Rare endocrine tumour guidelines

Idiopathic thickened pituitary stalk (TPS) and/or idiopathic central diabetes insipidus (CDI)

Guideline for the investigation and management of Children and Young People (CYP) aged < 19 years, presenting with a Thickened Pituitary Stalk (TPS) and/or Central Diabetes Insipidus (CDI) where the aetiology is not apparent at presentation

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

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Summary of content

This guideline is intended to be a reference document for clinicians presented with the challenge of managing Children and Young People (CYP) up to the age of 19 years presenting with a Thickened Pituitary Stalk (TPS) and/or Central Diabetes Insipidus (CDI) where the aetiology is not apparent at presentation. Care of such patients differs in key aspects from that of adults, particularly in aetiology. This guideline seeks to identify and address these, in terms of presentation, clinical assessment, diagnosis, management, follow-up and prognosis of affected patients. Through robust literature searches and a Delphi consensus exercise, available scientific evidence and expert opinion has been brought together to produce a pragmatic set of decision making and management guidelines intended to optimise the quality of care of CYP with apparently idiopathic TPS and/or CDI, and form the basis for future audits of practice and outcomes.

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Guideline stakeholders

We would like to thank all of the stakeholders who contributed comments to this guideline at various stages of development, including members of CCLG, BSPED and RCPCH.

Unrestricted funding

- Sandoz pharmaceuticals (now a division of Novartis Pharmaceuticals)
- Children's Cancer & Leukaemia Group (CCLG)
- British Society for Paediatric Endocrinology & Diabetes (BSPED)
- Pituitary Foundation
- Association of Multiple Endocrine Neoplastic Disorders (AMEND)
- Surviving Childhood Cranial tumours; Empowerment Surveillance Support (SUCCESS)
- British Neurosurgical Society

Disclosure of potential conflicts of interests

All Guideline Development Group (GDG) and Delphi consensus group participants were asked to disclose any conflicts of interests in a format adapted from NICE conflicts of interests policy (1). Conflicts were reviewed and all reported potential conflicts of interests are listed in Appendix 7.

Disclaimer

Healthcare providers need to use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may 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, clinical expertise and resources.

Target users of this guideline: Health professionals from a variety of disciplines (including paediatric endocrinology, oncology, neurosurgery, radiology, histopathology, and genetics) involved in the management and long-term follow-up of childhood and adolescent pituitary stalk thickening and central diabetes insipidus within the UK.

Acknowledgements

The GDG would like to thank all stakeholders, the Project Board, Delphi panellists and our external peer reviewers for their input into this guideline. We also would like to thank the librarians of University College London and University Hospitals of Leicester NHS Trust for their help in the literature search process. We are particularly grateful to the Quality Improvement Committee Clinical Leads for Evidence Base Medicine and Appraisals at the RCPCH, for their advice and appraisal during the guideline development process, and for the final endorsement of the guideline.

Dr Johannes Visser was an inspiring oncology colleague, a thoughtful mentor and kind friend to his peers and junior colleagues, as well as a driving force behind improved care for patients with LCH and germ cell tumours. It was this latter interest which brought him onto our collaborative 'guidelines for paediatric endocrine tumours' initiative back in 2013, and through which we, as his co-authors, came to know and admire him, eventually leading this specific guideline group to its long conclusion. That he should be felled by a malignancy himself just at its publication and at the peak of his career development - leaving a wife, young children and a thriving oncology service at Cambridge where he had recently been appointed - seems a cruel twist of fate he didn't deserve. We remember him with fondness and dedicate this guideline to his memory.

