myxomas, testicular and adrenal disease are characteristic, in addition to other pleiotropic manifestations.

Diagnosis: biochemical investigations

- **Specific: R32. A diagnosis of GH excess is supported by an elevated serum IGF-1 level in relation to the age-adjusted, sex-adjusted and Tanner stage-matched normal range** (strong recommendation, moderate quality evidence).

Elevated Tanner stage-matched and age-adjusted circulating serum IGF-1 concentration is a reliable marker for GH excess, but marginal or mild elevation in adolescence, during the peak growth spurt, needs cautious interpretation. IGF-1 values might be falsely normal or low in CYP with a GH-secreting adenoma and concurrent severe hypothyroidism, malnutrition or severe infection[414-416], or might be falsely elevated in CYP without GH-secreting adenoma in poorly-controlled diabetes mellitus, hepatic and/or renal failure. Oral oestrogens can also confound detection accuracy by reducing IGF-1 generation by the liver[417], whilst local Tanner stage-matched, sex-matched and age-matched normal ranges for the IGF-1 assay must be established to avoid notable inter-assay variability[418].

- **Specific: R33. Consider the diagnosis of GH excess in CYP whose serum GH levels fail to suppress below 1 µg/l in response to an oral glucose load (cut-off based on adult population); however, complete suppression of GH can be difficult to achieve in normal adolescence** (moderate recommendation, moderate quality evidence, Delphi 100%).

Algorithms for assessing GH excess in CYP are based on those established in adult patients[392,419,420]. In healthy adults, serum levels of GH should be suppressed after an oral glucose load: cut-off GH nadirs are 1 µg/l, or using sensitive GH assays, 0.4 µg/l[421,422]. GH nadir after glucose load in CYP undergoing puberty is sex and pubertal stage specific: the highest levels were observed in mid-puberty (Tanner stage 2–3), in girls more than boys (mean±2 SD GH nadir after 2.35 g/kg, maximum 100 g glucose load: in girls 0.22 µg/l ±0.03–1.57, in boys 0.21 µg/l ±0.09–0.48)[423]. However, an earlier study reported a lack of GH suppression (defined as <1 µg/l following 1.75 g/kg, maximum

75 g glucose load) in approximately 30% of children with tall stature (+3.1 ±0.8 height SD score)[424], rendering the diagnosis of GH excess by these criteria challenging in this patient group. An elevated serum IGF-1 concentration, with apparently normal serum GH values, might reflect early disease[425]. We suggest that biochemical results should be interpreted within a clinical assessment of phenotype that includes height velocity, pubertal stage and bone age.

From adult data, serum IGF-1 levels correlate linearly with GH levels only up to 4 µg/l and plateau at about 10 µg/l[426,427]. Baseline GH levels are predictive of surgical outcome (higher GH levels predict lower chance of remission after surgery)[428] and are key to monitoring the hormone-producing activity of the adenoma[427]. Thus, both GH and IGF-1 should be monitored at baseline and during follow-up in CYP with GH excess.

- **Specific: R34. In CYP with GH excess, offer dynamic pituitary assessment of possible hypofunction and hyperfunction of other anterior pituitary hormones** (strong recommendation, high quality evidence).

Hypofunction of other pituitary hormones caused by tumour mass compression or prolactin co-secretion has been noted in 25–35% of patients with somatotrophinomas[80,342]. Hypogonadism and consequent bone age delay are particularly relevant to GH excess, as they increase the time window for longitudinal growth. Co-secretion of other anterior pituitary hormones is common in both adults and CYP with GH excess. A review of 137 published CYP with acromegaly found that 65% had hyperprolactinaemia at presentation, while half showed both GH and prolactin immunostaining in the adenoma tissue[342]. Furthermore, 34–36% of CYP with gigantism had prolactin co-secretion in two large cohorts[80,81]. TSH can also be co-secreted by somatotrophinomas, but less frequently than prolactin. Patients require assessment and treatment of complications of GH excess, such as glucose intolerance and hypertension.

- **Specific: R35.1. Pituitary adenomas can be associated with syndromic diseases; offer clinical evaluation for associated syndromic causes of somatotrophinomas to CYP with GH excess** (strong recommendation, low quality evidence, Delphi 93%).
- **Specific: R35.2. Offer biochemical screening for pituitary hormone excess to all CYP with Carney complex, McCune–Albright syndrome and patients with MEN1 or MEN1-like disease** (strong recommendation, high quality evidence, Delphi 100%).

Several syndromes, including McCune-Albright syndrome, Carney complex, MEN1 or rarely MEN1-like diseases (MEN4, MEN5) and phaeochromocytoma–paraganglioma-related pituitary disease[16] can be associated with childhood-onset pituitary adenomas, including GH excess. The biochemical diagnosis of GH excess in the context of such syndromes is identical to sporadic cases of acromegaly[69,76,80,81,84,429,430]. In CYP with Carney complex, biochemical alterations of the GH axis without overt clinical acromegaly can often be observed. GH-releasing hormone-secreting pancreatic tumours should also be considered as a cause of GH excess in CYP with MEN1 syndrome[379,380]. GH hypersecretion, usually transient, occurs in 10% of infants and children with neurofibromatosis type 1 and optic pathway hypothalamic gliomas[431]; some of these patients have been treated temporarily with somatostatin analogues or pegvisomant[431-433]. GH excess is probably a result of hypothalamic dysregulation of the GH axis. Data on the aetiology of temporary GH excess in CYP with optic glioma, therapeutic interventions, the effects of GH excess on glioma growth itself and the observed evolution from GH excess to GH deficiency remain unexplained and poorly understood. The GDG suggest the establishment of a collaborative neuroendocrine oncology research study to gather evidence for these questions.

Treatment: pituitary surgery

- **Specific: R36. Offer surgery to reduce GH burden as the treatment of choice in the majority of CYP with GH-secreting adenomas, even where surgical cure is unlikely** (strong recommendation, moderate quality evidence, Delphi 93%).
- **Specific: R37.1. Consider preoperative medical therapy with somatostatin analogues and/or GH receptor antagonists to rapidly control signs and symptoms and support perioperative airway management** (weak recommendation, low quality evidence, Delphi 75%, GDG consensus)
- **Specific: R37.2. Consider preoperative medical therapy with somatostatin analogues and/or GH receptor antagonists to reduce height velocity, particularly if pituitary surgery is delayed** (weak recommendation, low quality evidence, Delphi 100%).

The goals of any therapy for GH excess include: normalisation of growth velocity, prevention of excessive height and suppression of IGF-1 into the normal range; adenoma shrinkage and visual preservation with potential restoration of other hormone function; and prevention of long-term morbidity. Surgery performed by an experienced neurosurgeon offers the prospect of complete remission and is therefore recommended as the first-line treatment for CYP with gigantism or acromegaly[110,250,406,434,435], as for adults[392,436-438]. Even if remission is thought to be unlikely following surgery, tumour debulking can reduce the circulating GH burden and facilitate more successful medical therapy and/or radiotherapy. In an experienced pituitary neurosurgical unit between 2003 and 2016, the surgical success rate in 17 CYP with GH excess was ~50%[439]. Re-operation could be considered in patients with notable residual tumour and inadequate response to somatostatin analogue therapy or if considerable tumour re-growth occurs.

A role for somatostatin analogues in safely reducing preoperative GH levels in adults with macroadenomas, with favourable effects on short-term cure, has been suggested by a systematic review, although long-term outcomes require further study[440]. Patients with severe cardiac and/or respiratory complications from GH excess might benefit from preoperative reduction of GH levels. Preoperatively, patients should be assessed for enlargement of the upper airway soft-tissue structures, including the tongue and epiglottis as well as jaw deformity, to prevent perioperative airway difficulties[441,442].

In the absence of prospective trials, factors predicting outcome of surgery in CYP with gigantism or acromegaly are limited, although retrospective studies and case reports suggest that a rapid reduction in growth velocity might be a favourable predictor[80,342,395].

In patients with genetic causes of acromegaly, the whole gland could be affected (typically in McCune–Albright syndrome, Carney complex and X-linked acrogigantism). Selective adenomectomy[443], radical surgery[411] or hypophysectomy[76,399] have all been described as surgical approaches in these conditions.

Treatment: medical therapies

- **Specific: R38.** Offer monotherapy or combination medical therapy in CYP with GH excess and post-operative residual disease (strong recommendation, moderate quality evidence, Delphi 100%).
- **Specific: R39.** Assess efficacy of medical treatment in CYP with GH excess by both auxological measurements and serum levels of GH and IGF-1 (strong recommendation, moderate quality evidence, Delphi 100%).

Studies of medical therapy in patients with post-operative residual GH excess have been conducted primarily in adults, although case series and case reports also confirm their utility in CYP[76,80,81,342,394-396,398,402,407,411,444]. Adjunctive post-operative long-acting somatostatin analogues reduce serum concentrations of GH to 'safe' levels and normalise serum levels of IGF-1 in approximately 35% of adult patients with GH-secreting adenoma[445] with less predictable tumour shrinkage in up to 40%. Retrospective studies have also confirmed the tumour shrinking effect of somatostatin analogues in adolescents with gigantism[76,80,81,395,411]. While no formal dosing recommendation exists for children, the dose of long-acting somatostatin analogues can be titrated to normalise IGF-1 levels. In adults, the starting monthly dose of lanreotide-autogel is 60 mg and of octreotide-LAR 10 mg, whereas for very young children the dose needs to be individualised. In CYP with acromegaly, numerous reports of the failure of somatostatin analogues to normalise IGF-1, satisfactorily reduce GH levels or initiate tumour shrinkage, suggest treatment resistance is more common in CYP than in adults[80,81,401,407,408,411,446-448]. CYP with *AIP* or *GPR101* mutations have more aggressive disease, over half of tumours are locally invasive at initial presentation and are less responsive to first-generation somatostatin analogue therapy[80,81,411,449], whereas the response to medical treatment in patients with Carney complex and McCune–Albright syndrome is more promising[76]. The second-generation somatostatin analogue, pasireotide, has also been used in adult patients with childhood-onset GH excess, with mixed results[450,451].

Regardless of the presence or absence of prolactin co-secretion, dopamine agonists (primarily cabergoline) can be used alone in CYP with mild GH excess, co-administered with somatostatin analogues where GH hypersecretion is not adequately controlled, or substituted for the latter where poorly tolerated[452-455]. However, the GH-lowering effect of dopamine agonists is only modest[342,398,401,407] and doses required in acromegaly are often high (see **R11** on cabergoline use).

Several studies and case reports have been published of the GH receptor antagonist, pegvisomant, normalising serum IGF-1 levels in CYP with acromegaly or gigantism when used in adequate doses[76,77,80,81,342,396,404,407,411,456-461]. This medication can suppress growth velocity, a clinical priority in CYP with gigantism, suggesting that earlier introduction could be beneficial. The dose of pegvisomant should be started at 10 mg daily and titrated until serum IGF-1 levels normalise. Patients treated with pegvisomant, require only IGF-1 measurements during follow-up. As pegvisomant has no direct pituitary action, careful radiological tumour monitoring is required. Tumour expansion described during pegvisomant treatment[342,393] might represent the natural history of the tumour rather than being secondary to reduced negative feedback from reductions in IGF-1. Combination therapy with pegvisomant and somatostatin analogues has also been successfully tried in CYP with GH excess[77,80,458,461]. Temozolomide therapy has been reported in a CYP patient with a GH-secreting tumour and another with a GH–prolactin co-secreting tumour (**Table 2**).

Treatment: pituitary radiotherapy

- **Specific: R40.1. Offer pituitary radiotherapy to CYP with GH-secreting adenoma and uncontrolled tumour growth and incomplete surgical and medical response, except for patients with skull base fibrous dysplasia** (strong recommendation, low quality evidence, Delphi 75%).
- **Specific: R40.2: After radiotherapy in CYP with GH-secreting adenoma, offer intermittent dose reduction or withdrawal of medical therapy to assess radiation efficacy on GH hypersecretion** (strong recommendation, low quality evidence, Delphi 100%).

Radiotherapy might be useful for CYP with gigantism or acromegaly who have post-operative residual tumour bulk and in whom surgery and medical therapy have failed to control GH–IGF-1

levels (see Radiotherapy section). Conventional conformal, stereotactic and proton beam radiotherapy have all been used successfully to control tumour growth and lower serum GH levels in CYP[80,144,342,393,462,463], although adult data indicate that it might take up to 10 years for radiotherapy to be fully effective in suppressing GH[170,464]. Therefore, medical therapy is probably required, at least as a temporary measure, in CYP who receive pituitary radiotherapy. Intermittent interruption of medical therapy for 1–3 months (to allow clearance of the drug), might be required to allow biochemical assessment of the efficacy of radiotherapy. After radiotherapy, first 6-monthly and later 12-monthly follow-ups should monitor the patient for development of hypopituitarism or recurrence.

GH excess in the context of McCune–Albright syndrome is typically accompanied by fibrous dysplasia of the craniofacial bones. In one study of patients with this syndrome, six of 112 patients, three of whom had prior pituitary irradiation, developed a skull base sarcoma[76]. While a causal link to pituitary radiation is not proven, the risk of sarcomatous transformation is higher in McCune-Albright syndrome than in isolated fibrous dysplasia[465]. Almost half of the patients with McCune-Albright syndrome are CYP (46%) at the time of diagnosis of GH excess. Given the uncertain transforming effect of GH–IGF-1 on dysplastic bone[466-469], alternative medical and surgical treatments, rather than radiotherapy, might be considered in this condition to control GH excess and preserve vision.

Follow-up and surveillance

- **Specific: R41. There is no evidence to suggest that CYP with GH excess require routine screening for colonic polyps during childhood** (strong recommendation, low quality evidence, Delphi 92%).
- **Specific: R42. Consider avoiding corrective surgery for jaw, spine and joint abnormalities in CYP with gigantism or acromegaly until GH and IGF-1 is at safe level** (weak recommendation, low quality evidence, GDG consensus).

While good evidence indicates an increased risk of colonic polyps in adults with acromegaly, such data are lacking in CYP, and the Delphi panel returned a 92% consensus against routine colonoscopy in CYP with GH excess.

Bone overgrowth induced by GH excess does not reverse with successful treatment of acromegaly, and while jaw and dental deformity can be troublesome, corrective surgery should be deferred until GH–IGF-1 levels are adequately controlled and jaw changes have stabilised[470].

Late recurrence of GH excess, up to 10 years after apparent remission, has been described[471]. Thus, long-term annual serum IGF-1 monitoring is necessary, with repeat biochemical (oral glucose tolerance tests) and radiological (MRI) assessment if recurrence is suspected. Due to the high rates of persistent post-operative disease in CYP with GH excess, many will receive long-term medical therapy or radiotherapy. Monitoring of their efficacy and adverse effects, together with management of secondary pituitary deficits and medical complications, requires experienced specialist support within a dedicated pituitary multidisciplinary team (MDT). Close interaction between paediatric and adult endocrine services is required to coordinate long-term medical care and the transition to adult services.

TSHoma

Epidemiology

TSH-secreting adenomas are extremely rare in children and the literature is limited to case reports.

In adults with TSHoma, the incidence has been estimated to be 0.26 cases per million per year; co-secretion of other pituitary hormones occurs in 25–42%[472]. Co-secretion of GH was also noted in an adolescent with gigantism and secondary hyperthyroidism[473].

Diagnosis

- **Specific: R43.** Consider assessment for TSHoma in CYP with hyperthyroxinaemia and an unsuppressed TSH, particularly in the presence of clinical thyrotoxicosis, neurological or visual deterioration (moderate recommendation, moderate quality evidence).
- **Specific: R44.** Consider assessment for thyroid hormone resistance and euthyroid hyperthyroxinaemia in the differential diagnosis of TSHoma in CYP (moderate recommendation, low quality evidence, Delphi 100%).

Patients with TSHomas present with elevated thyroid hormone levels and unsuppressed TSH, differentiating them from primary hyperthyroidism. Usually children have symptoms of hyperthyroidism, but some are reported to be asymptomatic[474]. Most TSHomas reported in children have presented as macroadenomas, thus mass effects can cause optic nerve compression and deficiency of other pituitary hormones[474-476]. Following the diagnosis of a TSHoma, investigation for pituitary hypofunction and hyperfunction with baseline and dynamic pituitary testing is recommended. Prompt treatment of any cortisol, GH or sex steroid deficiency is recommended to optimise surgical, growth and well-being outcomes.

An unsuppressed TSH in the setting of hyperthyroxinaemia can occur due to assay interference, and due to genetic causes of euthyroid hyperthyroxinaemia, such as familial dysalbuminaemic hyperthyroxinaemia and resistance to thyroid hormone. Of note, a child with a TSH-secreting microadenoma and resistance to thyroid hormone has been reported[105].

Treatment

- **Specific: R45. Consider preoperative somatostatin analogue treatment to normalise thyroid function in CYP with confirmed TSHoma** (moderate recommendation, low quality evidence, Delphi 73% and GDG consensus).
- **Specific: R46. Offer transsphenoidal surgery as the treatment of choice in CYP with TSHomas** (moderate recommendation, low quality evidence, Delphi 93%).

In adults with TSHoma, somatostatin analogues improve the symptoms of thyrotoxicosis, decrease serum free T_4 and TSH concentrations and can cause preoperative tumour shrinkage[477]. In one paediatric patient, somatostatin analogues reduced thyroid hormone levels and tumour size, thereby postponing definitive surgery[474,478]. Out of 44 patients aged 11–73 years on preoperative somatostatin analogue treatment, 84% had normalisation of thyroid function levels and 61% showed tumour shrinkage[479].

Surgery offers a potentially definitive cure. Even partial tumour debulking can be worthwhile in reducing TSH and free T_4 levels, decompressing the optic apparatus or improving effectiveness of subsequent medical therapy[475,476,479-482].

Follow-up and surveillance

- **Specific: R47. Disease monitoring with regular thyroid function tests and regular MRI surveillance, similar to the protocol described for NFPA, is suggested in CYP with confirmed TSHomas** (weak recommendation, low quality evidence, GDG consensus).

There is no evidence-base to inform a surveillance schedule in CYP with TSHoma and the natural history of disease progression is unknown. We therefore suggest a pragmatic approach to biochemical and MRI surveillance to detect secondary hyperthyroidism, and to identify early those with rapid tumour progression or recurrence, even if asymptomatic. We suggest monthly thyroid function tests for 6 months after initial treatment, but given the uncertainty regarding tumour progression, biochemical and MRI surveillance should be individualised.

- **Specific: R48. Consider pituitary radiotherapy in CYP with post-operative tumour remnant and resistance to medical therapy or relapsing TSHomas if reoperation is not an option** (moderate recommendation, low quality evidence, Delphi 92% and GDG consensus).

If surgery is unsuccessful or contraindicated and the paediatric patient with TSHoma fails to achieve normal thyroid function or shows tumour growth despite somatostatin analogue therapy, radiotherapy could be considered[480,483] (see Radiotherapy section). After radiotherapy, first 6-monthly and later 12-monthly follow-ups should monitor for the development of hypopituitarism or recurrence.

Incidentalomas and non-functioning pituitary adenomas

Epidemiology and aetiology

Clinically non-secreting pituitary adenomas account for 4–6% of all paediatric pituitary adenomas[70,484] and for 10% of a surgical series[478], in stark difference to adult pituitary patients where NFPAs account for 15–30% of clinically relevant pituitary adenomas and 50–60% of surgical series[485]. Depending on case selection criteria, NFPAs represent 13–56% of incidentally discovered pituitary lesions (incidentalomas) in large retrospective radiological series of CYP[486-488]. NFPAs also represent 25% of *MEN1*-associated pituitary lesions in CYP and small lesions detected by screening can be seen in patients with *AIP* variants[73-75,84]. NFPAs in CYP usually present in the second decade of life, with increasing incidence thereafter[73,185,484,489]. There is no consistent male or female predisposition[73,137,185,489-492], although a 2019 surgical series in CYP reported a slight female predominance[478].

Presentation

CYP with NFPAs, by definition, do not have features of a hypersecretory syndrome. Symptomatic NFPAs are macroadenomas, whereas microadenomas are usually discovered as a coincidental finding on an MRI scan. The clinical features of macroadenomas at presentation result from mass effects on surrounding structures. These include headache, visual field defects, pituitary apoplexy (probably more common than in adult NFPA[491,492]) with or without mild prolactin elevation, or hypopituitarism manifesting as secondary amenorrhoea, delayed puberty, hypothyroidism, hypocortisolaemia, growth failure and/or hyperprolactinaemia[73,137,185,478,484,489,490]. Headache, visual impairment and hypogonadism were the most common presenting features in a surgical series of CYP[492]. Immunohistochemistry for pituitary hormones in 14 NFPAs, from CYP aged 12–19 years, revealed six silent plurihormonal tumours, three silent lactotroph, one each of a silent gonadotroph and a corticotroph and three hormone-negative tumours (transcription factor staining not reported)[492]. These proportions are different from adult patients, where silent gonadotrophinomas represent the majority of NFPAs. Non-functioning pituitary microadenomas do not usually cause hypopituitarism or visual abnormalities[486].