Abbreviations

ACE - Angiotensin-Converting Enzyme
α-FP - Alpha Feto-Protein
AGREE II - Appraisal of Guidelines Research and Evaluation Instrument II
β-hCG - beta-human Chorionic Gonadotropin
BSPED - British Society for Paediatric Endocrinology and Diabetes
CCLG – Children's Cancer and Leukaemia Group
CDI - Central Diabetes Insipidus
CNS – Central Nervous System
CSF - CerebroSpinal Fluid
CT - Computed Tomography
CXR - Chest X Ray
CYP – Children and Young People
GCT - Germ Cell Tumours
GDG - Guideline Development Group
GRADE – Grading of Recommendations, Assessment, Development and Evaluation
ESPE – European Society of Paediatric Endocrinology
ESR - Erythrocyte Sedimentation Rate
FBC - Full Blood Count
FDG-PET - FluoroDeoxyGlucose Positron Emission Tomography
HS – Histiocyte Society
IGRAs - Interferon-Gamma Release Assays
LCH - Langerhans Cell Histiocytosis
MDT – Multi-Disciplinary Team
MRI – Magnetic Resonance Imaging
NICE - National Institute for Health and Clinical Excellence
UK - United Kingdom
PB – Project Board
RCPCH - Royal College of Paediatrics and Child Health
SOD - Septo-Optic Dysplasia
TB - Tuberculosis
TPS - Thickened Pituitary Stalk

Introduction

The investigation and management of idiopathic Thickened Pituitary Stalk (TPS) and/or Central Diabetes Insipidus (CDI) in Children and Young People (CYP) under 19 years of age is challenging, not only because of their rarity and the possible familial / genetic predisposition in this age group (compared to adults), but also because these patients may present to a range of different specialists. These include endocrinology and oncology, medical and surgical specialists. Depending on local arrangements, patients between ages 16 and 19 years may also present to adult or paediatric specialists.

The increased use of head Magnetic Resonance Imaging (MRI) during the investigation of other conditions also brings otherwise asymptomatic MRI anomalies, which may in the past have gone unnoticed, to medical attention.

Although there is more clinical experience and published research on the management of adults with these conditions, there remains a lack of high quality, randomised trials to inform treatment recommendations in CYP. This causes unacceptable inconsistencies and inequalities in care across units and specialties. Since children with these conditions have, on average, a further 68 life years ahead, their health related quality of survival is arguably paramount.

In order to achieve high quality care to improve survival and reduce secondary – long term – health-related morbidity in this young cohort, there is a need to involve age-specific and tumour-specific Multi-Disciplinary Teams (MDTs) from both paediatric and adult practice in a co-ordinated discussion. This MDT would aim to improve and expedite diagnosis (including complex endocrine and genetic screening of familial cases), acute decision-making, peri-operative care and long-term surveillance. Oncology treatment of CYP in the United Kingdom (UK) has been centralised over the last few decades to tertiary oncological centres (16 centres) linked to accredited secondary Paediatric Oncology Supportive Care Units (POSCUs). There is, however, no age-appropriate tertiary pituitary MDT embedded or mandated in the service provision in many centres; these need development and resourcing along a similar model.

Having recognised these challenges, the Project Board (PB) and the Guideline Development Groups (GDGs) have, in conjunction with Children's Cancer and Leukaemia Group (CCLG) and the British Society for Paediatric Endocrinology and Diabetes (BSPED) updated the 2005 CCLG / BSPED consensus guidelines on the management of six (one pituitary and five peripheral glandular) endocrine tumours in children (2) and additionally created two new (pituitary) guidelines. These guidelines on idiopathic TPS and/or CDI are one of the two new pituitary guidelines. These updates and new guidelines were developed according to Appraisal of Guidelines Research and Evaluation Instrument II (AGREE II) methodology to ensure high standards.

Background

TPS and CDI are rare conditions (3) which can occur in isolation or synchronously/metachronously in the same patient and the aetiology is often occult. CYP with idiopathic TPS/CDI represent a diagnostic conundrum as various oncological, congenital, inflammatory and infectious aetiologies can underlie these conditions.

We have extrapolated and summarised from 11 paediatric case series, the main etiologies responsible for TPS and/or CDI in children in Table 1 and Table 2 (Appendix 6). We noted considerable heterogeneity and selection bias across the studies which compromise the accuracy of the extrapolated relative incidence of different etiologies and this therefore requires future systematic study. Neoplasias are most commonly reported (45.5%), usually Langerhans Cell Histiocytosis (LCH) (16.1%) followed by germ cell tumours (GCT) (13.1%) and craniopharyngiomas (12.3%). Congenital lesions account for 19.1% of cases with the commonest being Septo-Optic Dysplasia (SOD) (5.8%). Only a minority were felt to have an infectious/inflammatory/autoimmune or post-traumatic aetiology. Lymphocytic hypophysitis were reported in just 0.9% of cases, largely without histological confirmation. An autoimmune aetiology was assumed in any patient with polyglandular autoimmune syndrome or another simultaneous autoimmune condition, and in patients in whom the TPS resolved spontaneously over time (4-6). Almost one third of the cases (29.1%) remained idiopathic at the time of reporting.