Diagnosis and investigation

- **Specific: R49. Identification of a pituitary incidentaloma or NFPA requires exclusion of clinical or laboratory evidence of pituitary hormone hypersecretion (except mild hyperprolactinaemia from pituitary stalk disruption); exclusion of elevation of serum level of alpha-fetoprotein (AFP) and β-human chorionic gonadotropin (βHCG) and the absence of other suprasellar and intracranial lesions** (strong recommendation, low quality evidence, Delphi 100%).
- **Specific: R50. Offer baseline and dynamic evaluation of pituitary function to assess hypopituitarism and exclude hormone excess in all CYP with suspected NFPA** (strong recommendation, low quality evidence, Delphi 100%).

If a pituitary mass is suspected on MRI, baseline and dynamic pituitary investigations should be undertaken as indicated clinically to confirm the absence of pituitary hormone excess from a functioning adenoma or the presence of hormone deficiency. The MRI appearance of a small Rathke cleft cyst or pars intermedia cyst can present a differential diagnosis for a clinically non-functioning microadenoma. Stalk compression from macroadenomas, or rarely microadenomas[493], can cause mild hyperprolactinaemia, usually below 2000 mU/l (94 µg/l)[198,199] but exceptionally up to 6000mU/l in one case of a large pituitary fossa tumour in an early adult study[197].

Intracranial germ-cell tumours, more common in the adolescent age group than NFPAs, can present with similar MRI appearances[494,495]. AFP and βHCG (markers of germ-cell tumours) should be measured in the serum, and if clinically or radiologically indicated, also in the cerebrospinal fluid[31]. Hypopituitarism is common in children with symptomatic non-functioning pituitary macroadenoma[73,185,478,484,489,490]. Basal and dynamic pituitary assessment is recommended following diagnosis of an NFPA, together with prompt replacement therapy of any cortisol, thyroid hormone, sex steroid and GH deficiency to optimise surgical, growth and well-being outcomes. Arginine vasopressin deficiency (also known as central diabetes insipidus) is an extremely infrequent finding at diagnosis of an NFPA, unless the tumour has undergone apoplexy[73,185,478,484,489,490], and its presence strongly suggests an alternative diagnosis such as a craniopharyngioma, histiocytosis or germ-cell tumour[30,31,496].

Visual deterioration is a well-described presentation of NFPA in CYP[185,484,489,490] and an urgent indication for surgery to decompress the optic apparatus if sight is threatened. Thus, early assessment of visual acuity and visual fields is mandated[30].

- **Specific: R51. There is no evidence to suggest a benefit of routine diagnostic biopsy in CYP of incidental pituitary masses whose radiological features are typical of a pituitary adenoma with no other intracranial abnormalities** (strong recommendation, low quality evidence, GDG consensus).

A pituitary biopsy is not required in clinically non-functioning lesions with MRI appearance strongly suggestive of a pituitary adenoma and no other intracranial abnormality, which remain asymptomatic, without visual or pituitary function compromise, unchanged in size over time and negative for serum βHCG and AFP. In these patients, the risk of a biopsy harming pituitary function is greater than the likelihood of achieving a 'tissue' diagnosis or a diagnosis requiring alternative management[31]. MRI surveillance should be instituted if the optic apparatus is not compressed.

Treatment

- **Specific: R52. Offer treatment to CYP with NFPA only if the patient is symptomatic (hypopituitarism), the visual pathway is threatened or there is interval tumour growth on MRI** (strong recommendation, low quality evidence, Delphi 94%).
- **Specific: R53. Offer transsphenoidal surgery as the treatment of choice in CYP with NFPA needing surgical intervention** (strong recommendation, high quality evidence, Delphi 100%).

The majority of non-functioning microadenomas in CYP are asymptomatic and detected incidentally or as part of a screening programme, with little data on their frequency, natural history or complication rates. By contrast, macroadenomas enlarge in over 40% of adult patients at five years[497], while there are no equivalent data in CYP. Surgical removal of a growing macroadenoma is an effective intervention to prevent further damage to surrounding tissues and cranial nerves[70,73,137,185,484,489,490].

- **Specific: R54. There is insufficient evidence to recommend medical therapy, including cabergoline, in CYP with NFPA** (moderate recommendation, low quality evidence, Delphi 80%).

No data are available to suggest that medical therapy (for example, dopamine agonists or somatostatin analogues) can induce tumour shrinkage in CYP with NFPA, and these medications are not recommended in adult guidelines. Some inconsistent reports of effectiveness in adults with NFPAs receiving somatostatin analogues[498] or dopamine agonists[499-502] suggest that dopamine agonists might reduce tumour growth in some recurrent cases[501,502].

- **Specific: R55. Consider second surgery or radiotherapy for CYP with recurrent or symptomatic NFPAs** (moderate recommendation, low quality evidence, Delphi 94% and GDG consensus).

Both surgery and radiotherapy have been used to treat recurrent NFPA[113,138,185,503,504] and the optimal treatment modality for CYP is not clear. The specialist age-appropriate pituitary MDT should make an individual treatment recommendation, accounting for tumour location and any hypothalamic or cavernous sinus invasion, ease of surgery and the age of the child. Local tumour control after radiotherapy for NFPA in CYP ranges from 80% to 97%[505]. After radiotherapy, first 6-monthly and later 12-monthly follow-ups should monitor for the potential development of hypopituitarism or recurrence. Temozolomide treatment was reported in one childhood-onset hormone-negative tumour (**Table 2**). Based on results from adults[506] and the above data, the GDG strengthened **R55**.

Follow-up and surveillance

- **Specific: R56. Following NFPA surgery in CYP, offer post-operative MRI surveillance at a minimum of 3 and 6 months, and 1, 2, 3 and 5 years after surgery** (strong recommendation, low quality evidence, Delphi 89%).
- **Specific: R57. In CYP with incidental NFPAs, offer MRI surveillance: for microincidentalomas: at 12 months and, if stable, at 1–2 year intervals for 3 years with gradual reduction thereafter; for macroincidentalomas: at 6 months and, if stable, annually for 3 years with gradual reduction thereafter** (strong recommendation, low quality evidence, Delphi 100%).

Although evidence in CYP following pituitary surgery for NFPAs is lacking, data in adults show a recurrence rate of non-irradiated operated pituitary adenomas of up to 38% of those with a visible residuum on post-operative MRI over a follow-up period of 5 years. A post-operative MRI at 3 months will assess the extent of residual tumour, with a further scan at 6 months to assess for

recurrence and, if stable, a gradual reduction in the annual scanning frequency as above, with screening continuing life-long[131,507].

The natural history of NFPA in CYP is unknown and could vary. In adults, macroadenomas tend to have higher growth rates than microadenomas (12.5 macroadenomas grow over 100 patient years versus 3.3 microadenomas)[508]. Microadenomas seem to follow a benign course in children[486], and follow-up can be gradually reduced and stopped[486-488]. For macroadenomas, we recommend life-long clinical surveillance (as in adults), with an individualised radiological (MRI) surveillance strategy to identify early those with rapid tumour progression or post-operative recurrence, even if asymptomatic.

Visual surveillance in patients with either operated or incidental macroadenomas should be adjusted to their individual needs. Retrospective pituitary imaging studies in CYP highlight the need to recognise that physiological pubertal pituitary hypertrophy can occur and draw attention to the lack of progression of microadenomas[486-488]. As more comprehensive data on incidentalomas or non-gonadotroph silent tumours in CYP are lacking, we suggest following adult guidelines for follow-up as above[131,507]. While the radiological surveillance of stable non-functioning microadenomas can cease after 1–3 years, macroadenomas need to be followed long-term[131,507]. We suggest a decreasing scanning interval for adenomas proven stable over years. The concerns regarding repeated gadolinium administration over prolonged imaging follow-up is discussed in the Radiology section.

Gonadotrophinomas in CYP

Functioning gonadotroph adenomas are exceedingly rare in CYP. They can result in isosexual precocious puberty or ovarian hyperstimulation syndrome[509,510]. Germ-cell tumours secreting βHCG can represent a differential diagnostic dilemma as symptoms can overlap with those of functioning gonadotrophinomas. Silent gonadotrophinomas are discussed above.

Conclusions

Children and young people are at a disadvantage compared with adults in accessing age-appropriate, highly specialised pituitary care for pituitary adenomas. The limited evidence base for the diagnosis and management of paediatric pituitary adenomas, combined with the typical lack of dedicated age-appropriate pituitary specialty teams and services within paediatric neuro-oncology centres, inequitably disadvantage CYP with pituitary adenomas with respect to optimal care and compromise their outcomes.

The incidence, type, symptomatology, aggressiveness and aetiology of their disease not only differs from that of adults, but their impact, treatment choice and timely remediation can carry far greater consequences on the developing body and brain and on secondary health, intellectual, visual and psychosocial adult outcomes. These can limit the quality of adult relationships, and represent challenges for parenting and employment over a long life-span.

The purpose of these recommendations, the first comprehensive guideline of its kind, is to raise awareness of the potentially occult and sometimes severe nature of this disease in CYP with diagnostic and treatment delays leading to potentially life-limiting complications, as well as to improve time to diagnosis and long-term health and wellbeing outcomes and create a future evidence-base for audit improvement. This will lead to more equalised and optimised healthcare for CYP with pituitary adenomas and will improve access to modern pituitary-specific specialist centres, novel therapies, research and long-term health and wellbeing monitoring. The latter must encompass transition to adult services; closer integration of paediatric and adult pituitary services and datasets can only benefit CYP.

Target users of this guideline are health professionals from a variety of disciplines (including paediatric endocrinology, adult endocrinology, pituitary and skull base neurosurgery, paediatric neurosurgery, oncology, paediatric ophthalmology, radiotherapy, radiology, histopathology and genetics) involved in the management and long-term follow-up of childhood and adolescents with pituitary adenomas. If the level of care required by the patient is best provided in centres with specific expertise in pituitary diseases in CYP, referral to such centres should be facilitated.

Key developments have occurred over the past few years regarding the diagnosis and treatment of pituitary adenomas. Genetic testing, intraoperative MRI and the introduction of pegvisomant are just a few examples. Due to the rarity of pituitary adenomas in CYP, data have necessarily been gathered from retrospective studies, case series, anecdotal case reports and experience from the adult population for most of the management recommendations we present here.

Facilitating referral and service pathways so that CYP can access centralised speciality pituitary multidisciplinary advisory panels across the age-range, and establishing national and international data registries of morbidity outcomes are in the best interest of CYP and vital to inform future best practice recommendations and to improve the long-term quality of life of these children and young people. Paediatric pituitary specialist centres offering expertise in diagnosis, treatment and follow-up of pituitary adenomas require urgent centralisation around major adult pituitary and paediatric neuro-oncology treatment centres, as these centres improve the evidence base for treatment and long-term patient benefit in such a rare, high survival condition of maturing children. Multi-professional pituitary expert teams will be best placed to meet the specific challenges and complexities of pituitary adenomas in children, gather the evidence needed to evaluate these consensus treatment recommendations in the future and improve the maturational, reproductive,

long-term health and functional outcomes for CYP with these eminently curable neoplasms. Having reviewed the evidence and sought consensus opinion on areas where evidence is contradictory or poor, the GDG has suggested some research recommendations.

Research recommendations

Set up of age-appropriate hypothalamic–pituitary multidisciplinary team support (neurosurgery, paediatric oncology, radiation oncology, endocrinology, neuroradiology, and neuropathology) including, where appropriate, adult pituitary specialists (for example, endocrinologists and skull base neurosurgeons) for children and young people under 19 years of age (CYP) with pituitary adenomas.

Collection of long-term data in CYP including local pituitary adenoma control, biochemical control, surgical outcome, secondary health effects (for example, endocrine, reproductive, visual, metabolic, joint and neurological effects), as well as psychosocial and employment health-related quality of life parameters, should be a mandatory part of the treatment and follow-up protocol.

The choice of radiotherapy modality and timing is unclear for CYP with pituitary adenomas who are unresponsive to surgical or medical therapy. Outstanding questions include:

- The timing of radiotherapy, for example after first relapse following initial treatment modality.
- The comparison of radiotherapy techniques, such as stereotactic radiosurgery versus conventionally fractionated radiotherapy.
- The prospective, long-term, endocrine, vascular, neurocognitive and second malignancy outcomes of patients who receive proton beam therapy versus intensity-modulated radiation therapy.
- Functional imaging for the diagnosis of pituitary adenomas in children, especially corticotroph adenomas that are not visible on state-of-the-art MRI.
- The use of overnight dexamethasone test in CYP with suspected Cushing's syndrome and the value of measuring serum levels of dexamethasone in CYP.
- The role and predictive value of the Ki-67 labelling index and the role of molecular characterisation in CYP with pituitary adenomas should be assessed in a large collaborative study, where histological data are correlated with long-term outcomes.
- The aetiology of temporary GH excess in CYP with optic glioma and the transition of GH excess to GH deficiency requires further collaborative neuroendocrine oncology.

Implementation evaluation and audit

To facilitate the implementation of the recommendations in this guideline, we strongly recommend co-operative paediatric and adult, specially commissioned, pituitary-specific multidisciplinary meetings and staff training in nominated specialist centres. Potential barriers to implementation include lack of funding for novel medical therapies, lack of paediatric-specific expertise for diagnostic procedures (petrosal sinus sampling) or treatments (surgical expertise or proton beam therapy). Outside the UK additional problems include lack of access to expert centres due to geography or insurance restrictions. Our guideline could support healthcare providers, patient advocates and policymakers to overcome these barriers and might facilitate achieving these services where they are currently not available. The literature will be reviewed again 5 years after publication of this guideline. If any new evidence is identified prior to the 5 years that notably changes the recommendations, then the update will occur sooner.

Audit criteria

The following key areas of recommendation will be audited:

- Care led by an endocrinologist in a specialist centre with expertise in managing pituitary tumours.
- Appropriate MDT involvement in care of complex cases; discussed in a national MDT.
- Surgical remission and complication rates in CYP outcomes.
- Participation in clinical trials and tumour banking.
- Appropriate use of hormonal assessment of all patients with pituitary fossa lesions, including preoperative assessment.
- Evidence for genetic testing in high-risk patients.
- Appropriate use of radiotherapy, including access to proton beam therapy, to optimise overall and progression-free survival.
- Event free survival, overall survival, endocrine and visual outcomes.
- Adequate, comprehensive planning for transition of care to adult services.

Resource implications

The purpose of these recommendations is to optimise healthcare for CYP with pituitary adenomas, raise awareness of its potentially occult and devastating nature, and improve time to diagnosis and long-term health and wellbeing outcomes. Paediatric pituitary centres offering expertise in all aspects of endocrine diagnosis and monitoring, state-of-the-art medical, surgical and radiation treatment need to be organised around major adult pituitary and paediatric neuro-oncology treatment centres as these improve patient benefit. Our guidelines call for formal recognition and some early resource towards a nationally commissioned, virtual paediatric pituitary MDT forum, of sufficient frequency and targeted multiprofessional pituitary expertise, to meet the specific challenges and complexities of these tumours in children, gather the evidence needed to evaluate these consensus treatment recommendations and improve patient health and functional outcomes from these potentially devastating, but curable, midline tumours.

Final considerations

The rarity of paediatric endocrine tumours like pituitary adenomas makes their management challenging to the extent that the multidisciplinary professionals involved in their care have repeatedly called for these society-commissioned, RCPCH endorsed, evidence- and consensus-based national guidelines, since 2010. During the process of developing this guideline, we have confirmed a general lack of high quality evidence relating to this age group and identified, through the consensus surveys necessarily undertaken, an unreserved professional mandate for both national speciality advisory panels and most importantly, a national register and evaluation of key management outcomes in these rare, eminently curable, young, survivor cohorts. If we are to enhance clinical trials and quality evidence, improve the health-related quality of survival, access to, and equity of, expertise in care, such a national register and formally commissioned centralised, virtual advisory panel needs to be expedited alongside the development of tertiary, dedicated paediatric, pituitary neuro-oncology MDTs and services.

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Author Contributions

All authors researched data for the article. M.K., J.C.B., J.A., J.H.D., M.R.D., J.E., D.F., N.G., C.E.H., T.S.J., S.S., I.S., N.T., F.M.S., H.L.S. and H.A.S. contributed substantially to discussion of the content. M.K., J.C.B., A.B., J.H.D., J.E., T.S.J., S.S., I.S., N.T., H.L.S. and H.A.S. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

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Disclaimer

Healthcare providers need to use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and might not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here is the responsibility of the treating clinician and must be made in the light of individual patient circumstances, the wishes of the patient and their family, clinical expertise and resources.

Related links

Rare endocrine tumour guidelines: https://www.cclg.org.uk/professionals/rare-endocrine-tumour-guidelines
NICE terminology: https://www.nice.org.uk/process/pmg20/chapter/glossary#recommendations
Pituitary Foundation: https://www.pituitary.org.uk/
AMEND: https://www.amend.org.uk/
Success Charity: https://successcharity.org.uk/
Child Growth Foundation: https://childgrowthfoundation.org/
Pituitary Network Association: https://pituitary.org/
World Alliance of Pituitary Organizations: https://www.wapo.org/

Supplementary information

Supplementary information is available for this guideline at www.cclg.org.uk/guidelines.

References

1 Fisher, B. J., Gaspar, L. E., Stitt, L. W. & Noone, B. E. Pituitary adenoma in adolescents: a biologically more aggressive disease? *Radiology* **192**, 869-872, doi:10.1148/radiology.192.3.8058963 (1994).

2 Beckers, A., Petrossians, P., Hanson, J. & Daly, A. F. The causes and consequences of pituitary gigantism. *Nat. Rev. Endocrinol.* **14**, 705-720, doi:10.1038/s41574-018-0114-1 (2018).

3 Barry, S. & Korbonits, M. Update on the Genetics of Pituitary Tumors. *Endocrinol. Metab. Clin. North Am.* **49**, 433-452, doi:10.1016/j.ecl.2020.05.005 (2020).

4 National Cancer Registration and Analysis Service. *Children, teenagers and young adults UK cancer statistics report 2021*, Public Health England <http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/cancer_in_children_teenagers_and_young_adults/> (Access date:*30/09/2022*).

5 Kelly, A. P., Greenfield, J. P., Dobri, G. A. & Schwartz, T. H. Pediatric pituitary adenomas are more aggressive, more likely to be hormone producing and are more difficult to cure than adult pituitary adenomas: case series and systematic literature review. *Childs Nerv. Syst.*, doi:10.1007/s00381-022-05445-3 (2022).

6 Jayant, S. S. *et al.* Paediatric Pituitary Adenomas: Clinical Presentation, Biochemical Profile and Long-Term Prognosis. *Neurol. India* **70**, 304-311, doi:10.4103/0028-3886.338667 (2022).

7 Asa, S. L. *et al.* From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. *Endocr. Relat. Cancer* **24**, C5-C8, doi:10.1530/ERC-17-0004 (2017).

8 Trouillas, J. *et al.* Aggressive pituitary tumours and carcinomas: two sides of the same coin? *Eur. J. Endocrinol.* **178**, C7-C9, doi:10.1530/EJE-18-0250 (2018).

9 Ho, K. K. Y. *et al.* A tale of pituitary adenomas: to NET or not to NET : Pituitary Society position statement. *Pituitary* **22**, 569-573, doi:10.1007/s11102-019-00988-2 (2019).

10 Ho, K. K. Y. *et al.* The tale in evolution: clarity, consistency and consultation, not contradiction and confusion. *Pituitary* **23**, 476-477, doi:10.1007/s11102-019-01027-w (2020).

11 Asa, S. L. *et al.* Pituitary neuroendocrine tumors (PitNETs): nomenclature evolution, not clinical revolution. *Pituitary* **23**, 322-325, doi:10.1007/s11102-019-01015-0 (2020).

12 Asa, S. L., Mete, O., Perry, A. & Osamura, R. Y. Overview of the 2022 WHO Classification of Pituitary Tumors. *Endocr. Pathol.* **33**, 6-26, doi:10.1007/s12022-022-09703-7 (2022).

13 Ho, K. K. Y. *et al.* Pituitary adenoma or neuroendocrine tumour: the need for an integrated prognostic classification. *Nat. Rev. Endocrinol.* **19**, 671-678, doi:10.1038/s41574-023-00883-8 (2023).

14 Castellanos, L. E., Misra, M., Smith, T. R., Laws, E. R. & Iorgulescu, J. B. The epidemiology and management patterns of pediatric pituitary tumors in the United States. *Pituitary* **24**, 412-419, doi:10.1007/s11102-020-01120-5 (2021).

15 National Cancer Registration and Analysis Service. *Cancer in children, teenagers and young adults*, <http://ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/cancer_in_children_teenagers_and_young_adults/> (Access date:*11/04/2023*).

16 Korbonits, M. *et al.* Consensus Guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: part 1, general recommendations *Nat. Rev. Endocrinol.* 20, 278-289, doi:10.1038/s41574-023-00948-8 (2024).

17 Korbonits, M. *et al.* Consensus Guideline for the diagnosis and management of pituitary adenomas in childhood and adolescence: part 2, specific diseases. *Nat. Rev. Endocrinol.* 20, 290-309, doi:10.1038/s41574-023-00949-7 (2024).