Scope and purpose

Aims and objectives

To provide guidelines for investigation, management and follow-up of idiopathic TPS and/or CDI in CYP before their 19th birthday.

We intend to provide an evidence base to optimise management and improve the quality of clinical care. The guideline will address:

- Aetiology of TPS and/or CDI where this is not apparent at presentation
- Radiological parameters for the diagnosis of TPS
- First- and second-line investigations required for CYP presenting with idiopathic TPS and/or CDI
- Indications for, and timing of, pituitary biopsy
- Recommendations for clinical and radiological follow-up, particularly where the cause of the TPS and/or CDI remains unknown

At the outset of the guideline development process, we had included two additional aims/objectives approved by the stakeholders, namely medical and surgical treatment, and complications of surgery (risk of endocrine and visual deficits). During guideline development, however, the GDG excluded these, recognising that given the wide spectrum of aetiologies these would be better covered in age-appropriate disease-specific guidelines.

Target population

- All CYP before their 19th birthday with a confirmed diagnosis of CDI where the aetiology is not apparent at presentation
- All CYP before their 19th birthday with TPS where the aetiology is not apparent at presentation
- Adults after their 19th birthday are excluded

Methodology

Introduction

The guideline aims to produce evidence-based guidance on the investigation, management, and follow-up of CYP with idiopathic TPS and/or CDI. A GDG, comprised of clinicians from a range of relevant specialties, was convened to oversee the development of the guideline. This guideline was developed in accordance with The AGREE II criteria (7) and the CCLG guideline development standard operating procedure, Version 5 (8). The methodology is summarised in Figure 1. All stages of the guideline development process were appraised by the Quality Improvement Committee of the RCPCH.

Developers and conflicts of interest

The members of the PB and GDG, guideline stakeholders and Delphi consensus group participants are listed in Appendix 1.

All GDG and Delphi consensus group participants were asked to disclose any conflicts of interests in a format adapted from NICE conflicts of interests policy (1). Conflicts were reviewed and all reported potential conflicts of interests are listed in Appendix 7.

The guideline development was sponsored by unrestricted grants from Sandoz Pharmaceuticals, the patient support groups Association of Multiple Endocrine Neoplastic Disorders (AMEND), Surviving Childhood Cranial tumours; Empowerment Surveillance Support (SUCCESS) and The Pituitary Foundation, and the professional societies, The British Society of Neurosurgeons, CCLG and BSPED. All except Sandoz were stakeholders. The latter had no role in development of guideline methodology or final guideline recommendations. The CCLG provided administrative support throughout the guideline and the RCPCH provided advice and appraisal to ensure that the process met rigorous AGREE II guideline standards.

Editorial independence

All GDG members declared any conflicts of interest prior to the guideline development starting, and periodically throughout the development of the guideline.

CCLG and BSPED did not influence the GDG's decisions or the guideline recommendations other than through their roles as stakeholders.

Developing the clinical questions

The GDG identified the guideline objectives and summarised these as a series of 64 PICO (Population, Intervention, Comparison, Outcome) clinical questions (9). The guideline objectives and clinical questions were reviewed by previously identified guideline stakeholders, to ensure no relevant area had been omitted and then finalised by the GDG, after incorporating stakeholder feedback (Appendix 2). The clinical questions guided the systematic literature search (Appendix 3), critical appraisal, and synthesis of evidence, and facilitated the development of recommendations by the GDG.

Identifying the evidence

Literature searches were conducted on core databases, comprising the Ovid MEDLINE database, the PubMed database, the EMBASE database, and the Cochrane Library. Searches were limited to the English language. Full inclusion/exclusion criteria, search terms and search strategies can be found in Appendix 3. The literature search strategy identified 3726 papers published between January 1990 and October 2014. Screening of titles and abstracts identified 560 papers potentially relevant to the guideline. An updated focussed literature search (see criteria in Appendix 3) covering the period November 2014 – July 2019 identified a further 8 relevant papers, whilst 16 additional relevant papers were identified by a subsequent direct search of the Pubmed database on specific topics where the initial search strategy did not identify the evidence needed.