18 Brouwers, M. C. *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *Can. Med. Assoc. J.* **182**, E839-842, doi:10.1503/cmaj.090449 (2010).

19 Children's Cancer and Leukaemia Group. *Children's Cancer and Leukaemia guideline development standard operating procedure, Version 5*, <https://www.cclg.org.uk/what-we-do/clinical-treatment-guidelines> (Access date:*19/01/2022*).

20 Schardt, C., Adams, M. B., Owens, T., Keitz, S. & Fontelo, P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med. Inform. Decis. Mak.* **7**, 16, doi:10.1186/1472-6947-7-16 (2007).

21 Atkins, D. *et al.* Grading quality of evidence and strength of recommendations. *BMJ* **328**, 1490, doi:10.1136/bmj.328.7454.1490 (2004).

22 Perry, A. *et al.* Pediatric Pituitary Adenoma: Case Series, Review of the Literature, and a Skull Base Treatment Paradigm. *J Neurol Surg B Skull Base* **79**, 91-114, doi:10.1055/s-0038-1625984 (2018).

23 Freund, K. *et al.* in *Horm. Res. Paediatr.* 496-497.

24 Batista, D. *et al.* Detection of adrenocorticotropin-secreting pituitary adenomas by magnetic resonance imaging in children and adolescents with Cushing disease. *J. Clin. Endocrinol. Metab.* **90**, 5134-5140, doi:10.1210/jc.2004-1778 (2005).

25 Patronas, N. *et al.* Spoiled gradient recalled acquisition in the steady state technique is superior to conventional postcontrast spin echo technique for magnetic resonance imaging detection of adrenocorticotropin-secreting pituitary tumors. *J. Clin. Endocrinol. Metab.* **88**, 1565-1569, doi:10.1210/jc.2002-021438 (2003).

26 Chowdhury, I. N., Sinaii, N., Oldfield, E. H., Patronas, N. & Nieman, L. K. A change in pituitary magnetic resonance imaging protocol detects ACTH-secreting tumours in patients with previously negative results. *Clin. Endocrinol. (Oxf.)* **72**, 502-506, doi:10.1111/j.1365-2265.2009.03646.x (2010).

27 Arbab, A. S. 3D gradient echo sequence provides better images in contrast-enhanced imaging of the pituitary gland at 3 T. *Imaging Med.* **2**, 129-130 (2010).

28 Kakite, S. *et al.* Three-dimensional gradient echo versus spin echo sequence in contrast-enhanced imaging of the pituitary gland at 3T. *Eur. J. Radiol.* **79**, 108-112, doi:10.1016/j.ejrad.2009.12.036 (2011).

29 Kasaliwal, R. *et al.* Volume interpolated 3D-spoiled gradient echo sequence is better than dynamic contrast spin echo sequence for MRI detection of corticotropin secreting pituitary microadenomas. *Clin. Endocrinol. (Oxf.)* **78**, 825-830, doi:10.1111/cen.12069 (2013).

30 Gan, H. W. *et al.* National UK guidelines for the management of paediatric craniopharyngioma. *Lancet Diabetes Endocrinol.* **11**, 694-706, doi:10.1016/S2213-8587(23)00162-6 (2023).

31 Cerbone, M. *et al.* Management of children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both: a national clinical practice consensus guideline. *Lancet Child Adolesc Health* **5**, 662-676, doi:10.1016/S2352-4642(21)00088-2 (2021).

32 Bashari, W. A. *et al.* Using Molecular Imaging to Enhance Decision Making in the Management of Pituitary Adenomas. *J. Nucl. Med.* **62**, 57S-62S, doi:10.2967/jnumed.120.251546 (2021).

33 Veldhuijzen van Zanten, S. E. M., Neggers, S., Valkema, R. & Verburg, F. A. Positive [(18)F]fluoroethyltyrosine PET/MRI in suspected recurrence of growth hormone-producing pituitary adenoma in a paediatric patient. *Eur. J. Nucl. Med. Mol. Imaging* **49**, 410-411, doi:10.1007/s00259-021-05458-1 (2021).

34 Pinker, K. *et al.* The value of high-field MRI (3T) in the assessment of sellar lesions. *Eur. J. Radiol.* **54**, 327-334, doi:10.1016/j.ejrad.2004.08.006 (2005).

35 Berkmann, S., Fandino, J., Muller, B., Remonda, L. & Landolt, H. Intraoperative MRI and endocrinological outcome of transsphenoidal surgery for non-functioning pituitary adenoma. *Acta Neurochir. (Wien.)* **154**, 639-647, doi:10.1007/s00701-012-1285-5 (2012).

36 Szerlip, N. J. *et al.* Transsphenoidal resection of sellar tumors using high-field intraoperative magnetic resonance imaging. *Skull Base* **21**, 223-232, doi:10.1055/s-0031-1277262 (2011).

37 Nimsky, C., von Keller, B., Ganslandt, O. & Fahlbusch, R. Intraoperative high-field magnetic resonance imaging in transsphenoidal surgery of hormonally inactive pituitary macroadenomas. *Neurosurgery* **59**, 105-114; discussion 105-114, doi:10.1227/01.NEU.0000219198.38423.1E (2006).

38 Wu, J. S. *et al.* Transsphenoidal pituitary macroadenomas resection guided by PoleStar N20 low-field intraoperative magnetic resonance imaging: comparison with early postoperative high-field magnetic resonance imaging. *Neurosurgery* **65**, 63-70; discussion 70-61, doi:10.1227/01.NEU.0000348549.26832.51 (2009).

39 Fomekong, E. *et al.* Intraoperative 3T MRI for pituitary macroadenoma resection: Initial experience in 73 consecutive patients. *Clin. Neurol. Neurosurg.* **126**, 143-149, doi:10.1016/j.clineuro.2014.09.001 (2014).

40 Zhang, H. *et al.* Analysis of 137 Patients Who Underwent Endoscopic Transsphenoidal Pituitary Adenoma Resection Under High-Field Intraoperative Magnetic Resonance Imaging Navigation. *World Neurosurg.* **104**, 802-815, doi:10.1016/j.wneu.2017.04.056 (2017).

41 Staartjes, V. E., Togni-Pogliorini, A., Stumpo, V., Serra, C. & Regli, L. Impact of intraoperative magnetic resonance imaging on gross total resection, extent of resection, and residual tumor volume in pituitary surgery: systematic review and meta-analysis. *Pituitary*, doi:10.1007/s11102-021-01147-2 (2021).

42 Holowka, S., Shroff, M. & Chavhan, G. B. Use and Safety of Gadolinium Based Contrast Agents in Pediatric MR Imaging. *Indian J. Pediatr.* **86**, 961-966, doi:10.1007/s12098-019-02891-x (2019).

43 Bonneville, J. F. A plea for the T2W MR sequence for pituitary imaging. *Pituitary* **22**, 195-197, doi:10.1007/s11102-018-0928-9 (2019).

44 Shah, R., D'Arco, F., Soares, B., Cooper, J. & Brierley, J. Use of gadolinium contrast agents in paediatric population: Donald Rumsfeld meets Hippocrates! *Br. J. Radiol.* **92**, 20180746, doi:10.1259/bjr.20180746 (2019).

45 Schieda, N. *et al.* Gadolinium-Based Contrast Agents in Kidney Disease: A Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists. *Can J Kidney Health Dis* **5**, 2054358118778573, doi:10.1177/2054358118778573 (2018).

46 Suharwardy, J. & Elston, J. The clinical presentation of children with tumours affecting the anterior visual pathways. *Eye (Lond.)* **11 (Pt 6)**, 838-844, doi:10.1038/eye.1997.215 (1997).

47 Drimtzias, E. *et al.* The ophthalmic natural history of paediatric craniopharyngioma: a long-term review. *J. Neurooncol.* **120**, 651-656, doi:10.1007/s11060-014-1600-5 (2014).

48 Avery, R. A., Bouffet, E., Packer, R. J. & Reginald, A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. *Invest. Ophthalmol. Vis. Sci.* **54**, 1034-1038, doi:10.1167/iovs.12-11385 (2013).

49 Avery, R. A. *et al.* Visual acuity in children with low grade gliomas of the visual pathway: implications for patient care and clinical research. *J. Neurooncol.* **110**, 1-7, doi:10.1007/s11060-012-0944-y (2012).

50 Beck, R. W. *et al.* Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology* **114**, 1804-1809, doi:10.1016/j.ophtha.2007.06.047 (2007).

51 Fulton, A. B., Hansen, R., Moskowitz, A. & Mayer, D. Normal and abnormal visual development in *Pediatric Ophthalmology and Strabismus* (2013).

52 Bialer, O. Y., Goldenberg-Cohen, N., Toledano, H., Snir, M. & Michowiz, S. Retinal NFL thinning on OCT correlates with visual field loss in pediatric craniopharyngioma. *Can. J. Ophthalmol.* **48**, 494-499, doi:10.1016/j.jcjo.2013.05.001 (2013).

53 Rufai, S. R. Handheld optical coherence tomography removes barriers to imaging the eyes of young children. *Eye (Lond.)* **25**, 127-143, doi:10.1038/s41433-021-01884-5 (2022).

54 Wenzel, D., Brandl, U., Beck, J. D., Cedzich, C. & Albert, F. Visual evoked potentials in tumors from orbita to occipital lobe in childhood. *Neurosurg. Rev.* **11**, 279-286, doi:10.1007/BF01741423 (1988).

55 Repka, M. X., Miller, N. R. & Miller, M. Visual outcome after surgical removal of craniopharyngiomas. *Ophthalmology* **96**, 195-199 (1989).

56 Stark, K. L., Kaufman, B., Lee, B. C., Primack, J. & Tychsen, L. Visual recovery after a year of craniopharyngioma-related amaurosis: report of a nine-year-old child and a review of pathophysiologic mechanisms. *J. AAPOS* **3**, 366-371 (1999).

57 Abrams, L. S. & Repka, M. X. Visual outcome of craniopharyngioma in children. *J. Pediatr. Ophthalmol. Strabismus* **34**, 223-228 (1997).

58 Fisher, P. G. *et al.* Outcomes and failure patterns in childhood craniopharyngiomas. *Childs Nerv. Syst.* **14**, 558-563 (1998).

59 Chanson, P. *et al.* Management of clinically non-functioning pituitary adenoma. *Ann. Endocrinol. (Paris)* **76**, 239-247, doi:10.1016/j.ando.2015.04.002 (2015).

60 Lopes, M. B. *et al.* Pituitary adenoma / pituitary neuroendocrine tumour in WHO Classification of Tumours Editorial Board. Central nervous system tumours in *WHO Classification of Tumours Series* Vol. 6 (ed J. B. Daniel) Ch. 12, 406-414 (International Agency for Research on Cancer, 2021).

61 Lloyd, R. V., Osamura, R. Y., Kloppel, G. & Rosai, J. *WHO Classification of Tumours of Endocrine Organs*. 4th edn, (International Agency for Research on Cancer, 2017).

62 Neou, M. *et al.* Pangenomic Classification of Pituitary Neuroendocrine Tumors. *Cancer Cell* **37**, 123-134 e125, doi:10.1016/j.ccell.2019.11.002 (2020).

63 Trouillas, J. *et al.* A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. *Acta Neuropathol.* **126**, 123-135, doi:10.1007/s00401-013-1084-y (2013).

64 Chen, J., Schmidt, R. E. & Dahiya, S. Pituitary Adenoma in Pediatric and Adolescent Populations. *J. Neuropathol. Exp. Neurol.* **78**, 626-632, doi:10.1093/jnen/nlz040 (2019).

65 Villa, C. *et al.* A standardised diagnostic approach to pituitary neuroendocrine tumours (PitNETs): a European Pituitary Pathology Group (EPPG) proposal. *Virchows Arch.* **475**, 687-692, doi:10.1007/s00428-019-02655-0 (2019).

66 Raverot, G. *et al.* European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur. J. Endocrinol.* **178**, G1-G24, doi:10.1530/EJE-17-0796 (2018).

67 Capper, D. *et al.* DNA methylation-based classification of central nervous system tumours. *Nature* **555**, 469-474, doi:10.1038/nature26000 (2018).

68 Vierimaa, O. *et al.* Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* **312**, 1228-1230, doi:10.1126/science.1126100 (2006).

69 Trivellin, G. *et al.* Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *N. Engl. J. Med.* **371**, 2363-2374, doi:10.1056/NEJMoa1408028 (2014).

70 Guaraldi, F., Storr, H. L., Ghizzoni, L., Ghigo, E. & Savage, M. O. Paediatric pituitary adenomas: a decade of change. *Horm. Res. Paediatr.* **81**, 145-155, doi:10.1159/000357673 (2014).

71 Hannah-Shmouni, F., Trivellin, G. & Stratakis, C. A. Genetics of gigantism and acromegaly. *Growth Horm. IGF Res.* **30-31**, 37-41, doi:10.1016/j.ghir.2016.08.002 (2016).

72 Denes, J. & Korbonits, M. The clinical aspects of pituitary tumour genetics. *Endocrine* **71**, 663-674, doi:10.1007/s12020-021-02633-0 (2021).

73 Daly, A. F. *et al.* Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *J. Clin. Endocrinol. Metab.* **95**, E373-383, doi:10.1210/jc.2009-2556 (2010).

74 Goudet, P. *et al.* MEN1 disease occurring before 21 years old: a 160-patient cohort study from the Groupe d'etude des Tumeurs Endocrines. *J. Clin. Endocrinol. Metab.* **100**, 1568-1577, doi:10.1210/jc.2014-3659 (2015).

75 Marques, P. *et al.* Significant Benefits of AIP Testing and Clinical Screening in Familial Isolated and Young-onset Pituitary Tumors. *J. Clin. Endocrinol. Metab.* **105**, e2247-2260, doi:10.1210/clinem/dgaa040 (2020).

76 Salenave, S., Boyce, A. M., Collins, M. T. & Chanson, P. Acromegaly and McCune-Albright syndrome. *J. Clin. Endocrinol. Metab.* **99**, 1955-1969, doi:10.1210/jc.2013-3826 (2014).

77 Rodd, C. *et al.* Somatic GPR101 duplication causing X-Linked acrogigantism (XLAG)-diagnosis and management. *J. Clin. Endocrinol. Metab.* **101**, 1927-1930, doi:10.1210/jc.2015-4366 (2016).

78 Korbonits, M., Storr, H. & Kumar, A. V. Familial pituitary adenomas - who should be tested for AIP mutations? *Clin. Endocrinol. (Oxf.)* **77**, 351-356, doi:10.1111/j.1365-2265.2012.04445.x (2012).

79 Thakker, R. V. *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J. Clin. Endocrinol. Metab.* **97**, 2990-3011, doi:jc.2012-1230 [pii];10.1210/jc.2012-1230 [doi] (2012).

80 Rostomyan, L. *et al.* Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. *Endocr. Relat. Cancer* **22**, 745-757, doi:10.1530/ERC-15-0320 (2015).

81 Iacovazzo, D. *et al.* Germline or somatic GPR101 duplication leads to X-linked acrogigantism: a clinico-pathological and genetic study. *Acta Neuropathol Commun* **4**, 56, doi:10.1186/s40478-016-0328-1 (2016).

82 Franke, M. *et al.* Duplications disrupt chromatin architecture and rewire GPR101-enhancer communication in X-linked acrogigantism. *Am. J. Hum. Genet.* **109**, 553-570, doi:10.1016/j.ajhg.2022.02.002 (2022).

83 Johnson, M. C. *et al.* Gps mutations in Chilean patients harboring growth hormone-secreting pituitary tumors. *J. Pediatr. Endocrinol. Metab.* **12**, 381-387, doi:10.1515/jpem.1999.12.3.381 (1999).

84 Hernandez-Ramirez, L. C. *et al.* Landscape of Familial Isolated and Young-Onset Pituitary Adenomas: Prospective Diagnosis in AIP Mutation Carriers. *J. Clin. Endocrinol. Metab.* **100**, E1242-1254, doi:10.1210/jc.2015-1869 (2015).

85 Watanabe, D. *et al.* GH/PRL-secreting pituitary macroadenoma associated with GNAS p.Gln227Leu mutation: pediatric case report and review. *Endocr. J.* **66**, 403-408, doi:10.1507/endocrj.EJ18-0370 (2019).

86 Cuny, T. *et al.* Genetic analysis in young patients with sporadic pituitary macroadenomas: besides AIP don't forget MEN1 genetic analysis. *Eur. J. Endocrinol.* **168**, 533-541, doi:10.1530/EJE-12-0763 (2013).

87 Salenave, S. *et al.* Macroprolactinomas in children and adolescents: factors associated with the response to treatment in 77 patients. *J. Clin. Endocrinol. Metab.* **100**, 1177-1186, doi:10.1210/jc.2014-3670 (2015).

88 Seabrook, A. J. *et al.* Multiple Endocrine Tumors Associated with Germline MAX Mutations: Multiple Endocrine Neoplasia Type 5? *J. Clin. Endocrinol. Metab.* **106**, 1163-1182, doi:10.1210/clinem/dgaa957 (2021).

89 Kobayashi, T., Usui, H., Tanaka, H. & Shozu, M. Variant Prolactin Receptor in Agalactia and Hyperprolactinemia. *N. Engl. J. Med.* **379**, 2230-2236, doi:10.1056/NEJMoa1805171 (2018).

90 Newey, P. J. *et al.* Mutant prolactin receptor and familial hyperprolactinemia. *N. Engl. J. Med.* **369**, 2012-2020, doi:10.1056/NEJMoa1307557 (2013).

91 Chasseloup, F. *et al.* Germline CDKN1B Loss-of-Function Variants Cause Pediatric Cushing's Disease With or Without an MEN4 Phenotype. *J. Clin. Endocrinol. Metab.* **105**, doi:10.1210/clinem/dgaa160 (2020).

92 Rix, M. *et al.* Cushing's disease in childhood as the first manifestation of multiple endocrine neoplasia syndrome type 1. *Eur. J. Endocrinol.* **151**, 709-715 (2004).

93 Stratakis, C. A. *et al.* Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. *J. Clin. Endocrinol. Metab.* **85**, 4776-4780, doi:10.1210/jcem.85.12.7064 (2000).

94 Hernandez-Ramirez, L. C. *et al.* Loss-of-function mutations in the CABLES1 gene are a novel cause of Cushing's disease. *Endocr. Relat. Cancer* **24**, 379-392, doi:10.1530/ERC-17-0131 (2017).

95 de Kock, L. *et al.* Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. *Acta Neuropathol.* **128**, 111-122, doi:10.1007/s00401-014-1285-z [doi] (2014).

96 Liu, A. P. Y. *et al.* Clinical Outcomes and Complications of Pituitary Blastoma. *J. Clin. Endocrinol. Metab.* **106**, 351-363, doi:10.1210/clinem/dgaa857 (2021).

97 Chhuon, Y. *et al.* Pituitary Blastoma in a 19-Year-Old Woman: A Case Report and Review of Literature. *World Neurosurg.* **139**, 310-313, doi:10.1016/j.wneu.2020.04.096 (2020).

98 Chong, A. S. *et al.* DICER1 syndrome in a young adult with pituitary blastoma. *Acta Neuropathol.* **32**, 969-977, doi:10.1007/s00401-021-02378-0 (2021).

99 Faucz, F. R. *et al.* Somatic USP8 Gene Mutations Are a Common Cause of Pediatric Cushing Disease. *J. Clin. Endocrinol. Metab.* **102**, 2836-2843, doi:10.1210/jc.2017-00161 (2017).

100 Reincke, M. *et al.* Mutations in the deubiquitinase gene USP8 cause Cushing's disease. *Nat. Genet.* **47**, 31-38, doi:10.1038/ng.3166 (2015).

101 Perez-Rivas, L. G. *et al.* The Gene of the Ubiquitin-Specific Protease 8 Is Frequently Mutated in Adenomas Causing Cushing's Disease. *J. Clin. Endocrinol. Metab.* **100**, E997-1004, doi:10.1210/jc.2015-1453 (2015).

102 Ma, Z. Y. *et al.* Recurrent gain-of-function USP8 mutations in Cushing's disease. *Cell Res.* **25**, 306-317, doi:10.1038/cr.2015.20 (2015).

103 Cohen, M. *et al.* Germline USP8 Mutation Associated With Pediatric Cushing Disease and Other Clinical Features: A New Syndrome. *J. Clin. Endocrinol. Metab.* **104**, 4676-4682, doi:10.1210/jc.2019-00697 (2019).

104 Tatsi, C. *et al.* Large Genomic Aberrations in Corticotropinomas Are Associated With Greater Aggressiveness. *J. Clin. Endocrinol. Metab.* **104**, 1792-1801, doi:10.1210/jc.2018-02164 (2019).

105 Teng, X. *et al.* A Patient With a Thyrotropin-Secreting Microadenoma and Resistance to Thyroid Hormone (P453T). *J. Clin. Endocrinol. Metab.* **100**, 2511-2514, doi:10.1210/jc.2014-3994 (2015).

106 Wass, J. A. H. & Lansdown, M. *Endocrinology, Getting It Right First Time (GIRFT) Programme National Specialty Report*, <https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/08/EndocrinologyReport-Aug21o-NEW.pdf> (Access date:*30/09/2022*).