Reviewing and synthesising the evidence

The full text of papers identified as potentially relevant to the guideline were reviewed and graded by the GDG. The quality of evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (10). The GRADE system was modified by assessing the overall quality of evidence provided by each paper rather than the quality of evidence related to each outcome (PICO question).

584 papers were evaluated for evidence to inform the guideline statements and those with contributory evidence are included in the evidence table (Appendix 4). Due to the extreme rarity of TPS and CDI in CYP, high quality evidence was lacking. Where there was little, or no, evidence in the paediatric literature, the authors have drawn on evidence from the adult literature, where available, and downgraded this accordingly.

Developing recommendations

Where the literature search identified moderate evidence to answer the PICO questions, the GDG made 9 guideline recommendations. Where an evidence base to formulate recommendations was lacking (i.e. no evidence, contradictory evidence, or very low quality evidence), an expert consensus was necessary. In several specific and contentious areas, the GDG felt that using a formal consensus methodology and engaging with professionals outside the GDG would improve the strength of the recommendations. These recommendations were evaluated using a formal consensus process (Delphi process) (11) (Appendix 5). A recommendation was deemed to have achieved consensus if 70% or more of the Delphi respondents (excluding those who indicated inadequate expertise in the posed question area to be able to comment) supported the recommendation as framed, or with minor modification. The degree of Delphi consensus (70 to 100%) was not taken into account to determine the strength of the recommendation. The strength of each recommendation was determined by the trade-off between the potential benefits and potential harms of the recommendation, taking into account the quality of the underpinning evidence, if present. The GDG applied this test to each recommendation to ensure the health benefits, side effects and risks have been considered. In addition, the GDG sought feedback from the stakeholders and two external expert reviewers to provide additional reassurance that an appropriate balance has been struck between the potential benefits and potential risks of each recommendation.

39 recommendations were developed by GDG consensus based on published case series/reports and GDG expert opinion, of which 23 with insufficient evidence and lacked GDG consensus (<100%) or considered as in need for additional support by the GDG were submitted to a Delphi expert consensus process, 9 of these going forward to a second round (appendix 5). All 23 recommendations achieved agreement in a Delphi consensus. 9 of these were reformulated or separated based on the panel's comments and put to a 2nd round. Thus 29 consensus recommendations were made. After a re-appraisal of the published evidence by the GDG, one guideline statement (defining TPS) was rewritten and Delphi consensus was judged not to be required for the final recommendation. One further recommendation was made by GDG consensus alone. The level of evidence (where present), the degree of Delphi consensus (where applicable) and the GDG Consensus (where applicable) were reported after each recommendation.

A consistent terminology is used across the guidelines to define the strength of recommendations. The NICE terminology of 'offer/consider' is used for recommendations referring to an intervention/action to be taken. The verb "offer" is used for interventions/actions which are strongly recommended. The verb "consider" is used for interventions/actions which are less strongly recommended.
For recommendations not directly referring to interventions/actions to be taken, the verb "should" is used for strong strength recommendations, the verbs "may" and "consider" are used for moderate strength recommendations, and the verb "note" is used for weak strength recommendations.

Areas highlighted by the literature review and consensus process in which the GDG felt further research would be valuable are reported under the heading, Research Recommendations.

Stakeholder involvement

The GDG included representatives from stakeholder organisations, and stakeholders were invited to comment on the draft guideline. The stakeholder consultation took place between August and October 2019, and during this time stakeholders were given the opportunity to comment on the guideline. All comments received were collated for consideration and discussion. Relevant changes were made to the guideline draft after careful consideration and discussion of the stakeholder feedback with the GDG.

Parent, carer and patient participation

Views from patients, survivors and their families were sought via the stakeholder feedback process through various patient support groups including the Childhood Cancer Parents' Alliance, Child Growth Foundation, Teenage and Young Adults with Cancer, and the Teenage Cancer Trust.

External peer review

In addition to the above stakeholder consultation, the draft guidelines were also peer reviewed by two international expert reviewers (one paediatric oncologist and one paediatric endocrinologist) and their comments considered by the GDG before the guidelines were finalised. This peer review took place between December 2018 and February 2019.