107 Casanueva, F. F. *et al.* Correction to: Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. *Pituitary* **21**, 663, doi:10.1007/s11102-018-0912-4 (2018).

108 Honegger, J. & Grimm, F. The experience with transsphenoidal surgery and its importance to outcomes. *Pituitary* **21**, 545-555, doi:10.1007/s11102-018-0904-4 (2018).

109 Oliveira, R. S. *et al.* Surgical management of pediatric Cushing's disease: an analysis of 15 consecutive cases at a specialized neurosurgical center. *Arq. Bras. Endocrinol. Metabol.* **54**, 17-23 (2010).

110 Dyer, E. H., Civit, T., Visot, A., Delalande, O. & Derome, P. Transsphenoidal surgery for pituitary adenomas in children. *Neurosurgery* **34**, 207-212; discussion 212 (1994).

111 Knappe, U. J. & Ludecke, D. K. Transnasal microsurgery in children and adolescents with Cushing's disease. *Neurosurgery* **39**, 484-492; discussion 492-483 (1996).

112 Massoud, A. F., Powell, M., Williams, R. A., Hindmarsh, P. C. & Brook, C. G. Transsphenoidal surgery for pituitary tumours. *Arch. Dis. Child.* **76**, 398-404 (1997).

113 Pandey, P., Ojha, B. K. & Mahapatra, A. K. Pediatric pituitary adenoma: a series of 42 patients. *J. Clin. Neurosci.* **12**, 124-127, doi:10.1016/j.jocn.2004.10.003 (2005).

114 Kanter, A. S. *et al.* Single-center experience with pediatric Cushing's disease. *J. Neurosurg.* **103**, 413-420, doi:10.3171/ped.2005.103.5.0413 (2005).

115 Joshi, S. M. *et al.* Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery* **57**, 281-285; discussion 281-285 (2005).

116 Gkourogianni, A. *et al.* Death in pediatric Cushing syndrome is uncommon but still occurs. *Eur. J. Pediatr.* **174**, 501-507, doi:10.1007/s00431-014-2427-y (2015).

117 Dhandapani, S. *et al.* Endonasal endoscopic versus microscopic transsphenoidal surgery in pituitary tumors among the young: A comparative study & meta-analysis. *Clin. Neurol. Neurosurg.* **200**, 106411, doi:10.1016/j.clineuro.2020.106411 (2021).

118 Saldarriaga, C. *et al.* Postoperative Diabetes Insipidus and Hyponatremia in Children after Transsphenoidal Surgery for Adrenocorticotropin Hormone and Growth Hormone Secreting Adenomas. *J. Pediatr.* **195**, 169-174 e161, doi:10.1016/j.jpeds.2017.11.042 (2018).

119 Koumas, C. *et al.* Outcomes following endoscopic endonasal resection of sellar and supresellar lesions in pediatric patients. *Childs Nerv. Syst.* **35**, 2099-2105, doi:10.1007/s00381-019-04258-1 (2019).

120 Lamas, C., del Pozo, C., Villabona, C. & Neuroendocrinology Group of the, S. Clinical guidelines for management of diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion after pituitary surgery. *Endocrinol Nutr* **61**, e15-24, doi:10.1016/j.endonu.2014.01.005 (2014).

121 de Vries, F. *et al.* Postoperative diabetes insipidus: how to define and grade this complication? *Pituitary* **24**, 284-291, doi:10.1007/s11102-020-01083-7 (2021).

122 Rajasekaran, S. *et al.* UK guidelines for the management of pituitary apoplexy. *Clin. Endocrinol. (Oxf.)* **74**, 9-20, doi:10.1111/j.1365-2265.2010.03913.x [doi] (2011).

123 Ozcetin, M., Karaci, M., Toroslu, E. & Edebali, N. A pediatric case of pituitary macroadenoma presenting with pituitary apoplexy and cranial nerve involvement: case report. *Turk Pediatri Ars* **51**, 162-165, doi:10.5152/TurkPediatriArs.2016.1945 (2016).

124 Villa, C. *et al.* Hyperplasia-adenoma sequence in pituitary tumorigenesis related to aryl hydrocarbon receptor interacting protein (AIP) gene mutation. *Endocr. Relat. Cancer* **18**, 347-356, doi:ERC-11-0059 [pii];10.1530/ERC-11-0059 [doi] (2011).

125 Williams, F. *et al.* Clinical experience in the screening and management of a large kindred with familial isolated pituitary adenoma due to an aryl hydrocarbon receptor interacting protein (AIP) mutation. *J. Clin. Endocrinol. Metab.* **99**, 1122-1131, doi:10.1210/jc.2013-2868 (2014).

126 Chao, C. C. & Lin, C. J. Pituitary apoplexy in a teenager--case report. *Pediatr. Neurol.* **50**, 648-651, doi:10.1016/j.pediatrneurol.2014.02.004 (2014).

127 Sakalas, R., David, R. B., Vines, F. S. & Becker, D. P. Pituitary apoplexy in a child. Case report. *J. Neurosurg.* **39**, 519-522, doi:10.3171/jns.1973.39.4.0519 (1973).

128 Culpin, E. *et al.* Pituitary tumour apoplexy within prolactinomas in children: a more aggressive condition? *Pituitary* **21**, 474-479, doi:10.1007/s11102-018-0900-8 (2018).

129 Deopujari, C. E., Shah, N. J., Shaikh, S. T., Karmarkar, V. S. & Mohanty, C. B. Endonasal endoscopic skullbase surgery in children. *Childs Nerv. Syst.* **35**, 2091-2098, doi:10.1007/s00381-019-04167-3 (2019).

130 Storr, H. L. *et al.* Endonasal endoscopic transsphenoidal pituitary surgery: early experience and outcome in paediatric Cushing's disease. *Clin. Endocrinol. (Oxf.)* **80**, 270-276, doi:10.1111/cen.12275 (2014).

131 Deutschbein, T. *et al.* First German Guideline on Diagnostics and Therapy of Clinically Non-Functioning Pituitary Tumors. *Exp. Clin. Endocrinol. Diabetes* **129**, 250-264, doi:10.1055/a-1373-4087 (2021).

132 Chivukula, S. *et al.* Endoscopic endonasal skull base surgery in the pediatric population. *J. Neurosurg. Pediatr.* **11**, 227-241, doi:10.3171/2012.10.PEDS12160 (2013).

133 Massimi, L. *et al.* Quality of postoperative course in children: endoscopic endonasal surgery versus sublabial microsurgery. *Acta Neurochir. (Wien.)* **153**, 843-849, doi:10.1007/s00701-010-0929-6 (2011).

134 Kinoshita, Y. *et al.* Post-operative hyponatremia in patients with pituitary adenoma: post-operative management with a uniform treatment protocol. *Endocr. J.* **58**, 373-379 (2011).

135 Grigsby, P. W., Thomas, P. R., Simpson, J. R. & Fineberg, B. B. Long-term results of radiotherapy in the treatment of pituitary adenomas in children and adolescents. *Am. J. Clin. Oncol.* **11**, 607-611 (1988).

136 Partington, M. D., Davis, D. H., Laws, E. R., Jr. & Scheithauer, B. W. Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. *J. Neurosurg.* **80**, 209-216, doi:10.3171/jns.1994.80.2.0209 (1994).

137 De Menis, E. *et al.* Pituitary adenomas in childhood and adolescence. Clinical analysis of 10 cases. *J. Endocrinol. Invest.* **24**, 92-97, doi:10.1007/BF03343820 (2001).

138 Mehrazin, M. Pituitary tumors in children: clinical analysis of 21 cases. *Childs Nerv. Syst.* **23**, 391-398, doi:10.1007/s00381-006-0259-4 (2007).

139 van den Bergh, A. C. *et al.* Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. *Int. J. Radiat. Oncol. Biol. Phys.* **67**, 863-869, doi:10.1016/j.ijrobp.2006.09.049 (2007).

140 Chang, E. F. *et al.* Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. *J. Neurosurg.* **108**, 736-745, doi:10.3171/JNS/2008/108/4/0736 (2008).

141 Jennings, A. S., Liddle, G. W. & Orth, D. N. Results of treating childhood Cushing's disease with pituitary irradiation. *N. Engl. J. Med.* **297**, 957-962, doi:10.1056/NEJM197711032971801 (1977).

142 Yordanova, G. *et al.* Long-term outcomes of children treated for Cushing's disease: a single center experience. *Pituitary* **19**, 612-624, doi:10.1007/s11102-016-0756-8 (2016).

143 Fraioli, M. F., Novegno, F., Catena, E., Fraioli, C. & Moschettoni, L. Multidisciplinary treatment of giant invasive prolactinomas in paediatric age: long-term follow-up in two children. *Childs Nerv. Syst.* **26**, 1233-1237, doi:10.1007/s00381-010-1129-7 (2010).

144 Shrivastava, A. *et al.* Outcomes After Gamma Knife Stereotactic Radiosurgery in Pediatric Patients with Cushing Disease or Acromegaly: A Multi-Institutional Study. *World Neurosurg.* **125**, e1104-e1113, doi:10.1016/j.wneu.2019.01.252 (2019).

145 Pomeraniec, I. J., Dallapiazza, R. F., Xu, Z., Jane, J. A., Jr. & Sheehan, J. P. Early versus late Gamma Knife radiosurgery following transsphenoidal resection for nonfunctioning pituitary macroadenomas: a matched cohort study. *J. Neurosurg.* **125**, 202-212, doi:10.3171/2015.5.JNS15581 (2016).

146 Jalali, R. *et al.* Stereotactic conformal radiotherapy for pituitary adenomas: technique and preliminary experience. *Clin. Endocrinol. (Oxf.)* **52**, 695-702 (2000).

147 Colin, P. *et al.* Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *Int. J. Radiat. Oncol. Biol. Phys.* **62**, 333-341, doi:10.1016/j.ijrobp.2004.09.058 (2005).

148 Mackley, H. B. *et al.* Intensity-modulated radiotherapy for pituitary adenomas: the preliminary report of the Cleveland Clinic experience. *Int. J. Radiat. Oncol. Biol. Phys.* **67**, 232-239, doi:10.1016/j.ijrobp.2006.08.039 (2007).

149 Elhateer, H. *et al.* Fractionated stereotactic radiotherapy in the treatment of pituitary macroadenomas. *Curr. Oncol.* **15**, 286-292 (2008).

150 Arauz, R. & Rodriguez, M. in *19th Annual Scientific Meeting of the Society for Neuro-Oncology*. (Oxford Journals).

151 Almeldin, D., Fersht, N. & Kosmin, M. *Radiotherapy for Pituitary Tumors*, ENDOTEXT <https://www.ncbi.nlm.nih.gov/pubmed/25905190> (Access date:*30/09/2023*).

152 Brada, M. *et al.* The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin. Endocrinol. (Oxf.)* **38**, 571-578 (1993).

153 Tsang, R. W. *et al.* Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. *Int. J. Radiat. Oncol. Biol. Phys.* **30**, 557-565 (1994).

154 Snead, F. E., Amdur, R. J., Morris, C. G. & Mendenhall, W. M. Long-term outcomes of radiotherapy for pituitary adenomas. *Int. J. Radiat. Oncol. Biol. Phys.* **71**, 994-998, doi:10.1016/j.ijrobp.2007.11.057 (2008).

155 Erridge, S. C. *et al.* Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. *Radiother. Oncol.* **93**, 597-601, doi:10.1016/j.radonc.2009.09.011 (2009).

156 Storr, H. L. *et al.* Clinical and endocrine responses to pituitary radiotherapy in pediatric Cushing's disease: an effective second-line treatment. *J. Clin. Endocrinol. Metab.* **88**, 34-37, doi:10.1210/jc.2002-021032 (2003).

157 Bolsi, A., Fogliata, A. & Cozzi, L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. *Radiother. Oncol.* **68**, 1-14 (2003).

158 Ronson, B. B. *et al.* Fractionated proton beam irradiation of pituitary adenomas. *Int. J. Radiat. Oncol. Biol. Phys.* **64**, 425-434, doi:10.1016/j.ijrobp.2005.07.978 (2006).

159 Merchant, T. E. *et al.* Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr. Blood Cancer* **51**, 110-117, doi:10.1002/pbc.21530 (2008).

160 Combs, S. E. *et al.* Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base. *Acta Oncol.* **52**, 1504-1509, doi:10.3109/0284186X.2013.818255 (2013).

161 Plowman, P. N. Pituitary adenoma radiotherapy-when, who and how? *Clin. Endocrinol. (Oxf.)* **51**, 265-271 (1999).

162 Loeffler, J. S. & Shih, H. A. Radiation therapy in the management of pituitary adenomas. *J. Clin. Endocrinol. Metab.* **96**, 1992-2003, doi:10.1210/jc.2011-0251 (2011).

163 Grabenbauer, G. G., Ernst-Stecken, A., Schneider, F., Lambrecht, U. & Ganslandt, O. Radiosurgery of functioning pituitary adenomas: Comparison of different treatment techniques including dynamic and conformal arcs, shaped beams, and IMRT. *Int. J. Radiat. Oncol. Biol. Phys.* **66**, S33-S39, doi:10.1016/j.ijrobp.2006.05.076 (2006).

164 Sheehan, J. P. *et al.* Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium. *J. Neurosurg.* **102**, 678-691, doi:10.3171/jns.2005.102.4.0678 (2005).

165 Sheehan, J. P. *et al.* Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J. Neurosurg.* **119**, 446-456, doi:10.3171/2013.3.JNS12766 (2013).

166 Xu, Z., Lee Vance, M., Schlesinger, D. & Sheehan, J. P. Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. *Neurosurgery* **72**, 630-637; 636-637, doi:10.1227/NEU.0b013e3182846e44 (2013).

167 Mitsumori, M. *et al.* Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. *Int. J. Radiat. Oncol. Biol. Phys.* **42**, 573-580 (1998).

168 Brada, M. *et al.* Cerebrovascular mortality in patients with pituitary adenoma. *Clin. Endocrinol. (Oxf.)* **57**, 713-717 (2002).

169 Sattler, M. G. *et al.* The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone. *Radiother. Oncol.* **104**, 125-130, doi:10.1016/j.radonc.2012.04.024 (2012).

170 Minniti, G. *et al.* The long-term efficacy of conventional radiotherapy in patients with GH-secreting pituitary adenomas. *Clin. Endocrinol. (Oxf.)* **62**, 210-216, doi:10.1111/j.1365-2265.2005.02199.x (2005).

171 Burman, P., van Beek, A. P., Biller, B. M., Camacho-Hubner, C. & Mattsson, A. F. Radiotherapy, especially at young age, increases the risk for de novo brain tumors in patients treated for pituitary/sellar lesions. *J. Clin. Endocrinol. Metab.* **102**, 1051-1058, doi:10.1210/jc.2016-3402 (2017).

172 Swerdlow, A. J. *et al.* Risk of Meningioma in European Patients Treated With Growth Hormone in Childhood: Results From the SAGhE Cohort. *J. Clin. Endocrinol. Metab.* **104**, 658-664, doi:10.1210/jc.2018-01133 (2019).

173 Swerdlow, A. J. *et al.* Cancer Risks in Patients Treated With Growth Hormone in Childhood: The SAGhE European Cohort Study. *J. Clin. Endocrinol. Metab.* **102**, 1661-1672, doi:10.1210/jc.2016-2046 (2017).

174 Chen, J. *et al.* Fertility issues in hypopituitarism. *Rev. Endocr. Metab. Disord.*, doi:10.1007/s11154-023-09863-9 (2023).

175 Vila, G. & Fleseriu, M. Fertility and Pregnancy in Women With Hypopituitarism: A Systematic Literature Review. *J. Clin. Endocrinol. Metab.* **105**, doi:10.1210/clinem/dgz112 (2020).

176 Morris, G. C., Lloyd-Evans, E. & Cahill, D. J. Induction of spermatogenesis in men with hypogonadotropic hypogonadism. *J. Assist. Reprod. Genet.* **38**, 803-807, doi:10.1007/s10815-020-02058-0 (2021).

177 Barrio, R., de Luis, D., Alonso, M., Lamas, A. & Moreno, J. C. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. *Fertil. Steril.* **71**, 244-248, doi:10.1016/s0015-0282(98)00450-6 (1999).

178 Hall, R., Manski-Nankervis, J., Goni, N., Davies, M. C. & Conway, G. S. Fertility outcomes in women with hypopituitarism. *Clin. Endocrinol. (Oxf.)* **65**, 71-74, doi:10.1111/j.1365-2265.2006.02550.x (2006).

179 Hoffmann, A., Adelmann, S., Lohle, K., Claviez, A. & Muller, H. L. Pediatric prolactinoma: initial presentation, treatment, and long-term prognosis. *Eur. J. Pediatr.* **177**, 125-132, doi:10.1007/s00431-017-3042-5 (2018).

180 Colao, A. *et al.* Prolactinomas in children and adolescents. Clinical presentation and long-term follow-up. *J. Clin. Endocrinol. Metab.* **83**, 2777-2780, doi:10.1210/jcem.83.8.5001 (1998).

181 Fideleff, H. L., Boquete, H. R., Suarez, M. G. & Azaretzky, M. Prolactinoma in children and adolescents. *Horm. Res.* **72**, 197-205, doi:10.1159/000236081 (2009).

182 Arya, V. B. *et al.* Prolactinoma in childhood and adolescence-Tumour size at presentation predicts management strategy: Single centre series and a systematic review and meta-analysis. *Clin. Endocrinol. (Oxf.)* **94**, 413-423, doi:10.1111/cen.14394 (2021).

183 Kunwar, S. & Wilson, C. B. Pediatric pituitary adenomas. *J. Clin. Endocrinol. Metab.* **84**, 4385-4389, doi:10.1210/jcem.84.12.6240 (1999).

184 Acharya, S. V. *et al.* Clinical profile and long term follow up of children and adolescents with prolactinomas. *Pituitary* **12**, 186-189, doi:10.1007/s11102-008-0149-8 (2009).

185 Cannavo, S. *et al.* Clinical presentation and outcome of pituitary adenomas in teenagers. *Clin. Endocrinol. (Oxf.)* **58**, 519-527 (2003).

186 Breil, T. *et al.* Clinical Features and Response to Treatment of Prolactinomas in Children and Adolescents: A Retrospective Single-Centre Analysis and Review of the Literature. *Horm. Res. Paediatr.* **89**, 157-165, doi:10.1159/000486280 (2018).

187 Alikasifoglu, A., Celik, N. B., Ozon, Z. A., Gonc, E. N. & Kandemir, N. Management of prolactinomas in children and adolescents; which factors define the response to treatment? *Pituitary*, doi:10.1007/s11102-021-01184-x (2021).

188 Sonigo, C. *et al.* Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. *J. Clin. Invest.* **122**, 3791-3795, doi:10.1172/JCI63937 (2012).

189 Eren, E. *et al.* Clinical and Laboratory Characteristics of Hyperprolactinemia in Children and Adolescents: National Survey. *J. Clin. Res. Pediatr. Endocrinol.* **11**, 149-156, doi:10.4274/jcrpe.galenos.2018.2018.0206 (2019).

190 Casanueva, F. F. *et al.* Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin. Endocrinol. (Oxf.)* **65**, 265-273, doi:10.1111/j.1365-2265.2006.02562.x (2006).

191 Vilar, L. *et al.* Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. *J. Endocrinol. Invest.* **31**, 436-444 (2008).

192 Kinoshita, Y. *et al.* Pituitary adenomas in childhood and adolescence with a focus on intratumoral hemorrhage. *Pituitary* **17**, 1-6, doi:10.1007/s11102-012-0456-y (2014).

193 Petersenn, S. *et al.* Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. *Nat. Rev. Endocrinol.*, doi:10.1038/s41574-023-00886-5 (2023).

194 Richmond, I. L. & Wilson, C. B. Pituitary adenomas in childhood and adolescence. *J. Neurosurg.* **49**, 163-168, doi:10.3171/jns.1978.49.2.0163 (1978).

195 Melmed, S. *et al.* Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **96**, 273-288, doi:10.1210/jc.2010-1692 (2011).

196 Aitkenhead, H. & Heales, S. J. Establishment of paediatric age-related reference intervals for serum prolactin to aid in the diagnosis of neurometabolic conditions affecting dopamine metabolism. *Ann. Clin. Biochem.* **50**, 156-158, doi:10.1258/acb.2012.012080 (2013).

197 Ross, R. J. *et al.* The relationship between serum prolactin and immunocytochemical staining for prolactin in patients with pituitary macroadenomas. *Clin. Endocrinol. (Oxf.)* **23**, 227-235 (1985).

198 Karavitaki, N. *et al.* Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin. Endocrinol. (Oxf.)* **65**, 524-529 (2006).

199 Korevaar, T., Wass, J. A., Grossman, A. B. & Karavitaki, N. Disconnection hyperprolactinaemia in nonadenomatous sellar/parasellar lesions practically never exceeds 2000 mU/l. *Clin. Endocrinol. (Oxf.)* **76**, 602-603, doi:10.1111/j.1365-2265.2011.04226.x (2012).