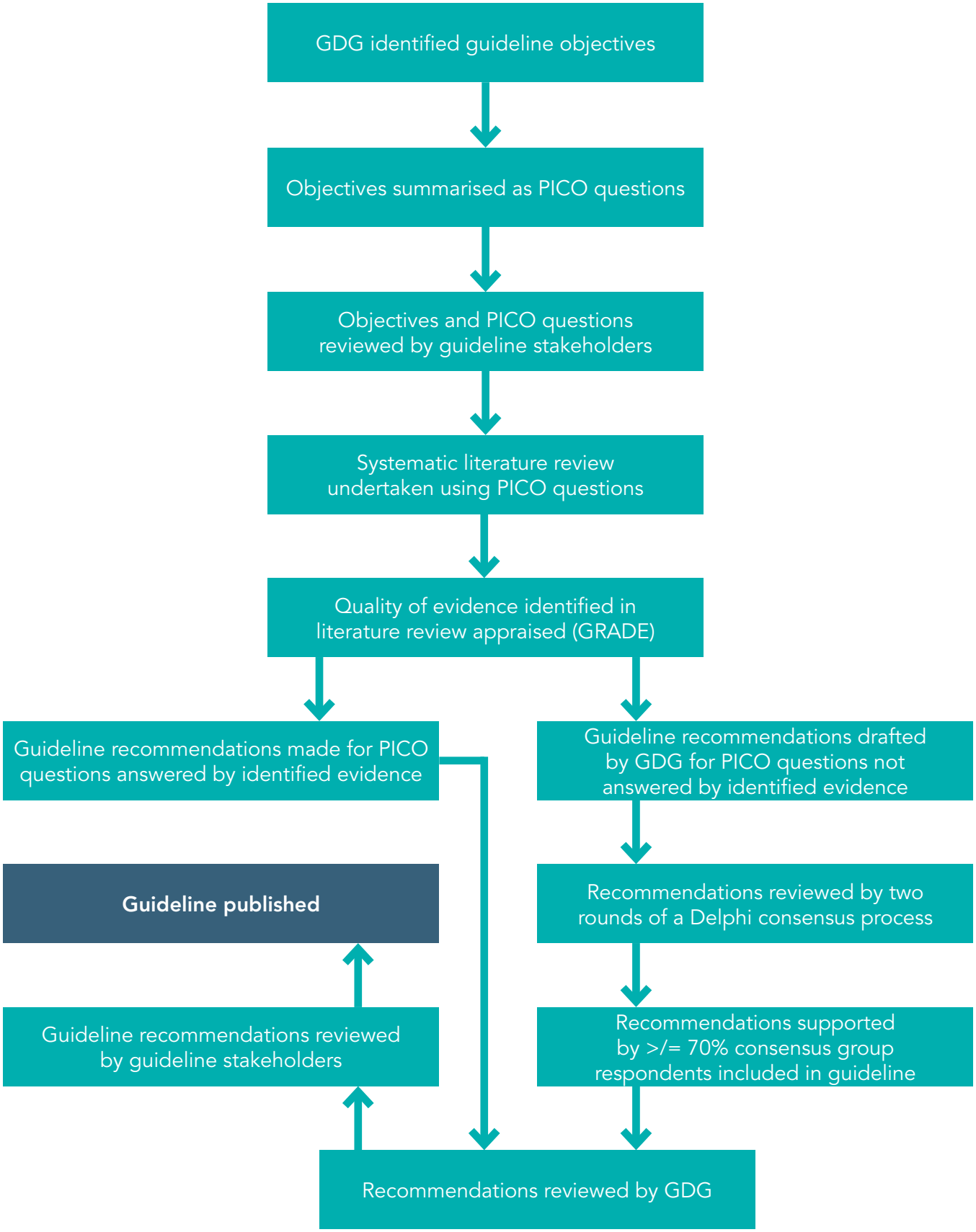
Implementation

In order to facilitate the implementation of these recommendations, we recommend the setup of multidisciplinary team meetings and we encourage the training of staff in specialised centres in the various diagnostic and/or management options. We foresee some potential barriers to the implementation of certain recommendations in this guideline. For example, there could be lack of expertise in the diagnostic procedures (such as stalk size interpretation and stalk biopsy in children).

Guideline update

The literature will be reviewed five years after guideline publication. The same search terms outlined in Appendix 3 will be used and new search terms will be added if required in order to reflect new diagnoses, techniques, and/or treatments. If relevant, the GDG will update the guideline (or appropriate section) according to the evidence identified. Prior to updating the guideline, this evidence will be checked and healthcare professionals and patient views will be sought to assess whether all or part of the guideline requires updating. If important new evidence is published at other times, which is likely to influence the recommendations, it may be decided that a more rapid update of some recommendations is necessary, e.g. if a guideline for the management of TPS/CDI in CYP is published by another body.

Figure 1: Guideline development process



Summary of recommendations

1. Service provision

2. Initial clinical assessment
   - 2.1. Definition criteria for pituitary stalk thickening
   - 2.2. Dedicated pituitary MRI images to detect pituitary stalk thickening
   - 2.3. Additional MRI findings increasing suspicion of pathology
   - 2.4. Systematic history and clinical evaluation

3. First line investigations
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   - 3.3. Ophthalmology
   - 3.4. Imaging
   - 3.5. Investigations of specific conditions as clinically indicated

4. Second line investigations
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   - 4.2. Imaging

5. Biopsy

6. Treatment

7. Surveillance
   - 7.1. Surveillance for all CYP presenting with TPS and/or CDI
   - 7.2. Reduced surveillance for CYP with stable isolated TPS
   - 7.3. Reduced surveillance for CYP with stable isolated CDI

8. Transition

Recommendations

The recommendations are given below in Sections 1-7 followed by a summary of the evidence for each recommendation

1. Service provision

1.1. Offer age-appropriate care, provided by an endocrinologist in a specialist centre with expertise in managing pituitary tumours, to all Children and Young People (CYP) with thickened pituitary stalk (TPS) or central diabetes insipidus (CDI). *(Low/Moderate quality evidence, Delphi consensus 100%)*

1.2. The endocrinologist providing care for those with TPS or CDI should liaise closely with a multidisciplinary team representing expertise in pituitary tumours from paediatric and adult services, including endocrinology, pituitary surgery, neuroradiology, neuropathology and neuro-oncology. *(Low/Moderate quality evidence, Delphi consensus 100%)*

1.3. Given the rarity of pituitary tumours in children and young people, a national clinical database and facilitated centralised review of images, histology and decision making process should be developed. *(Delphi consensus 90%)*

1.4. A centralised, national, pituitary multidisciplinary team (MDT) may require commissioning to facilitate review of complex cases. *(Delphi consensus 90%)*

1.5. Offer all patients the opportunity to contribute to tissue banking and relevant ethically approved national and international biology and treatment studies. *(Delphi consensus 100%)*

2. Initial clinical assessment

2.1. Definition criteria for pituitary stalk thickening

2.1.1. Consider that a pituitary stalk may be pathologically thickened and require further investigation and MRI surveillance if there is uniform/focal thickening (≥ 3 mm at the pituitary insertion and/or ≥ 4 mm at the level of optic chiasm) in the sagittal and/or coronal plane. *(Low/moderate quality evidence, Delphi consensus 100%)*

2.1.2. Consider further investigation and MRI surveillance for stalks measuring between 2 and 3 mm at the pituitary insertion and/or between 3 and 4 mm at the level of optic chiasm if associated with other clinical features increasing the risk of pathology (such as CDI, anterior pituitary or visual deficits). *(Low/moderate quality evidence)*

2.1.3 The interpretation of the stalk appearances requires neuroradiological expertise. The size criteria alone do not always allow differentiation between pathological thickening and physiological variants given the absence of normative data in children and the inter and intraindividual variability in the stalk measurements. *(Low/Moderate quality evidence)*

2.2. Dedicated pituitary MRI images to detect pituitary stalk thickening

Offer head and dedicated pituitary MRI to all CYP with suspected TPS and/or CDI. This should include uncontrasted 2D thinly sliced (<3mm) with no gap T1 and T2 weighted images in sagittal and coronal planes (and ideally at least one 3D highly weighted T2 sequence) to assess the possibility of uniform and/or focal thickening of the pituitary stalk in both planes. *(Moderate quality evidence, Delphi consensus 100%)*