200 Sharma, L. K., Sharma, N., Gadpayle, A. K. & Dutta, D. Prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism. *Eur. J. Intern. Med.* **35**, 106-110, doi:10.1016/j.ejim.2016.07.012 (2016).

201 Honbo, K. S., van Herle, A. J. & Kellett, K. A. Serum prolactin levels in untreated primary hypothyroidism. *Am. J. Med.* **64**, 782-787 (1978).

202 Keye, W. R., Yuen, B. H., Knopf, R. F. & Jaffe, R. B. Amenorrhea, hyperprolactinemia and pituitary enlargement secondary to primary hypothyroidism. Successful treatment with thyroid replacement. *Obstet. Gynecol.* **48**, 697-702 (1976).

203 Ahmed, M., Banna, M., Sakati, N. & Woodhouse, N. Pituitary gland enlargement in primary hypothyroidism: a report of 5 cases with follow-up data. *Horm. Res.* **32**, 188-192, doi:10.1159/000181287 (1989).

204 Molitch, M. E. Pathologic hyperprolactinemia. *Endocrinol. Metab. Clin. North Am.* **21**, 877-901 (1992).

205 Sievertsen, G. D., Lim, V. S., Nakawatase, C. & Frohman, L. A. Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. *J. Clin. Endocrinol. Metab.* **50**, 846-852, doi:10.1210/jcem-50-5-846 (1980).

206 Lim, V. S., Kathpalia, S. C. & Frohman, L. A. Hyperprolactinemia and impaired pituitary response to suppression and stimulation in chronic renal failure: reversal after transplantation. *J. Clin. Endocrinol. Metab.* **48**, 101-107, doi:10.1210/jcem-48-1-101 (1979).

207 Yavuz, D., Topcu, G., Ozener, C., Akalin, S. & Sirikci, O. Macroprolactin does not contribute to elevated levels of prolactin in patients on renal replacement therapy. *Clin. Endocrinol. (Oxf.)* **63**, 520-524, doi:10.1111/j.1365-2265.2005.02375.x (2005).

208 Cowden, E. A., Ratcliffe, W. A., Ratcliffe, J. G., Dobbie, J. W. & Kennedy, A. C. Hyperprolactinaemia in renal disease. *Clin. Endocrinol. (Oxf.)* **9**, 241-248 (1978).

209 Hou, S. H., Grossman, S. & Molitch, M. E. Hyperprolactinemia in patients with renal insufficiency and chronic renal failure requiring hemodialysis or chronic ambulatory peritoneal dialysis. *Am. J. Kidney Dis.* **6**, 245-249 (1985).

210 Opladen, T. *et al.* Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH(4)) deficiencies. *Orphanet J. Rare Dis.* **15**, 126, doi:10.1186/s13023-020-01379-8 (2020).

211 Vitturi, N. *et al.* High prolactin levels in dihydropteridine reductase deficiency: A sign of therapy failure or additional pathology? *JIMD Rep* **61**, 48-51, doi:10.1002/jmd2.12236 (2021).

212 Soto-Pedre, E., Newey, P. J., Bevan, J. S., Greig, N. & Leese, G. P. The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland: the Prolactin Epidemiology, Audit and Research Study (PROLEARS). *Clin. Endocrinol. (Oxf.)* **86**, 60-67, doi:10.1111/cen.13156 (2017).

213 Torre, D. L. & Falorni, A. Pharmacological causes of hyperprolactinemia. *Ther. Clin. Risk Manag.* **3**, 929-951 (2007).

214 Rosenbloom, A. L. Hyperprolactinemia with antipsychotic drugs in children and adolescents. *Int. J. Pediatr. Endocrinol.* **2010**, 159402, doi:10.1155/2010/159402 (2010).

215 Jerrell, J. M., Bacon, J., Burgis, J. T. & Menon, S. Hyperprolactinemia-related adverse events associated with antipsychotic treatment in children and adolescents. *J. Adolesc. Health* **45**, 70-76, doi:10.1016/j.jadohealth.2008.11.010 (2009).

216 Rosenbloom, A. L. Correction: Hyperprolactinemia with antipsychotic drugs in children and adolescents. *Int. J. Pediatr. Endocrinol.* **2013**, 13, doi:10.1186/1687-9856-2013-13 (2013).

217 Donadio, F. *et al.* Patients with macroprolactinaemia: clinical and radiological features. *Eur. J. Clin. Invest.* **37**, 552-557, doi:10.1111/j.1365-2362.2007.01823.x (2007).

218 McKenna, T. J. Should macroprolactin be measured in all hyperprolactinaemic sera? *Clin. Endocrinol. (Oxf.)* **71**, 466-469, doi:10.1111/j.1365-2265.2009.03577.x (2009).

219 Hattori, N. Macroprolactinemia: a new cause of hyperprolactinemia. *J. Pharmacol. Sci.* **92**, 171-177 (2003).

220 Chahal, J. & Schlechte, J. Hyperprolactinemia. *Pituitary* **11**, 141-146, doi:10.1007/s11102-008-0107-5 (2008).

221 Glezer, A. *et al.* Human macroprolactin displays low biological activity via its homologous receptor in a new sensitive bioassay. *J. Clin. Endocrinol. Metab.* **91**, 1048-1055, doi:10.1210/jc.2005-1831 (2006).

222 Gibney, J., Smith, T. P. & McKenna, T. J. The impact on clinical practice of routine screening for macroprolactin. *J. Clin. Endocrinol. Metab.* **90**, 3927-3932, doi:10.1210/jc.2004-2234 (2005).

223 Fideleff, H. L. *et al.* Macroprolactinemia in childhood and adolescence: a cause of asymptomatic hyperprolactinemia. *Horm. Res.* **53**, 16-19, doi:23507 (2000).

224 Tutunculer, F., Darendeliler, F., Aygun, M. & Hekim, N. Macroprolactinemia in childhood and adolescence: a cause of hyperprolactinemia. *Turk. J. Pediatr.* **48**, 143-147 (2006).

225 St-Jean, E., Blain, F. & Comtois, R. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. *Clin. Endocrinol. (Oxf.)* **44**, 305-309 (1996).

226 do Carmo Dias Gontijo, M., de Souza Vasconcellos, L. & Ribeiro-Oliveira, A., Jr. Hook effect and linear range in prolactin assays: distinct confounding entities. *Pituitary* **19**, 458-459, doi:10.1007/s11102-014-0632-3 (2016).

227 Barkan, A. L. & Chandler, W. F. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. *Neurosurgery* **42**, 913-915; discussion 915-916 (1998).

228 Petakov, M. S. *et al.* Pituitary adenomas secreting large amounts of prolactin may give false low values in immunoradiometric assays. The hook effect. *J. Endocrinol. Invest.* **21**, 184-188, doi:10.1007/BF03347299 (1998).

229 Boesten, L. S. M., Krabbe, J. G. & de Rijke, Y. B. The high dose hook effect in prolactinomas; following the guidelines? *Ned Tijdschr Klin Chem Labgeneesk* **40**, 230-233 (2015).

230 Webster, J. *et al.* Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentre study. European Multicentre Cabergoline Dose-finding Study Group. *Clin. Endocrinol. (Oxf.)* **37**, 534-541 (1992).

231 Colao, A. *et al.* Macroprolactinoma shrinkage during cabergoline treatment is greater in naive patients than in patients pretreated with other dopamine agonists: a prospective study in 110 patients. *J. Clin. Endocrinol. Metab.* **85**, 2247-2252, doi:10.1210/jcem.85.6.6657 (2000).

232 Berinder, K., Stackenas, I., Akre, O., Hirschberg, A. L. & Hulting, A. L. Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. *Clin. Endocrinol. (Oxf.)* **63**, 450-455, doi:10.1111/j.1365-2265.2005.02364.x (2005).

233 Webster, J. *et al.* A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *N. Engl. J. Med.* **331**, 904-909, doi:10.1056/NEJM199410063311403 (1994).

234 Catli, G. *et al.* Hyperprolactinemia in children: clinical features and long-term results. *J. Pediatr. Endocrinol. Metab.* **25**, 1123-1128, doi:10.1515/jpem-2012-0130 (2012).

235 Cuevas, J. L. *et al.* [Visual outcome in patients with macroprolactinoma treated with dopamine agonists]. *Rev. Med. Chil.* **141**, 687-694, doi:10.4067/S0034-98872013000600001 (2013).

236 Bulwer, C. *et al.* Cabergoline-related impulse control disorder in an adolescent with a giant prolactinoma. *Clin. Endocrinol. (Oxf.)* **86**, 862-864, doi:10.1111/cen.13339 (2017).

237 Lam, G., Mehta, V. & Zada, G. Spontaneous and medically induced cerebrospinal fluid leakage in the setting of pituitary adenomas: review of the literature. *Neurosurg. Focus* **32**, E2, doi:10.3171/2012.4.FOCUS1268 (2012).

238 Vilar, L. *et al.* Controversial issues in the management of hyperprolactinemia and prolactinomas - An overview by the Neuroendocrinology Department of the Brazilian Society of Endocrinology and Metabolism. *Arch. Endocrinol. Metab.* **62**, 236-263, doi:10.20945/2359-3997000000032 (2018).

239 Molitch, M. E., Drummond, J. & Korbonits, M. *Prolactinoma Management*, ENDOTEXT <https://www.ncbi.nlm.nih.gov/pubmed/25905397> (Access date:*30/09/2023*).

240 Maiter, D. Management of Dopamine Agonist-Resistant Prolactinoma. *Neuroendocrinology* **109**, 42-50, doi:10.1159/000495775 (2019).

241 Ono, M. *et al.* Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J. Clin. Endocrinol. Metab.* **93**, 4721-4727, doi:10.1210/jc.2007-2758 (2008).

242 Bulwer, C. *et al.* Managing rare, resistant, macro- and giant prolactinomas causing raised intracranial pressure in children: lessons learnt at a single centre. Horm Res Paediatr. 2013;80 Suppl 1:165..

243 Ono, M. *et al.* Individualized high-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas. *J. Clin. Endocrinol. Metab.* **95**, 2672-2679, doi:10.1210/jc.2009-2605 (2010).

244 Vroonen, L. *et al.* Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients. *Eur. J. Endocrinol.* **167**, 651-662, doi:10.1530/EJE-12-0236 (2012).

245 de Castro, L. F. *et al.* Beneficial Effects of High Doses of Cabergoline in the Treatment of Giant Prolactinoma Resistant to Dopamine Agonists: A Case Report with a 21-Year Follow-Up. *Horm. Res. Paediatr.* **89**, 63-70, doi:10.1159/000479511 (2018).

246 Brichta, C. M., Wurm, M., Krebs, A., Schwab, K. O. & van der Werf-Grohmann, N. Start low, go slowly - mental abnormalities in young prolactinoma patients under cabergoline therapy. *J. Pediatr. Endocrinol. Metab.* **32**, 969-977, doi:10.1515/jpem-2018-0475 (2019).

247 Eisenhauer, E. A. *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* **45**, 228-247, doi:10.1016/j.ejca.2008.10.026 (2009).

248 Spinks, J. J. & Ryan, F. J. Cabergoline resistance in pediatric prolactinomas. *J. Pediatr. Hematol. Oncol.* **31**, 377-379, doi:10.1097/MPH.0b013e31819b71eb (2009).

249 Huang, C., Ezzat, S., Asa, S. L. & Hamilton, J. Dopaminergic resistant prolactinomas in the peripubertal population. *J. Pediatr. Endocrinol. Metab.* **19**, 951-953, doi:10.1515/jpem.2006.19.7.951 (2006).

250 Kreutzer, J., Vance, M. L., Lopes, M. B. & Laws, E. R. Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J. Clin. Endocrinol. Metab.* **86**, 4072-4077, doi:10.1210/jcem.86.9.7819 (2001).

251 Primeau, V., Raftopoulos, C. & Maiter, D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. *Eur. J. Endocrinol.* **166**, 779-786, doi:10.1530/EJE-11-1000 (2012).

252 Qu, X. *et al.* Surgical outcomes and prognostic factors of transsphenoidal surgery for prolactinoma in men: a single-center experience with 87 consecutive cases. *Eur. J. Endocrinol.* **164**, 499-504, doi:10.1530/EJE-10-0961 (2011).

253 Akin, S. *et al.* Reasons and results of endoscopic surgery for prolactinomas: 142 surgical cases. *Acta Neurochir. (Wien.)* **158**, 933-942, doi:10.1007/s00701-016-2762-z (2016).

254 Babey, M., Sahli, R., Vajtai, I., Andres, R. H. & Seiler, R. W. Pituitary surgery for small prolactinomas as an alternative to treatment with dopamine agonists. *Pituitary* **14**, 222-230, doi:10.1007/s11102-010-0283-y (2011).

255 Kreutzer, J. *et al.* Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. *Eur. J. Endocrinol.* **158**, 11-18, doi:10.1530/EJE-07-0248 (2008).

256 Abe, T. & Ludecke, D. K. Transnasal surgery for prolactin-secreting pituitary adenomas in childhood and adolescence. *Surg. Neurol.* **57**, 369-378; discussion 378-369 (2002).

257 Cozzi, R. *et al.* Italian Association of Clinical Endocrinologists (AME) and International Chapter of Clinical Endocrinology (ICCE). Position statement for clinical practice: prolactin-secreting tumors. *Eur. J. Endocrinol.* **186**, P1-P33, doi:10.1530/EJE-21-0977 (2022).

258 Yang, A. *et al.* Clinical, Hormonal, and Neuroradiological Characteristics and Therapeutic Outcomes of Prolactinomas in Children and Adolescents at a Single Center. *Front. Endocrinol. (Lausanne)* **11**, 527, doi:10.3389/fendo.2020.00527 (2020).

259 Zamanipoor Najafabadi, A. H. *et al.* Surgery as a Viable Alternative First-Line Treatment for Prolactinoma Patients. A Systematic Review and Meta-Analysis. *J. Clin. Endocrinol. Metab.* **105**, doi:10.1210/clinem/dgz144 (2020).

260 Trifiro, G. *et al.* Risk of cardiac valve regurgitation with dopamine agonist use in Parkinson's disease and hyperprolactinaemia: a multi-country, nested case-control study. *Drug Saf.* **35**, 159-171, doi:10.2165/11594940-000000000-00000 (2012).

261 Stiles, C. E., Tetteh-Wayoe, E. T., Bestwick, J., Steeds, R. P. & Drake, W. M. A meta-analysis of the prevalence of cardiac valvulopathy in hyperprolactinemic patients treated with Cabergoline. *J. Clin. Endocrinol. Metab.* **104**, 523-538, doi:10.1210/jc.2018-01071 (2019).

262 Stiles, C. E. *et al.* Incidence of Cabergoline-Associated Valvulopathy in Primary Care Patients With Prolactinoma Using Hard Cardiac Endpoints. *J. Clin. Endocrinol. Metab.* **106**, e711-e720, doi:10.1210/clinem/dgaa882 (2021).

263 Zanettini, R. *et al.* Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N. Engl. J. Med.* **356**, 39-46, doi:10.1056/NEJMoa054830 (2007).

264 Caputo, C., Prior, D. & Inder, W. J. The need for annual echocardiography to detect cabergoline-associated valvulopathy in patients with prolactinoma: a systematic review and additional clinical data. *Lancet Diabetes Endocrinol.* **3**, 906-913, doi:10.1016/S2213-8587(14)70212-8 (2015).

265 Stiles, C. E., Steeds, R. P. & Drake, W. M. Monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia. *Ann. Endocrinol. (Paris)*, doi:10.1016/j.ando.2020.02.007 (2020).

266 Steeds, R. *et al.* Echocardiography and monitoring patients receiving dopamine agonist therapy for hyperprolactinaemia: A joint position statement of the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology. *Clin. Endocrinol. (Oxf.)* **90**, 662-669, doi:10.1111/cen.13940 (2019).

267 Raverot, G. *et al.* Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a French multicenter experience. *J. Clin. Endocrinol. Metab.* **95**, 4592-4599, doi:10.1210/jc.2010-0644 (2010).

268 Kaltsas, G. A., Nomikos, P., Kontogeorgos, G., Buchfelder, M. & Grossman, A. B. Clinical review: Diagnosis and management of pituitary carcinomas. *J. Clin. Endocrinol. Metab.* **90**, 3089-3099, doi:10.1210/jc.2004-2231 (2005).

269 Kars, M., Roelfsema, F., Romijn, J. A. & Pereira, A. M. Malignant prolactinoma: case report and review of the literature. *Eur. J. Endocrinol.* **155**, 523-534, doi:10.1530/eje.1.02268 (2006).

270 Popadic, A., Witzmann, A., Buchfelder, M., Eiter, H. & Komminoth, P. Malignant prolactinoma: case report and review of the literature. *Surg. Neurol.* **51**, 47-54; discussion 54-45 (1999).

271 Lim, S., Shahinian, H., Maya, M. M., Yong, W. & Heaney, A. P. Temozolomide: a novel treatment for pituitary carcinoma. *Lancet Oncol.* **7**, 518-520, doi:10.1016/S1470-2045(06)70728-8 (2006).

272 McCormack, A. I. *et al.* Low O6-methylguanine-DNA methyltransferase (MGMT) expression and response to temozolomide in aggressive pituitary tumours. *Clin. Endocrinol. (Oxf.)* **71**, 226-233, doi:10.1111/j.1365-2265.2008.03487.x (2009).

273 Hagen, C., Schroeder, H. D., Hansen, S., Hagen, C. & Andersen, M. Temozolomide treatment of a pituitary carcinoma and two pituitary macroadenomas resistant to conventional therapy. *Eur. J. Endocrinol.* **161**, 631-637, doi:10.1530/EJE-09-0389 (2009).

274 Kovacs, K. *et al.* Temozolomide therapy in a man with an aggressive prolactin-secreting pituitary neoplasm: Morphological findings. *Hum. Pathol.* **38**, 185-189, doi:10.1016/j.humpath.2006.07.014 (2007).

275 Bush, Z. M. *et al.* Temozolomide treatment for aggressive pituitary tumors: correlation of clinical outcome with O(6)-methylguanine methyltransferase (MGMT) promoter methylation and expression. *J. Clin. Endocrinol. Metab.* **95**, E280-290, doi:10.1210/jc.2010-0441 (2010).

276 McCormack, A. *et al.* Treatment of aggressive pituitary tumours and carcinomas: results of a European Society of Endocrinology (ESE) survey 2016. *Eur. J. Endocrinol.* **178**, 265-276, doi:10.1530/EJE-17-0933 (2018).

277 Holthouse, D. J., Robbins, P. D., Kahler, R., Knuckey, N. & Pullan, P. Corticotroph pituitary carcinoma: case report and literature review. *Endocr. Pathol.* **12**, 329-341, doi:10.1385/ep:12:3:329 (2001).

278 Guzel, A. *et al.* Pituitary carcinoma presenting with multiple metastases: case report. *J. Child Neurol.* **23**, 1467-1471, doi:10.1177/0883073808319078 (2008).

279 Graf, C. J., Blinderman, E. E. & Terplan, K. L. Pituitary carcinoma in a child with distant metastases. *J. Neurosurg.* **19**, 254-259, doi:10.3171/jns.1962.19.3.0254 (1962).

280 Kovacs, G. L. *et al.* ACTH-secreting Crooke cell carcinoma of the pituitary. *Eur. J. Clin. Invest.* **43**, 20-26, doi:10.1111/eci.12010 (2013).

281 Bengtsson, D. *et al.* Long-term outcome and MGMT as a predictive marker in 24 patients with atypical pituitary adenomas and pituitary carcinomas given treatment with temozolomide. *J. Clin. Endocrinol. Metab.* **100**, 1689-1698, doi:10.1210/jc.2014-4350 (2015).

282 Colao, A. *et al.* Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N. Engl. J. Med.* **349**, 2023-2033, doi:10.1056/NEJMoa022657 (2003).

283 Barber, T. M. *et al.* Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma. *Clin. Endocrinol. (Oxf.)* **75**, 819-824, doi:10.1111/j.1365-2265.2011.04136.x (2011).

284 Dekkers, O. M. *et al.* Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* **95**, 43-51, doi:10.1210/jc.2009-1238 (2010).

285 Hu, J., Zheng, X., Zhang, W. & Yang, H. Current drug withdrawal strategy in prolactinoma patients treated with cabergoline: a systematic review and meta-analysis. *Pituitary* **18**, 745-751, doi:10.1007/s11102-014-0617-2 (2015).

286 Colao, A. *et al.* Prolactinomas in adolescents: persistent bone loss after 2 years of prolactin normalization. *Clin. Endocrinol. (Oxf.)* **52**, 319-327 (2000).

287 Newell-Price, J., Bertagna, X., Grossman, A. B. & Nieman, L. K. Cushing's syndrome. *Lancet* **367**, 1605-1617, doi:10.1016/S0140-6736(06)68699-6 (2006).

288 Magiakou, M. A. & Chrousos, G. P. Cushing's syndrome in children and adolescents: current diagnostic and therapeutic strategies. *J. Endocrinol. Invest.* **25**, 181-194 (2002).

289 Weber, A. *et al.* Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. *Clin. Endocrinol. (Oxf.)* **43**, 19-28 (1995).

290 Verges, B. *et al.* Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *J. Clin. Endocrinol. Metab.* **87**, 457-465, doi:10.1210/jcem.87.2.8145 (2002).