2.3. Additional MRI findings which increase suspicion of pathology

2.3.1. The additional absence of a bright spot on the T1 non-contrasted scan and/or a significant reduction or enlargement of the pituitary, though not diagnostic, should increase suspicion of pathology. *(Moderate quality evidence, Delphi consensus 100%)*

2.3.2. Consider a disease-tailored diagnostic approach if extra-pituitary MRI finding suggest a specific underlying aetiology (e.g. skull lesions for Langerhans Cell Histiocytosis (LCH) or pineal lesions for bifocal germinoma or LCH). *(Moderate quality evidence)*

2.4. Systematic history and clinical evaluation

If the aetiology for a confirmed TPS and /or CDI is not apparent at presentation and a systematic history and clinical evaluation assessing for the commonest causes in CYP (Table 1, 2 and 3) have failed to reveal a potential focus for testing, or if focussed testing has proved uninformative, a stepwise decision-making approach for investigation and surveillance should be adopted in all patients *(Management Flow-Chart, Figure 3). (GDG consensus)*

3. First line investigations

3.1. Serum tumour markers, haematology, liver and renal function

3.1.1. Offer measurement of serum beta-human Chorionic Gonadotropin (β-hCG) and Alpha Feto-Protein (αFP) to all CYP with radiologically confirmed TPS and/or idiopathic CDI. *(Moderate quality evidence, Delphi consensus 92%)*

3.1.2. Although non-specific, consider performing Erythrocyte Sedimentation Rate (ESR), Full Blood Count (FBC), liver function, urea, creatinine, and electrolytes, to aid the diagnostic process. *(Delphi consensus 92%)*

3.2. Endocrinology

Offer an early endocrine assessment of growth and pubertal status, posterior pituitary function (i.e. urinary concentrating capacity) and baseline as well as dynamic tests of anterior pituitary function, including growth hormone and cortisol reserve to all CYP with TPS and/or CDI *(Moderate quality evidence, Delphi consensus 100%)*

3.3. Opthalmology

Offer a formal baseline assessment of visual acuity and, if child is able to co-operate, visual fields by optometry, to all CYP with TPS and/or CDI, especially if the TPS is proximal or abutting chiasm *(Moderate quality evidence, Delphi consensus 100%)*

3.4. Imaging

Offer a skeletal survey, abdominal ultrasound and a chest x-ray to all CYP with idiopathic TPS and/or CDI in whom initial blood tests have failed to reveal the aetiology *(Moderate quality evidence, Delphi consensus 87%)*

3.5. Investigations of specific conditions as clinically indicated

3.5.1. Infectious and inflammatory/autoimmune disease

3.5.1.1. Consider testing for Tuberculosis (TB) or autoimmune disease, as per local practice, if indicated by history and clinical examination. (*Low-moderate quality evidence, Delphi consensus 92%)*

3.5.1.2. Serum Angiotensin-Converting Enzyme (ACE) to screen for neurosarcoidosis in CYP with TPS and/or CDI is not recommended. *(Low-moderate quality evidence, Delphi consensus 100%)*

3.5.2. Congenital midline brain abnormalities [also called Septo-Optic Dysplasia (SOD) spectrum]

Offer genetic counselling and, where appropriate, molecular genetic testing for SOD spectrum, if imaging (midline anomalies, optic nerve hypoplasia), age and ophthalmology are consistent with this diagnosis. *(Moderate quality evidence)*

3.5.3. Familial CDI

Offer genetic counselling and genetic testing for inherited forms of CDI in CYP with isolated CDI and neither pituitary stalk thickening nor other midline neuroimaging abnormalities suggestive of SOD, especially if there is a family history and/or early childhood presentation. *(Moderate quality evidence, Delphi consensus 100%)*

4. Second line investigations

4.1. Lumbar puncture

4.1.1. Indications

Consider a diagnostic lumbar puncture if, after initial blood tests and imaging, the aetiology is not apparent and the patient meets one or more of the following criteria a) TPS ≥ 6.5-7mm or progressive enlargement of TPS over time b) TPS associated with CDI c) TPS with evolving anterior pituitary deficiencies and/or pituitary enlargement and/or deteriorating visual function. *(Moderate quality evidence, Delphi consensus 93%)*