291 Storr, H. L. *et al.* Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. *Eur. J. Endocrinol.* **164**, 667-674, doi:10.1530/EJE-10-1120 (2011).

292 Storr, H. L. *et al.* Prepubertal Cushing's disease is more common in males, but there is no increase in severity at diagnosis. *J. Clin. Endocrinol. Metab.* **89**, 3818-3820, doi:10.1210/jc.2003-031531 (2004).

293 Magiakou, M. A. *et al.* Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N. Engl. J. Med.* **331**, 629-636, doi:10.1056/NEJM199409083311002 (1994).

294 Libuit, L. G. *et al.* A gender-dependent analysis of Cushing's disease in childhood: pre- and postoperative follow-up. *Clin. Endocrinol. (Oxf.)* **83**, 72-77, doi:10.1111/cen.12644 (2015).

295 Pecori Giraldi, F., Moro, M., Cavagnini, F. & Study Group on the Hypothalamo-Pituitary-Adrenal Axis of the Italian Society of, E. Gender-related differences in the presentation and course of Cushing's disease. *J. Clin. Endocrinol. Metab.* **88**, 1554-1558, doi:10.1210/jc.2002-021518 (2003).

296 Lonser, R. R. *et al.* Outcome of surgical treatment of 200 children with Cushing's disease. *J. Clin. Endocrinol. Metab.* **98**, 892-901, doi:10.1210/jc.2012-3604 (2013).

297 Fahlbusch, R. *et al.* Neurosurgical management of Cushing's disease in children in *Frontiers in pediatric endocrinology* 68-72 (Oxford: Blackwell scientific publications, 1994).

298 Storr, H. L. *et al.* Factors influencing cure by transsphenoidal selective adenomectomy in paediatric Cushing's disease. *Eur. J. Endocrinol.* **152**, 825-833, doi:10.1530/eje.1.01921 (2005).

299 Khadilkar, V. V., Khadilkar, A. V. & Navrange, J. R. Cushing's disease in an 11-month-old child. *Indian Pediatr.* **41**, 274-276 (2004).

300 Damiani, D. *et al.* Pituitary macroadenoma and Cushing's disease in pediatric patients: patient report and review of the literature. *J. Pediatr. Endocrinol. Metab.* **11**, 665-669 (1998).

301 Storr, H. L. & Savage, M. O. MANAGEMENT OF ENDOCRINE DISEASE: Paediatric Cushing's disease. *Eur. J. Endocrinol.* **173**, R35-45, doi:10.1530/EJE-15-0013 (2015).

302 Shah, N. S. *et al.* Cushing disease in children and adolescents: twenty years' experience in a tertiary care center in India. *Endocr. Pract.* **17**, 369-376, doi:10.4158/EP10143.OR (2011).

303 Shah, N. S. & Lila, A. Childhood Cushing disease: a challenge in diagnosis and management. *Horm. Res. Paediatr.* **76 Suppl 1**, 65-70, doi:10.1159/000329173 (2011).

304 Shah, S., Waldman, A. D. & Mehta, A. Advances in pituitary imaging technology and future prospects. *Best Pract. Res. Clin. Endocrinol. Metab.* **26**, 35-46, doi:10.1016/j.beem.2011.08.003 (2012).

305 Wedrychowicz, A. *et al.* Cushing disease in children and adolescents - assessment of the clinical course, diagnostic process, and effects of the treatment - experience from a single paediatric centre. *Pediatr. Endocrinol. Diabetes Metab.* **25**, 127-143, doi:10.5114/pedm.2019.87179 (2019).

306 Nieman, L. K. *et al.* The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab.* **93**, 1526-1540, doi:10.1210/jc.2008-0125 (2008).

307 Fleseriu, M. *et al.* Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol.* **9**, 847-875, doi:10.1016/S2213-8587(21)00235-7 (2021).

308 Greening, J. E. *et al.* Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. *J. Endocrinol. Invest.* **29**, 885-887, doi:10.1007/BF03349191 (2006).

309 Newell-Price, J., Jorgensen, J. O. & Grossman, A. The diagnosis and differential diagnosis of Cushing's syndrome. *Horm. Res.* **51 Suppl 3**, 81-94, doi:53167 (1999).

310 Arnaldi, G. *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J. Clin. Endocrinol. Metab.* **88**, 5593-5602, doi:10.1210/jc.2003-030871 (2003).

311 Batista, D. L., Riar, J., Keil, M. & Stratakis, C. A. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. *Pediatrics* **120**, e575-586, doi:10.1542/peds.2006-2402 (2007).

312 Carroll, P. V. *et al.* Successful treatment of childhood-onset Cushing's disease is associated with persistent reduction in growth hormone secretion. *Clin. Endocrinol. (Oxf.)* **60**, 169-174 (2004).

313 Savage, M. O. & Storr, H. L. Pediatric Cushing's disease: Management Issues. *Indian J. Endocrinol. Metab.* **16**, S171-175, doi:10.4103/2230-8210.104032 (2012).

314 Savage, M. O. & Storr, H. L. Fundamental principles of clinical and biochemical evaluation underlie the diagnosis and therapy of Cushing's syndrome. *J. Pediatr. Endocrinol. Metab.* **27**, 1029-1031, doi:10.1515/jpem-2014-0400 (2014).

315 Ferrigno, R. *et al.* Paediatric Cushing's disease: Epidemiology, pathogenesis, clinical management and outcome. *Rev. Endocr. Metab. Disord.* **22**, 817-835, doi:10.1007/s11154-021-09626-4 (2021).

316 Martinelli, C. E., Jr., Sader, S. L., Oliveira, E. B., Daneluzzi, J. C. & Moreira, A. C. Salivary cortisol for screening of Cushing's syndrome in children. *Clin. Endocrinol. (Oxf.)* **51**, 67-71 (1999).

317 Raff, H., Auchus, R. J., Findling, J. W. & Nieman, L. K. Urine free cortisol in the diagnosis of Cushing's syndrome: is it worth doing and, if so, how? *J. Clin. Endocrinol. Metab.* **100**, 395-397, doi:10.1210/jc.2014-3766 (2015).

318 Gafni, R. I., Papanicolaou, D. A. & Nieman, L. K. Nighttime salivary cortisol measurement as a simple, noninvasive, outpatient screening test for Cushing's syndrome in children and adolescents. *J. Pediatr.* **137**, 30-35, doi:10.1067/mpd.2000.106226 (2000).

319 Putignano, P., Dubini, A. & Cavagnini, F. Urinary free cortisol is unrelated to physiological changes in urine volume in healthy women. *Clin. Chem.* **46**, 879 (2000).

320 Ueland, G. A. *et al.* Bedtime Salivary Cortisol as a Screening Test for Cushing Syndrome in Children. *J. Endocr. Soc.* **5**, bvab033, doi:10.1210/jendso/bvab033 (2021).

321 Stratakis, C. A. Cushing syndrome in pediatrics. *Endocrinol. Metab. Clin. North Am.* **41**, 793-803, doi:10.1016/j.ecl.2012.08.002 (2012).

322 Esfahanian, F. & Kazemi, R. Overnight dexamethasone suppression test in the diagnosis of Cushing's disease. *Acta Med. Iran.* **48**, 222-225 (2010).

323 Biller, B. M. *et al.* Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J. Clin. Endocrinol. Metab.* **93**, 2454-2462, doi:10.1210/jc.2007-2734 (2008).

324 Dias, R. *et al.* The discriminatory value of the low-dose dexamethasone suppression test in the investigation of paediatric Cushing's syndrome. *Horm. Res.* **65**, 159-162, doi:10.1159/000091830 (2006).

325 Isidori, A. M. *et al.* Discriminatory value of the low-dose dexamethasone suppression test in establishing the diagnosis and differential diagnosis of Cushing's syndrome. *J. Clin. Endocrinol. Metab.* **88**, 5299-5306, doi:10.1210/jc.2003-030510 (2003).

326 Guemes, M. *et al.* Management of Cushing syndrome in children and adolescents: experience of a single tertiary centre. *Eur. J. Pediatr.* **175**, 967-976, doi:10.1007/s00431-016-2727-5 (2016).

327 Viru-Loza, M. A. & Quispe, A. V. Diagnostic Power of Bilateral Inferior Petrosal Sinus Sampling with Desmopressin in Paediatric Cushing's Disease. *J. Clin. Res. Pediatr. Endocrinol.* **14**, 334-338, doi:10.4274/jcrpe.galenos.2022.2022-12-9 (2022).

328 Zheng, X. *et al.* Diagnosis, Manifestations, Laboratory Investigations, and Prognosis in Pediatric and Adult Cushing's Disease in a Large Center in China. *Front. Endocrinol. (Lausanne)* **12**, 749246, doi:10.3389/fendo.2021.749246 (2021).

329 Turan, H. *et al.* Diagnostic Value of Bilateral Petrosal Sinus Sampling in Children with Cushing Disease: A Multi-center Study. *J. Clin. Res. Pediatr. Endocrinol.* **14**, 29-36, doi:10.4274/jcrpe.galenos.2021.2021.0152 (2022).

330 Oldfield, E. H. *et al.* Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N. Engl. J. Med.* **325**, 897-905, doi:10.1056/NEJM199109263251301 (1991).

331 Moszczynska, E. *et al.* The Effects of Sampling Lateralization on Bilateral Inferior Petrosal Sinus Sampling for Pediatric Cushing's Disease-A Single Endocrinology Centre Experience and Review of the Literature. *Front. Endocrinol. (Lausanne)* **12**, 650967, doi:10.3389/fendo.2021.650967 (2021).

332 Cavalcante, L. *et al.* High accuracy of bilateral and simultaneous petrosal sinus sampling with desmopressin for the differential diagnosis of pediatric ACTH-dependent Cushing's syndrome. *Pituitary* **23**, 507-514, doi:10.1007/s11102-020-01051-1 (2020).

333 Chen, S. *et al.* The effects of sampling lateralization on bilateral inferior petrosal sinus sampling and desmopressin stimulation test for pediatric Cushing's disease. *Endocrine* **63**, 582-591, doi:10.1007/s12020-018-1779-x (2019).

334 Lienhardt, A. *et al.* Relative contributions of inferior petrosal sinus sampling and pituitary imaging in the investigation of children and adolescents with ACTH-dependent Cushing's syndrome. *J. Clin. Endocrinol. Metab.* **86**, 5711-5714, doi:10.1210/jcem.86.12.8086 (2001).

335 Kaltsas, G. A. *et al.* A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. *J. Clin. Endocrinol. Metab.* **84**, 487-492, doi:10.1210/jcem.84.2.5437 (1999).

336 Batista, D. *et al.* An assessment of petrosal sinus sampling for localization of pituitary microadenomas in children with Cushing disease. *J. Clin. Endocrinol. Metab.* **91**, 221-224, doi:10.1210/jc.2005-1096 (2006).

337 Lefournier, V. *et al.* Accuracy of bilateral inferior petrosal or cavernous sinuses sampling in predicting the lateralization of Cushing's disease pituitary microadenoma: influence of catheter position and anatomy of venous drainage. *J. Clin. Endocrinol. Metab.* **88**, 196-203, doi:10.1210/jc.2002-020374 (2003).

338 Andereggen, L. *et al.* Influence of inferior petrosal sinus drainage symmetry on detection of adenomas in Cushing's syndrome. *J. Neuroradiol.* **48**, 10-15, doi:10.1016/j.neurad.2019.05.004 (2021).

339 Jarial, K. D. S. *et al.* Prolactin-adjusted ACTH Ratio in Predicting Lateralization of ACTH Source During Simultaneous Bilateral Inferior Petrosal Sinus Sampling in Patients with Cushing's Disease. *Indian J. Endocrinol. Metab.* **23**, 56-59, doi:10.4103/ijem.IJEM_486_18 (2019).

340 De Sousa, S. M. C., McCormack, A. I., McGrath, S. & Torpy, D. J. Prolactin correction for adequacy of petrosal sinus cannulation may diminish diagnostic accuracy in Cushing's disease. *Clin. Endocrinol. (Oxf.)* **87**, 515-522, doi:10.1111/cen.13401 (2017).

341 Linglart, A. & Visot, A. [Cushing's disease in children and adolescents]. *Neurochirurgie* **48**, 271-280 (2002).

342 Personnier, C. *et al.* Clinical features and treatment of pediatric somatotropinoma: case study of an aggressive tumor due to a new AIP mutation and extensive literature review. *Horm. Res. Paediatr.* **75**, 392-402, doi:10.1159/000327831 (2011).

343 Alexandraki, K. I. *et al.* Long-term remission and recurrence rates in Cushing's disease: predictive factors in a single-centre study. *Eur. J. Endocrinol.* **168**, 639-648, doi:10.1530/EJE-12-0921 (2013).

344 Acharya, S. V. *et al.* Radiotherapy in paediatric Cushing's disease: efficacy and long term follow up of pituitary function. *Pituitary* **13**, 293-297, doi:10.1007/s11102-010-0231-x (2010).

345 Howlett, T. A. *et al.* Megavoltage pituitary irradiation in the management of Cushing's disease and Nelson's syndrome: long-term follow-up. *Clin. Endocrinol. (Oxf.)* **31**, 309-323 (1989).

346 Sheehan, J. P., Xu, Z. & Lobo, M. J. External beam radiation therapy and stereotactic radiosurgery for pituitary adenomas. *Neurosurg. Clin. N. Am.* **23**, 571-586, doi:10.1016/j.nec.2012.06.011 (2012).

347 Groselj, U., Sikonja, J. & Battelino, T. Osilodrostat for Cushing disease and its role in pediatrics. *Horm. Res. Paediatr.*, doi:10.1159/000522054 (2022).

348 Guven, A., Baltacioglu, F., Dursun, F., Cebeci, A. N. & Kirmizibekmez, H. Remission with cabergoline in adolescent boys with Cushing's disease. *J. Clin. Res. Pediatr. Endocrinol.* **5**, 194-198, doi:10.4274/Jcrpe.1007 (2013).

349 Chan, L. F. *et al.* Use of intravenous etomidate to control acute psychosis induced by the hypercortisolaemia in severe paediatric Cushing's disease. *Horm. Res. Paediatr.* **75**, 441-446, doi:10.1159/000324419 (2011).

350 Greening, J. E. *et al.* Efficient short-term control of hypercortisolaemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm. Res.* **64**, 140-143, doi:10.1159/000088587 (2005).

351 McArthur, R. G., Hayles, A. B. & Salassa, R. M. Childhood Cushing disease: results of bilateral adrenalectomy. *J. Pediatr.* **95**, 214-219 (1979).

352 Barber, T. M. *et al.* Nelson's syndrome. *Eur. J. Endocrinol.* **163**, 495-507, doi:10.1530/EJE-10-0466 (2010).

353 Barber, T. M., Adams, E. & Wass, J. A. Nelson syndrome: definition and management. *Handb. Clin. Neurol.* **124**, 327-337, doi:10.1016/B978-0-444-59602-4.00022-8 (2014).

354 Reincke, M. *et al.* Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations. *Eur. J. Endocrinol.* **184**, P1-P16, doi:10.1530/EJE-20-1088 (2021).

355 Lebrethon, M. C. *et al.* Linear growth and final height after treatment for Cushing's disease in childhood. *J. Clin. Endocrinol. Metab.* **85**, 3262-3265, doi:10.1210/jcem.85.9.6817 (2000).

356 Dupuis, C. C. *et al.* Abnormal puberty in paediatric Cushing's disease: relationship with adrenal androgen, sex hormone binding globulin and gonadotrophin concentrations. *Clin. Endocrinol. (Oxf.)* **66**, 838-843, doi:10.1111/j.1365-2265.2007.02822.x (2007).

357 Hayles, A. B., Hahn, H. B., Jr., Sprague, R. G., Bahn, R. C. & Priestley, J. T. Hormone-secreting tumors of the adrenal cortex in children. *Pediatrics* **37**, 19-25 (1966).

358 Gourgari, E. *et al.* Post-operative growth is different in various forms of pediatric Cushing's syndrome. *Endocr. Relat. Cancer* **21**, L27-31, doi:10.1530/ERC-14-0405 (2014).

359 Magiakou, M. A., Mastorakos, G. & Chrousos, G. P. Final stature in patients with endogenous Cushing's syndrome. *J. Clin. Endocrinol. Metab.* **79**, 1082-1085, doi:10.1210/jcem.79.4.7962277 (1994).

360 Magiakou, M. A., Mastorakos, G., Gomez, M. T., Rose, S. R. & Chrousos, G. P. Suppressed spontaneous and stimulated growth hormone secretion in patients with Cushing's disease before and after surgical cure. *J. Clin. Endocrinol. Metab.* **78**, 131-137, doi:10.1210/jcem.78.1.7507118 (1994).

361 Acharya, S. V. *et al.* Bone age and factors affecting skeletal maturation at diagnosis of paediatric Cushing's disease. *Pituitary* **13**, 355-360, doi:10.1007/s11102-010-0246-3 (2010).

362 Peters, C. J. *et al.* Factors influencing skeletal maturation at diagnosis of paediatric Cushing's disease. *Horm. Res.* **68**, 231-235, doi:10.1159/000101336 (2007).

363 Hughes, N. R., Lissett, C. A. & Shalet, S. M. Growth hormone status following treatment for Cushing's syndrome. *Clin. Endocrinol. (Oxf.)* **51**, 61-66 (1999).

364 Davies, J. H. *et al.* Final adult height and body mass index after cure of paediatric Cushing's disease. *Clin. Endocrinol. (Oxf.)* **62**, 466-472, doi:10.1111/j.1365-2265.2005.02244.x (2005).

365 Boronat, M. *et al.* Combined treatment with GH and anastrozole in a pubertal boy with Cushing's disease and postsurgical GH deficiency. *Eur. J. Endocrinol.* **166**, 1101-1105, doi:10.1530/EJE-12-0036 (2012).

366 Leong, G. M. *et al.* Effects of child- and adolescent-onset endogenous Cushing syndrome on bone mass, body composition, and growth: a 7-year prospective study into young adulthood. *J. Bone Miner. Res.* **22**, 110-118, doi:10.1359/jbmr.061010 (2007).

367 Estrada, J. *et al.* The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N. Engl. J. Med.* **336**, 172-177, doi:10.1056/NEJM199701163360303 (1997).

368 Chan, L. F. *et al.* Long-term anterior pituitary function in patients with paediatric Cushing's disease treated with pituitary radiotherapy. *Eur. J. Endocrinol.* **156**, 477-482, doi:10.1530/EJE-06-0588 (2007).

369 Nicholl, R. M. *et al.* Acceleration of pubertal development following pituitary radiotherapy for Cushing's disease. *Clin. Oncol. (R. Coll. Radiol.)* **5**, 393-394 (1993).

370 Dorn, L. D. *et al.* Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. *Clin. Endocrinol. (Oxf.)* **43**, 433-442 (1995).

371 Dorn, L. D. *et al.* The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *J. Clin. Endocrinol. Metab.* **82**, 912-919, doi:10.1210/jcem.82.3.3834 (1997).

372 Merke, D. P. *et al.* Children experience cognitive decline despite reversal of brain atrophy one year after resolution of Cushing syndrome. *J. Clin. Endocrinol. Metab.* **90**, 2531-2536, doi:10.1210/jc.2004-2488 (2005).

373 Ragnarsson, O., Berglund, P., Eder, D. N. & Johannsson, G. Long-term cognitive impairments and attentional deficits in patients with Cushing's disease and cortisol-producing adrenal adenoma in remission. *J. Clin. Endocrinol. Metab.* **97**, E1640-1648, doi:10.1210/jc.2012-1945 (2012).

374 Hou, B. *et al.* Reversibility of impaired brain structures after transsphenoidal surgery in Cushing's disease: a longitudinal study based on an artificial intelligence-assisted tool. *J. Neurosurg.*, 1-10, doi:10.3171/2019.10.JNS191400 (2020).

375 Keil, M. F. *et al.* Quality of life in children and adolescents 1-year after cure of Cushing syndrome: a prospective study. *Clin. Endocrinol. (Oxf.)* **71**, 326-333, doi:10.1111/j.1365-2265.2008.03515.x (2009).

376 Batista, D. L., Oldfield, E. H., Keil, M. F. & Stratakis, C. A. Postoperative testing to predict recurrent Cushing disease in children. *J. Clin. Endocrinol. Metab.* **94**, 2757-2765, doi:10.1210/jc.2009-0302 (2009).

377 Leinung, M. C. *et al.* Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. *J. Clin. Endocrinol. Metab.* **80**, 2475-2479, doi:10.1210/jcem.80.8.7629245 (1995).

378 Kirschner, L. S. *et al.* Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nat. Genet.* **26**, 89-92, doi:10.1038/79238 (2000).

379 Srirangam Nadhamuni, V. *et al.* GHRH secretion from a pancreatic neuroendocrine tumor causing gigantism in a patient with MEN1 *EDM* **67**, doi:10.1530/EDM-20-0208 (2021).

380 Borson-Chazot, F. *et al.* Acromegaly induced by ectopic secretion of GHRH: a review 30 years after GHRH discovery. *Ann. Endocrinol. (Paris)* **73**, 497-502, doi:10.1016/j.ando.2012.09.004 (2012).

381 Burton, T., Le Nestour, E., Neary, M. & Ludlam, W. H. Incidence and prevalence of acromegaly in a large US health plan database. *Pituitary* **19**, 262-267, doi:10.1007/s11102-015-0701-2 (2016).

382 Daly, A. F. *et al.* High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J. Clin. Endocrinol. Metab.* **91**, 4769-4775, doi:10.1210/jc.2006-1668 (2006).

383 Fernandez, A., Karavitaki, N. & Wass, J. A. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin. Endocrinol. (Oxf.)* **72**, 377-382, doi:10.1111/j.1365-2265.2009.03667.x (2010).

384 Gruppetta, M., Mercieca, C. & Vassallo, J. Prevalence and incidence of pituitary adenomas: a population based study in Malta. *Pituitary* **16**, 545-553, doi:10.1007/s11102-012-0454-0 (2013).

385 Raappana, A., Koivukangas, J., Ebeling, T. & Pirila, T. Incidence of pituitary adenomas in Northern Finland in 1992-2007. *J. Clin. Endocrinol. Metab.* **95**, 4268-4275, doi:10.1210/jc.2010-0537 (2010).

386 Fontana, E. & Gaillard, R. [Epidemiology of pituitary adenoma: results of the first Swiss study]. *Rev. Med. Suisse* **5**, 2172-2174 (2009).

387 Agustsson, T. T. *et al.* The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. *Eur. J. Endocrinol.* **173**, 655-664, doi:10.1530/EJE-15-0189 (2015).

388 Al-Dahmani, K. *et al.* Sellar Masses: An Epidemiological Study. *Can. J. Neurol. Sci.* **43**, 291-297, doi:10.1017/cjn.2015.301 (2016).

389 Cazabat, L. *et al.* Germline AIP mutations in apparently sporadic pituitary adenomas: prevalence in a prospective single-center cohort of 443 patients. *J. Clin. Endocrinol. Metab.* **97**, E663-670, doi:10.1210/jc.2011-2291 (2012).

390 Mindermann, T. & Wilson, C. B. Pediatric pituitary adenomas. *Neurosurgery* **36**, 259-268; discussion 269 (1995).

391 Naves, L. A. *et al.* Aggressive tumor growth and clinical evolution in a patient with X-linked acro-gigantism syndrome. *Endocrine* **51**, 236-244, doi:10.1007/s12020-015-0804-6 (2016).

392 Katznelson, L. *et al.* Acromegaly: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **99**, 3933-3951, doi:10.1210/jc.2014-2700 (2014).

393 Ali, O., Banerjee, S., Kelly, D. F. & Lee, P. D. Management of type 2 diabetes mellitus associated with pituitary gigantism. *Pituitary* **10**, 359-364, doi:10.1007/s11102-007-0060-8 (2007).

394 Ciresi, A., Amato, M. C., Galluzzo, A. & Giordano, C. Complete biochemical control and pituitary adenoma disappearance in a child with gigantism: efficacy of octreotide therapy. *J. Endocrinol. Invest.* **34**, 162-163, doi:10.1007/BF03347049 (2011).

395 Colao, A. *et al.* Growth hormone excess with onset in adolescence: clinical appearance and long-term treatment outcome. *Clin. Endocrinol. (Oxf.)* **66**, 714-722, doi:10.1111/j.1365-2265.2007.02809.x (2007).

396 Goldenberg, N. *et al.* Treatment of pituitary gigantism with the growth hormone receptor antagonist pegvisomant. *J. Clin. Endocrinol. Metab.* **93**, 2953-2956, doi:10.1210/jc.2007-2283 (2008).

397 Kuzuya, T. *et al.* A case of pituitary gigantism who had two episodes of diabetic ketoacidosis followed by complete recovery of diabetes. *Endocrinol. Jpn.* **30**, 329-334 (1983).

398 Maheshwari, H. G. *et al.* Long-acting peptidomimergic control of gigantism caused by pituitary acidophilic stem cell adenoma. *J. Clin. Endocrinol. Metab.* **85**, 3409-3416, doi:10.1210/jcem.85.9.6824 (2000).

399 Moran, A. *et al.* Gigantism due to pituitary mammosomatotroph hyperplasia. *N. Engl. J. Med.* **323**, 322-327, doi:10.1056/NEJM199008023230507 (1990).

400 Narayanaswamy, V., Rettig, K. R. & Bhowmick, S. K. Excessive growth. *Clin. Pediatr. (Phila.)* **47**, 705-708, doi:10.1177/0009922807311740 (2008).

401 Nozieres, C. *et al.* Sporadic and genetic forms of paediatric somatotropinoma: a retrospective analysis of seven cases and a review of the literature. *Orphanet J. Rare Dis.* **6**, 67, doi:10.1186/1750-1172-6-67 (2011).

402 Otsuka, F. *et al.* Long-term effects of octreotide on pituitary gigantism: its analgesic action on cluster headache. *Endocr. J.* **51**, 449-452 (2004).

403 Rhee, N., Jeong, K., Yang, E. M. & Kim, C. J. Gigantism caused by growth hormone secreting pituitary adenoma. *Ann Pediatr Endocrinol Metab* **19**, 96-99, doi:10.6065/apem.2014.19.2.96 (2014).

404 Rix, M., Laurberg, P., Hoejberg, A. S. & Brock-Jacobsen, B. Pegvisomant therapy in pituitary gigantism: successful treatment in a 12-year-old girl. *Eur. J. Endocrinol.* **153**, 195-201, doi:10.1530/eje.1.01956 (2005).

405 Tourtelot, J. B. & Vesely, D. L. Pituitary tumor with gigantism, acromegaly and preclinical Cushing's disease diagnosed from the 10th row. *Am. J. Med. Sci.* **346**, 169-171, doi:10.1097/MAJ.0b013e3182831919 (2013).

406 Abe, T., Tara, L. A. & Ludecke, D. K. Growth hormone-secreting pituitary adenomas in childhood and adolescence: features and results of transnasal surgery. *Neurosurgery* **45**, 1-10 (1999).

407 Bergamaschi, S. *et al.* Eight-year follow-up of a child with a GH/prolactin-secreting adenoma: efficacy of pegvisomant therapy. *Horm. Res. Paediatr.* **73**, 74-79, doi:10.1159/000271919 (2010).

408 Bowden, S. A., Sotos, J. F., Stratakis, C. A. & Weil, R. J. Successful treatment of an invasive growth hormone-secreting pituitary macroadenoma in an 8-year-old boy. *J. Pediatr. Endocrinol. Metab.* **20**, 643-647 (2007).

409 Ritzen, E. M., Wettrell, G., Davies, G. & Grant, D. B. Management of pituitary gigantism. The role of bromocriptine and radiotherapy. *Acta Paediatr. Scand.* **74**, 807-814 (1985).

410 Prezio, J. A., Griffin, J. E. & O'Brien, J. J. Acromegalic gigantism. The Buffalo giant. *Am. J. Med.* **31**, 966-976 (1961).

411 Beckers, A. *et al.* X-linked acrogigantism syndrome: clinical profile and therapeutic responses. *Endocr. Relat. Cancer* **22**, 353-367, doi:10.1530/ERC-15-0038 (2015).

412 Daly, A. F. *et al.* GHRH excess and blockade in X-LAG syndrome. *Endocr. Relat. Cancer* **23**, 161-170, doi:10.1530/ERC-15-0478 (2016).

413 Gordon, R. J. *et al.* Childhood acromegaly due to X-linked acrogigantism: long term follow-up. *Pituitary* **19**, 560-564, doi:10.1007/s11102-016-0743-0 (2016).

414 Clayton, K. L. *et al.* Loss of the normal relationships between growth hormone, growth hormone-binding protein and insulin-like growth factor-I in adolescents with insulin-dependent diabetes mellitus. *Clin. Endocrinol. (Oxf.)* **41**, 517-524 (1994).

415 Weber, M. M., Auernhammer, C. J., Lee, P. D., Engelhardt, D. & Zachoval, R. Insulin-like growth factors and insulin-like growth factor binding proteins in adult patients with severe liver disease before and after orthotopic liver transplantation. *Horm. Res.* **57**, 105-112, doi:57960 (2002).

416 Haspolat, K. *et al.* Relationships between leptin, insulin, IGF-1 and IGFBP-3 in children with energy malnutrition. *Clin. Biochem.* **40**, 201-205, doi:10.1016/j.clinbiochem.2006.11.008 (2007).

417 Svan, H., Ritzen, E. M., Hall, K. & Johansson, L. Estrogen treatment of tall girls: dose dependency of effects on subsequent growth and IGF-I levels in blood. *Acta Paediatr. Scand.* **80**, 328-332 (1991).

418 Pokrajac, A. *et al.* Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. *Clin. Endocrinol. (Oxf.)* **67**, 65-70, doi:10.1111/j.1365-2265.2007.02836.x (2007).

419 Katznelson, L. *et al.* American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Acromegaly--2011 update: executive summary. *Endocr. Pract.* **17**, 636-646 (2011).

420 Fleseriu, M. *et al.* A Pituitary Society update to acromegaly management guidelines. *Pituitary* **24**, 1-13, doi:10.1007/s11102-020-01091-7 (2021).

421 Freda, P. U., Reyes, C. M., Nuruzzaman, A. T., Sundeen, R. E. & Bruce, J. N. Basal and glucose-suppressed GH levels less than 1 microg/L in newly diagnosed acromegaly. *Pituitary* **6**, 175-180 (2003).

422 Schilbach, K. *et al.* Determinants of the growth hormone nadir during oral glucose tolerance test in adults. *Eur. J. Endocrinol.* **181**, 55-67, doi:10.1530/EJE-19-0139 (2019).

423 Misra, M., Cord, J., Prabhakaran, R., Miller, K. K. & Klibanski, A. Growth hormone suppression after an oral glucose load in children. *J. Clin. Endocrinol. Metab.* **92**, 4623-4629, doi:10.1210/jc.2007-1244 (2007).

424 Holl, R. W. *et al.* Suppression of growth hormone by oral glucose in the evaluation of tall stature. *Horm. Res.* **51**, 20-24, doi:23308 (1999).

425 Dimaraki, E. V., Jaffe, C. A., DeMott-Friberg, R., Chandler, W. F. & Barkan, A. L. Acromegaly with apparently normal GH secretion: implications for diagnosis and follow-up. *J. Clin. Endocrinol. Metab.* **87**, 3537-3542, doi:10.1210/jcem.87.8.8658 (2002).

426 Barkan, A. L., Beitins, I. Z. & Kelch, R. P. Plasma insulin-like growth factor-I/somatomedin-C in acromegaly: correlation with the degree of growth hormone hypersecretion. *J. Clin. Endocrinol. Metab.* **67**, 69-73, doi:10.1210/jcem-67-1-69 [doi] (1988).

427 Oldfield, E. H. *et al.* Correlation between GH and IGF-1 during treatment for acromegaly. *J. Neurosurg.* **126**, 1959-1966, doi:10.3171/2016.8.JNS161123 (2017).

428 Nomikos, P., Buchfelder, M. & Fahlbusch, R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *Eur. J. Endocrinol.* **152**, 379-387, doi:10.1530/eje.1.01863 (2005).

429 Stratakis, C. A., Kirschner, L. S. & Carney, J. A. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J. Clin. Endocrinol. Metab.* **86**, 4041-4046, doi:10.1210/jcem.86.9.7903 (2001).

430 Daly, A. F. *et al.* Pheochromocytomas and pituitary adenomas in three patients with MAX exon deletions. *Endocr. Relat. Cancer* **25**, L37-L42, doi:10.1530/ERC-18-0065 (2018).

431 Cambiaso, P. *et al.* Growth hormone excess in children with neurofibromatosis type-1 and optic glioma. *Am. J. Med. Genet. A* **173**, 2353-2358, doi:10.1002/ajmg.a.38308 (2017).

432 Drimmie, F. M. *et al.* Gigantism due to growth hormone excess in a boy with optic glioma. *Clin. Endocrinol. (Oxf.)* **53**, 535-538, doi:10.1046/j.1365-2265.2000.01041.x (2000).

433 Main, K. M., Sehested, A. & Feldt-Rasmussen, U. Pegvisomant treatment in a 4-year-old girl with neurofibromatosis type 1. *Horm. Res.* **65**, 1-5, doi:10.1159/000089486 (2006).

434 Ahmed, S. *et al.* Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. *Clin. Endocrinol. (Oxf.)* **50**, 561-567 (1999).

435 Bhansali, A. *et al.* Adolescent acromegaly: clinical parameters and treatment outcome. *J. Pediatr. Endocrinol. Metab.* **23**, 1047-1054 (2010).

436 Jallad, R. S., Musolino, N. R., Kodaira, S., Cescato, V. A. & Bronstein, M. D. Does partial surgical tumour removal influence the response to octreotide-LAR in acromegalic patients previously resistant to the somatostatin analogue? *Clin. Endocrinol. (Oxf.)* **67**, 310-315, doi:10.1111/j.1365-2265.2007.02885.x (2007).

437 Petrossians, P. *et al.* Gross total resection or debulking of pituitary adenomas improves hormonal control of acromegaly by somatostatin analogs. *Eur. J. Endocrinol.* **152**, 61-66 (2005).

438 Karavitaki, N. *et al.* Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide. *Clin. Endocrinol. (Oxf.)* **68**, 970-975, doi:10.1111/j.1365-2265.2007.03139.x (2008).

439 Nagata, Y. *et al.* Growth hormone-producing pituitary adenomas in childhood and young adulthood: clinical features and outcomes. *Pituitary* **21**, 1-9, doi:10.1007/s11102-017-0836-4 (2018).

440 Yang, C., Li, G., Jiang, S., Bao, X. & Wang, R. Preoperative Somatostatin Analogues in Patients with Newly-diagnosed Acromegaly: A Systematic Review and Meta-analysis of Comparative Studies. *Sci. Rep.* **9**, 14070, doi:10.1038/s41598-019-50639-6 (2019).

441 Khan, Z. H. & Rasouli, M. R. Intubation in patients with acromegaly: experience in more than 800 patients. *Eur. J. Anaesthesiol.* **26**, 354-355, doi:10.1097/EJA.0b013e32831bc6fb (2009).

442 Seidman, P. A., Kofke, W. A., Policare, R. & Young, M. Anaesthetic complications of acromegaly. *Br. J. Anaesth.* **84**, 179-182 (2000).

443 Cuny, T. *et al.* Acromegaly in Carney complex. *Pituitary* **22**, 456-466, doi:10.1007/s11102-019-00974-8 (2019).

444 Daniel, A., d'Emden, M. & Duncan, E. Pituitary gigantism treated successfully with the growth hormone receptor antagonist, pegvisomant. *Intern Med J* **43**, 345-347, doi:10.1111/imj.12077 (2013).

445 Espinosa-de-los-Monteros, A. L., Gonzalez, B., Vargas, G., Sosa, E. & Mercado, M. Octreotide LAR treatment of acromegaly in "real life": long-term outcome at a tertiary care center. *Pituitary* **18**, 290-296, doi:10.1007/s11102-014-0570-0 (2015).

446 Zimmerman, D. *et al.* Congenital gigantism due to growth hormone-releasing hormone excess and pituitary hyperplasia with adenomatous transformation. *J. Clin. Endocrinol. Metab.* **76**, 216-222, doi:10.1210/jcem.76.1.8421089 (1993).

447 Tajima, T. *et al.* Case study of a 15-year-old boy with McCune-Albright syndrome combined with pituitary gigantism: effect of octreotide-long acting release (LAR) and cabergoline therapy. *Endocr. J.* **55**, 595-599 (2008).

448 Gelber, S. J., Heffez, D. S. & Donohoue, P. A. Pituitary gigantism caused by growth hormone excess from infancy. *J. Pediatr.* **120**, 931-934 (1992).

449 Burren, C., Williams, E., Coxson, E. & Korbonits, M. Effective Long-term Pediatric Pegvisomant Monotherapy to Final Height in X-linked Acrogigantism. *JCEM Case reports* **1**, 1, doi:10.1210/jcemcr/luad028 (2023).

450 Daly, A. F. *et al.* AIP-mutated acromegaly resistant to first-generation somatostatin analogs: long-term control with pasireotide LAR in two patients. *Endocr Connect* **8**, 367-377, doi:10.1530/EC-19-0004 (2019).

451 Tahara, S., Murakami, M., Kaneko, T. & Shimatsu, A. Efficacy and safety of long-acting pasireotide in Japanese patients with acromegaly or pituitary gigantism: results from a multicenter, open-label, randomized, phase 2 study. *Endocr. J.* **64**, 735-747, doi:10.1507/endocrj.EJ16-0624 (2017).

452 Cozzi, R., Attanasio, R., Lodrini, S. & Lasio, G. Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin. Endocrinol. (Oxf.)* **61**, 209-215, doi:10.1111/j.1365-2265.2004.02082.x (2004).

453 Gatta, B., Hau, D. H., Catargi, B., Roger, P. & Tabarin, A. Re-evaluation of the efficacy of the association of cabergoline to somatostatin analogues in acromegalic patients. *Clin. Endocrinol. (Oxf.)* **63**, 477-478, doi:10.1111/j.1365-2265.2005.02329.x (2005).

454 Sandret, L., Maison, P. & Chanson, P. Place of cabergoline in acromegaly: a meta-analysis. *J. Clin. Endocrinol. Metab.* **96**, 1327-1335, doi:10.1210/jc.2010-2443 (2011).

455 Abs, R. *et al.* Cabergoline in the treatment of acromegaly: a study in 64 patients. *J. Clin. Endocrinol. Metab.* **83**, 374-378, doi:10.1210/jcem.83.2.4556 (1998).

456 Müssig, K. *et al.* Pegvisomant treatment in gigantism caused by a growth hormone-secreting giant pituitary adenoma. *Exp. Clin. Endocrinol. Diabetes* **115**, 198-202, doi:10.1055/s-2007-956172 (2007).

457 Boguszewski, C. L. *et al.* Brazilian multicenter study on pegvisomant treatment in acromegaly. *Arch. Endocrinol. Metab.* **63**, 328-336, doi:10.20945/2359-3997000000159 (2019).

458 Tessaris, D. *et al.* Growth hormone-Insulin-like growth factor 1 axis hyperactivity on bone fibrous dysplasia in McCune-Albright Syndrome. *Clin. Endocrinol. (Oxf.)* **89**, 56-64, doi:10.1111/cen.13722 (2018).

459 Garcia, W. R., Cortes, H. T. & Romero, A. F. Pituitary gigantism: a case series from Hospital de San Jose (Bogota, Colombia). *Arch. Endocrinol. Metab.* **63**, 385-393, doi:10.20945/2359-3997000000150 (2019).

460 Brue, T. *et al.* Which patients with acromegaly are treated with pegvisomant? An overview of methodology and baseline data in ACROSTUDY. *Eur. J. Endocrinol.* **161 Suppl 1**, S11-17, doi:10.1530/EJE-09-0333 (2009).

461 Dutta, P. *et al.* Surgery, Octreotide, Temozolomide, Bevacizumab, Radiotherapy, and Pegvisomant Treatment of an AIP Mutation Positive Child. *J. Clin. Endocrinol. Metab.* **104**, 3539-3544, doi:10.1210/jc.2019-00432 (2019).

462 Castinetti, F., Morange, I., Dufour, H., Regis, J. & Brue, T. Radiotherapy and radiosurgery in acromegaly. *Pituitary* **12**, 3-10, doi:10.1007/s11102-007-0078-y (2009).

463 Lee, C. C. *et al.* Stereotactic radiosurgery for acromegaly. *J. Clin. Endocrinol. Metab.* **99**, 1273-1281, doi:10.1210/jc.2013-3743 (2014).

464 Jenkins, P. J., Bates, P., Carson, M. N., Stewart, P. M. & Wass, J. A. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. *J. Clin. Endocrinol. Metab.* **91**, 1239-1245, doi:10.1210/jc.2005-1616 (2006).

465 Schwartz, D. T. & Alpert, M. The Malignant Transformation of Fibrous Dysplasia. *Am. J. Med. Sci.* **247**, 1-20 (1964).

466 Galland, F. *et al.* McCune-Albright syndrome and acromegaly: effects of hypothalamopituitary radiotherapy and/or pegvisomant in somatostatin analog-resistant patients. *J. Clin. Endocrinol. Metab.* **91**, 4957-4961, doi:10.1210/jc.2006-0561 (2006).

467 Hansen, M. R. & Moffat, J. C. Osteosarcoma of the Skull Base after Radiation Therapy in a Patient with McCune-Albright Syndrome: Case Report. *Skull Base* **13**, 79-83, doi:10.1055/s-2003-820562 (2003).

468 Ruggieri, P., Sim, F. H., Bond, J. R. & Unni, K. K. Osteosarcoma in a patient with polyostotic fibrous dysplasia and Albright's syndrome. *Orthopedics* **18**, 71-75 (1995).

469 Ruggieri, P., Sim, F. H., Bond, J. R. & Unni, K. K. Malignancies in fibrous dysplasia. *Cancer* **73**, 1411-1424 (1994).

470 Hampton, R. E. Acromegaly and resulting myofascial pain and temporomandibular joint dysfunction: review of the literature and report of case. *J. Am. Dent. Assoc.* **114**, 625-631 (1987).

471 Biermasz, N. R., van Dulken, H. & Roelfsema, F. Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *J. Clin. Endocrinol. Metab.* **85**, 4596-4602, doi:10.1210/jcem.85.12.7042 (2000).

472 Onnestam, L. *et al.* National incidence and prevalence of TSH-secreting pituitary adenomas in Sweden. *J. Clin. Endocrinol. Metab.* **98**, 626-635, doi:10.1210/jc.2012-3362 (2013).

473 Pereira, B. D. *et al.* Monomorphous Plurihormonal Pituitary Adenoma of Pit-1 Lineage in a Giant Adolescent with Central Hyperthyroidism. *Endocr. Pathol.* **27**, 25-33, doi:10.1007/s12022-015-9395-2 (2016).

474 Rabbiosi, S. *et al.* Asymptomatic thyrotropin-secreting pituitary macroadenoma in a 13-year-old girl: successful first-line treatment with somatostatin analogs. *Thyroid* **22**, 1076-1079, doi:10.1089/thy.2012.0077 (2012).

475 Kessler, M., David, R., Pawelczak, M., Hanono, A. & Shah, B. Thyrotropin-secreting pituitary adenoma in an adolescent boy: challenges in management. *Pediatrics* **126**, e474-478, doi:10.1542/peds.2009-2354 (2010).

476 Nakayama, Y. *et al.* Thyroid-stimulating hormone (thyrotropin)-secretion pituitary adenoma in an 8-year-old boy: case report. *Pituitary* **15**, 110-115, doi:10.1007/s11102-010-0275-y (2012).

477 Amlashi, F. G. & Tritos, N. A. Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. *Endocrine* **52**, 427-440, doi:10.1007/s12020-016-0863-3 (2016).

478 Barzaghi, L. R. *et al.* Pediatric Pituitary Adenomas: Early and Long-Term Surgical Outcome in a Series of 85 Consecutive Patients. *Neurosurgery* **85**, 65-74, doi:10.1093/neuros/nyy204 (2019).

479 Fukuhara, N. *et al.* Short-term preoperative octreotide treatment for TSH-secreting pituitary adenoma. *Endocr. J.* **62**, 21-27, doi:10.1507/endocrj.EJ14-0118 (2015).

480 Avramides, A. *et al.* TSH-secreting pituitary macroadenoma in an 11-year-old girl. *Acta Paediatr.* **81**, 1058-1060 (1992).

481 Polak, M. *et al.* A human TSH-secreting adenoma: endocrine, biochemical and morphological studies. Evidence of somatostatin receptors by using quantitative autoradiography. Clinical and biological improvement by SMS 201-995 treatment. *Acta Endocrinol. (Copenh.)* **124**, 479-486 (1991).

482 Suntornlohanakul, S., Vasiknanont, P., Mo-Suwan, L., Phuenpathom, N. & Chongchitnant, N. TSH secreting pituitary adenoma in children: a case report. *J. Med. Assoc. Thai.* **73**, 175-178 (1990).

483 Mazerkina, N. *et al.* Thyrotropin-secreting pituitary adenoma in an 11-year-old boy with type 1 autoimmune polyglandular syndrome. *J. Pediatr. Endocrinol. Metab.* **29**, 237-240, doi:10.1515/jpem-2015-0018 (2016).

484 Yamaguchi-Okada, M., Inoshita, N., Nishioka, H., Fukuhara, N. & Yamada, S. Clinicopathological analysis of nonfunctioning pituitary adenomas in patients younger than 25 years of age. *J. Neurosurg. Pediatr.* **9**, 511-516, doi:10.3171/2012.1.PEDS11330 (2012).

485 Saeger, W. *et al.* Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur. J. Endocrinol.* **156**, 203-216, doi:10.1530/eje.1.02326 (2007).

486 Thaker, V. V., Lage, A. E., Kumari, G., Silvera, V. M. & Cohen, L. E. Clinical Course of Nonfunctional Pituitary Microadenoma in Children: A Single-Center Experience. *J. Clin. Endocrinol. Metab.* **104**, 5906-5912, doi:10.1210/jc.2019-01252 (2019).

487 Souteiro, P. *et al.* Pituitary incidentalomas in paediatric age are different from those described in adulthood. *Pituitary* **22**, 124-128, doi:10.1007/s11102-019-00940-4 (2019).

488 Shareef, M. *et al.* Pituitary incidentalomas in paediatric population: Incidence and characteristics. *Clin. Endocrinol. (Oxf.)* **94**, 269–276, doi:10.1111/cen.14353 (2021).

489 Nishio, S. *et al.* Pituitary tumours in adolescence: clinical behaviour and neuroimaging features of seven cases. *J. Clin. Neurosci.* **8**, 231-234, doi:10.1054/jocn.2000.0758 (2001).

490 Steele, C. A. *et al.* Pituitary adenomas in childhood, adolescence and young adulthood: presentation, management, endocrine and metabolic outcomes. *Eur. J. Endocrinol.* **163**, 515-522, doi:10.1530/EJE-10-0519 (2010).

491 Zhang, N., Zhou, P., Meng, Y., Ye, F. & Jiang, S. A retrospective review of 34 cases of pediatric pituitary adenoma. *Childs Nerv. Syst.* **33**, 1961-1967, doi:10.1007/s00381-017-3538-3 (2017).

492 Wang, H. *et al.* Nonfunctioning pituitary adenomas in pediatric and adolescent patients: a clinical analysis of a series of 14 patients. *J. Neurooncol.* **148**, 179-186, doi:10.1007/s11060-020-03512-w (2020).

493 Kruse, A., Astrup, J., Gyldensted, C. & Cold, G. E. Hyperprolactinaemia in patients with pituitary adenomas. The pituitary stalk compression syndrome. *Br. J. Neurosurg.* **9**, 453-457 (1995).

494 Sautner, D., Saeger, W. & Ludecke, D. K. Tumors of the sellar region mimicking pituitary adenomas. *Exp. Clin. Endocrinol.* **101**, 283-289, doi:10.1055/s-0029-1211245 (1993).

495 Kidooka, M., Okada, T., Nakajima, M. & Handa, J. Intra- and suprasellar germinoma mimicking a pituitary adenoma--case report. *Neurol. Med. Chir. (Tokyo)* **35**, 96-99 (1995).

496 Sbardella, E. *et al.* A clinical approach to parasellar lesions in the transition age. *J. Neuroendocrinol.* **33**, e12995, doi:10.1111/jne.12995 (2021).

497 Karavitaki, N. *et al.* What is the natural history of nonoperated nonfunctioning pituitary adenomas? *Clin. Endocrinol. (Oxf.)* **67**, 938-943, doi:10.1111/j.1365-2265.2007.02990.x (2007).

498 Warnet, A. *et al.* The effect of somatostatin analogue on chiasmal dysfunction from pituitary macroadenomas. *J. Neurosurg.* **71**, 687-690, doi:10.3171/jns.1989.71.5.0687 (1989).

499 Lohmann, T. *et al.* Minor tumour shrinkage in nonfunctioning pituitary adenomas by long-term treatment with the dopamine agonist cabergoline. *Pituitary* **4**, 173-178 (2001).

500 Pivonello, R. *et al.* Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. *J. Clin. Endocrinol. Metab.* **89**, 1674-1683, doi:10.1210/jc.2003-030859 (2004).

501 Greenman, Y. *et al.* Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. *Eur. J. Endocrinol.* **175**, 63-72, doi:10.1530/EJE-16-0206 (2016).

502 Batista, R. L. *et al.* Cabergoline in the Management of Residual Nonfunctioning Pituitary Adenoma: A Single-Center, Open-Label, 2-Year Randomized Clinical Trial. *Am. J. Clin. Oncol.* **42**, 221-227, doi:10.1097/COC.0000000000000505 (2019).

503 Wilson, P. J., De-Loyde, K. J., Williams, J. R. & Smee, R. I. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the Linear Accelerator (Linac). *J. Clin. Neurosci.* **19**, 370-374, doi:10.1016/j.jocn.2011.07.025 (2012).

504 Keshavarzi, S. *et al.* Initial clinical experience with frameless optically guided stereotactic radiosurgery/radiotherapy in pediatric patients. *Childs Nerv. Syst.* **25**, 837-844, doi:10.1007/s00381-009-0840-8 (2009).

505 Becker, G. *et al.* Radiation therapy in the multimodal treatment approach of pituitary adenoma. *Strahlenther. Onkol.* **178**, 173-186, doi:10.1007/s00066-002-0826-x (2002).

506 Tampourlou, M. *et al.* Outcome of nonfunctioning pituitary adenomas that regrow after primary treatment: a study from two large UK centers. *J. Clin. Endocrinol. Metab.* **102**, 1889-1897, doi:10.1210/jc.2016-4061 (2017).

507 Freda, P. U. *et al.* Pituitary incidentaloma: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **96**, 894-904, doi:10.1210/jc.2010-1048 (2011).

508 Fernandez-Balsells, M. M. *et al.* Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. *J. Clin. Endocrinol. Metab.* **96**, 905-912, doi:10.1210/jc.2010-1054 (2011).

509 Gryngarten, M. G. *et al.* Spontaneous ovarian hyperstimulation syndrome caused by a follicle-stimulating hormone-secreting pituitary macroadenoma in an early pubertal girl. *Horm. Res. Paediatr.* **73**, 293-298, doi:10.1159/000284395 (2010).

510 Ntali, G., Capatina, C., Grossman, A. & Karavitaki, N. Clinical review: Functioning gonadotroph adenomas. *J. Clin. Endocrinol. Metab.* **99**, 4423-4433, doi:10.1210/jc.2014-2362 (2014).

511 Kolnikaj, T. S., Musat, M., Salehidoost, R. & Korbonits, M. Pharmacological Causes of Hyperprolactinemia in *Endotext* (eds K. R. Feingold *et al.*) (2024).

512 Bunker, M. T., Marken, P. A., Schneiderhan, M. E. & Ruehter, V. L. Attenuation of antipsychotic-induced hyperprolactinemia with clozapine. *J. Child Adolesc. Psychopharmacol.* **7**, 65-69, doi:10.1089/cap.1997.7.65 (1997).

513 Wudarsky, M. *et al.* Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *J. Child Adolesc. Psychopharmacol.* **9**, 239-245, doi:10.1089/cap.1999.9.239 (1999).

514 Rosenbloom, A. L. Hyperprolactinemia with antipsychotic drugs in children and adolescents. *Int. J. Pediatr. Endocrinol.* **2010**, doi:10.1155/2010/159402 (2010).

515 Apter, A. *et al.* Effect of chlorpromazine on hypothalamic-pituitary-gonadal function in 10 adolescent schizophrenic boys. *Am. J. Psychiatry* **140**, 1588-1591, doi:10.1176/ajp.140.12.1588 (1983).

516 Hellings, J. A., Arnold, L. E. & Han, J. C. Dopamine antagonists for treatment resistance in autism spectrum disorders: review and focus on BDNF stimulators loxapine and amitriptyline. *Expert Opin. Pharmacother.* **18**, 581-588, doi:10.1080/14656566.2017.1308483 (2017).

517 Simeon, J., Lawrence, S. & Simeon, S. Effects of pimozide on prolactin in children [proceedings]. *Psychopharmacol. Bull.* **15**, 40-42 (1979).

518 Sallee, F. R., Dougherty, D., Sethuraman, G. & Vrindavanam, N. Prolactin monitoring of haloperidol and pimozide treatment in children with Tourette's syndrome. *Biol. Psychiatry* **40**, 1044-1050, doi:10.1016/0006-3223(95)00596-X (1996).

519 Savitz, A. *et al.* Long-Term Safety of Paliperidone Extended Release in Adolescents with Schizophrenia: An Open-Label, Flexible Dose Study. *J. Child Adolesc. Psychopharmacol.* **25**, 548-557, doi:10.1089/cap.2014.0130 (2015).

520 Gopal, S. *et al.* Evaluation of Potentially Prolactin-Related Adverse Events and Sexual Maturation in Adolescents with Schizophrenia Treated with Paliperidone Extended-Release (ER) for 2 Years: A Post Hoc Analysis of an Open-Label Multicenter Study. *CNS Drugs* **31**, 797-808, doi:10.1007/s40263-017-0437-9 (2017).

521 Troost, P. W. *et al.* Prolactin release in children treated with risperidone: impact and role of CYP2D6 metabolism. *J. Clin. Psychopharmacol.* **27**, 52-57, doi:10.1097/JCP.0b013e31802e68d5 (2007).

522 Anderson, G. M. *et al.* Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. *Biol. Psychiatry* **61**, 545-550, doi:10.1016/j.biopsych.2006.02.032 (2007).

523 Stevens, J. R., Kymissis, P. I. & Baker, A. J. Elevated prolactin levels in male youths treated with risperidone and quetiapine. *J. Child Adolesc. Psychopharmacol.* **15**, 893-900, doi:10.1089/cap.2005.15.893 (2005).

524 Koch, M. T., Carlson, H. E., Kazimi, M. M. & Correll, C. U. Antipsychotic-Related Prolactin Levels and Sexual Dysfunction in Mentally Ill Youth: A 3-Month Cohort Study. *J. Am. Acad. Child Adolesc. Psychiatry* **62**, 1021-1050, doi:10.1016/j.jaac.2023.03.007 (2023).

525 Stepanova, E., Grant, B. & Findling, R. L. Asenapine Treatment in Pediatric Patients with Bipolar I Disorder or Schizophrenia: A Review. *Paediatr. Drugs* **20**, 121-134, doi:10.1007/s40272-017-0274-9 (2018).

526 Stocks, J. D., Taneja, B. K., Baroldi, P. & Findling, R. L. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. *J. Child Adolesc. Psychopharmacol.* **22**, 102-111, doi:10.1089/cap.2011.0087 (2012).

527 FDA. *Review and Evaluation of Clinical Data, Lurasidone*, <https://www.fda.gov/media/133816/download> (Access date:*30/09/2023*).

528 Gjessing Jensen, K. Severe Hyperprolactinemia during Lurasidone Treatment in a 16-year Old Girl with Schizophrenia - A Case Report. *Scand J Child Adolesc Psychiatr Psychol* **10**, 87-88, doi:10.2478/sjcapp-2022-0009 (2022).

529 Malone, R. P., Delaney, M. A., Hyman, S. B. & Cater, J. R. Ziprasidone in adolescents with autism: an open-label pilot study. *J. Child Adolesc. Psychopharmacol.* **17**, 779-790, doi:10.1089/cap.2006.0126 (2007).

530 Yoo, H. K. *et al.* A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J. Clin. Psychiatry* **74**, e772-780, doi:10.4088/JCP.12m08189 (2013).

531 Varol Tas, F. & Guvenir, T. Amisulpride treatment of adolescent patients with schizophrenia or schizo-affective disorders. *Eur. Child Adolesc. Psychiatry* **18**, 511-513, doi:10.1007/s00787-009-0009-8 (2009).

532 FDA. *Brexpiprazole in Pediatric Patients with Schizophrenia Aged 13 to 17*, <https://www.fda.gov/media/155985/download> (Access date:*30/09/2023*).

533 Hanna, G. L., McCracken, J. T. & Cantwell, D. P. Prolactin in childhood obsessive-compulsive disorder: clinical correlates and response to clomipramine. *J. Am. Acad. Child Adolesc. Psychiatry* **30**, 173-178, doi:10.1097/00004583-199103000-00002 (1991).

534 Overtoom, C. C. *et al.* Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. *Behav. Brain Res.* **145**, 7-15, doi:10.1016/s0166-4328(03)00097-4 (2003).

535 Conners, C. K. *et al.* Bupropion hydrochloride in attention deficit disorder with hyperactivity. *J. Am. Acad. Child Adolesc. Psychiatry* **35**, 1314-1321, doi:10.1097/00004583-199610000-00018 (1996).

536 Turkoglu, S. Citalopram-Induced Galactorrhea in an Adolescent. *Clin. Neuropharmacol.* **39**, 331, doi:10.1097/WNF.0000000000000178 (2016).

537 McGrane, I. R., Morefield, C. M. & Aytes, K. L. Probable Galactorrhea Associated with Sequential Trials of Escitalopram and Duloxetine in an Adolescent Female. *J. Child Adolesc. Psychopharmacol.* **29**, 788-789, doi:10.1089/cap.2019.0099 (2019).

538 Iancu, I., Ratzoni, G., Weitzman, A. & Apter, A. More fluoxetine experience. *J. Am. Acad. Child Adolesc. Psychiatry* **31**, 755-756, doi:10.1097/00004583-199207000-00032 (1992).

539 Ekinci, N., Gunes, S., Kalinli, M. & Ekinci, O. Sertraline-Related Amenorrhea in an Adolescent. *Clin. Neuropharmacol.* **42**, 99-100, doi:10.1097/WNF.0000000000000336 (2019).

540 Alacqua, M. *et al.* Use and tolerability of newer antipsychotics and antidepressants: a chart review in a paediatric setting. *Pharm. World Sci.* **30**, 44-50, doi:10.1007/s11096-007-9139-6 (2008).

541 FDA. *FDA Adverse Event Reporting System (FAERS) Public Dashboard*, <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis> (Access date:*26/09/2023*).

542 Nicolson, R., Craven-Thuss, B., Smith, J., McKinlay, B. D. & Castellanos, F. X. A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **44**, 640-646, doi:10.1097/01.chi.0000163279.39598.44 (2005).

543 Preeyasombat, C., Mahachoklertwattana, P., Sriphrapradang, A. & Choubtam, L. Prolactin (PRL) release in normal and growth hormone deficient children after oral metoclopramide. *J. Med. Assoc. Thai.* **76 Suppl 2**, 34-41 (1993).

544 Ijaiya, K. Prolactin response to exercise, metoclopramide and other provacative agents in children. *Eur. J. Pediatr.* **134**, 231-237, doi:10.1007/BF00441478 (1980).

545 Deprettere, A. R., Van Acker, K. J. & Du Caju, M. V. Increased serum prolactin but normal TSH during prolonged domperidone treatment in children. *Eur. J. Pediatr.* **146**, 189-191, doi:10.1007/BF02343232 (1987).

546 Cho, E., Ho, S., Gerber, P. & Davidson, A. G. Monitoring of serum prolactin in pediatric patients with cystic fibrosis who are receiving domperidone. *Can. J. Hosp. Pharm.* **62**, 119-126, doi:10.4212/cjhp.v62i2.440 (2009).

547 Jabbar, A., Khan, R. & Farrukh, S. N. Hyperprolactinaemia induced by proton pump inhibitor. *J. Pak. Med. Assoc.* **60**, 689-690 (2010).

548 Stoff, D. M. *et al.* Neuroendocrine responses to challenge with dl-fenfluramine and aggression in disruptive behavior disorders of children and adolescents. *Psychiatry Res.* **43**, 263-276, doi:10.1016/0165-1781(92)90059-c (1992).

549 Tack, L. J. W. *et al.* Consecutive Cyproterone Acetate and Estradiol Treatment in Late-Pubertal Transgender Female Adolescents. *J. Sex. Med.* **14**, 747-757, doi:10.1016/j.jsxm.2017.03.251 (2017).

550 Mendhekar, D. N. Clonidine-induced gynecomastia and hyperprolactinemia in a 6-year-old child. *J. Clin. Psychiatry* **66**, 1616-1617, doi:10.4088/jcp.v66n1219f (2005).

551 Whitelaw, B. C. *et al.* Temozolomide in the management of dopamine agonist-resistant prolactinomas. *Clin. Endocrinol. (Oxf.)* **76**, 877-886, doi:10.1111/j.1365-2265.2012.04373.x (2012).

552 Felker, J., Patterson, B., Wrubel, D. & Janss, A. Successful treatment of a child with a prolactin secreting macroadenoma with temozolomide. *J. Pediatr. Endocrinol. Metab.* **29**, 1413-1415, doi:10.1515/jpem-2016-0159 (2016).

553 Lasolle, H. *et al.* Temozolomide treatment can improve overall survival in aggressive pituitary tumors and pituitary carcinomas. *Eur. J. Endocrinol.* **176**, 769-777, doi:10.1530/EJE-16-0979 (2017).

554 Chentli, F., Yaker, F. A., Azzoug, S. & Belhimer, F. Temozolomide: Anti-tumor effect on giant, invasive and resistant pediatric prolactinoma. *Indian J. Endocrinol. Metab.* **17**, 1136-1138, doi:10.4103/2230-8210.122657 (2013).

555 Bickler, S. W. *et al.* Preoperative diagnostic evaluation of children with Cushing's syndrome. *J. Pediatr. Surg.* **29**, 671-676, doi:10.1016/0022-3468(94)90738-2 (1994).

556 Shapiro, L. *et al.* Investigation for Paediatric Cushing's Syndrome Using Twenty-Four-Hour Urinary Free Cortisol Determination. *Horm. Res. Paediatr.* **86**, 21-26, doi:10.1159/000446913 (2016).

557 Thoren, M. *et al.* Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation. *Acta Paediatr. Scand.* **75**, 388-395 (1986).