4.1.2. Markers of GCT and LCH

When a diagnostic lumbar puncture is undertaken, offer measurement of β-hCG and αFP in the cerebrospinal fluid (CSF), together with CSF cytology. *(Moderate quality of evidence, Delphi consensus 100%)*

4.1.3. Tuberculosis and neurosarcoidosis

4.1.3.1. Consider CSF analysis for TB in those at risk. *(Moderate quality evidence, Delphi consensus 78%)*

4.1.3.2. Consider CSF ACE if neurosarcoidosis is strongly suspected. *(Low quality evidence, Delphi consensus 78%)*

4.2. Imaging

4.2.1. Consider whole body imaging to detect distant occult LCH lesions more amenable to biopsy, in CYP whose TPS and/or CDI remain idiopathic after initial blood tests, imaging and CSF screening but are nevertheless concerning for neoplasia (TPS is ≥ 6.5-7mm and/or is associated with CDI and/or changes in the pituitary size and/or is progressive and/or there is an evolving endocrinopathy and/or there is deteriorating visual function). *(Moderate quality evidence, Delphi consensus 90%)*

4.2.2. Whole body imaging may consist of FluoroDeoxyGlucose Positron Emission Tomography MRI / CT (^{18}FDG PET MRI / ^{18}FDG PET CT) or whole body MRI, depending on the local availability. *(Moderate quality evidence, Delphi consensus 90%)*

5. Biopsy

5.1. In CYP who continue to pose a diagnostic dilemma after appropriate repeat neuroimaging, whole body imaging and, if necessary, repeat CSF testing, consider a biopsy of the TPS if there is a very large (≥ 6.5-7mm) or progressively enlarging stalk and/or evolving hypopituitarism and/or there is visual deterioration. *(Low-Moderate quality evidence, Delphi consensus 100%)*

5.2. A biopsy should only be undertaken if it is judged by the MDT to be of sufficient size to yield a diagnostic sample and the benefits outweigh the risk of the procedure. *(Delphi consensus 100%)*

5.3. Pituitary surgery on CYP should be undertaken by a pituitary surgeon nominated by the MDT. There should be ready access to transsphenoidal, endoscopic and base of skull techniques and readily available age-appropriate endocrine support. *(Low quality evidence, Delphi consensus 90%*

6. Treatment

6.1. When an underlying aetiology is identified, the management should be dictated by this. Do not offer empiric disease-specific treatment without a confirmed aetiological diagnosis. *(Delphi consensus 93%)*

7. Surveillance

7.1. Surveillance for all CYP presenting with TPS and/or CDI

7.1.1. Offer regular surveillance including history, examination, endocrine +/- visual assessment and pituitary MRI to all CYP with idiopathic TPS and/or CDI. *(Moderate quality of evidence, Delphi consensus 100%)*

7.1.2. In the absence of new symptoms/signs and if the MRI appearances are stable, consider the following frequency of surveillance: 3-monthly intervals for 6 months, 6-monthly intervals until 2-3 years and annually thereafter. *(Low quality evidence, Delphi consensus 100%)*

7.1.3. If surveillance reveals progressive endocrinopathies and/or evolving visual disturbance and/or progressively enlarging TPS, consider repeating first and second line investigations (+/- biopsy). *(Moderate quality evidence)*

7.2. Reduced surveillance for CYP with stable isolated TPS

Consider reducing the MRI surveillance frequency and/or to discharge patients if, after 5 years of stable imaging appearances, growth and puberty are complete, in CYP presenting with isolated TPS and no evidence of any anterior or posterior pituitary dysfunction, in whom the TPS either normalises or remains stable at under 4.5-5 mm in maximal diameter. *(Low quality of evidence, Delphi consensus 100%)*

7.3. Reduced surveillance for CYP with stable isolated CDI

7.3.1. Familial CDI

In CYP with isolated CDI in whom a mutation responsible for familial CDI is documented, MRI surveillance should be discontinued. *(Moderate quality of evidence)*

7.3.2. Isolated idiopathic CDI

7.3.2.1. Consider discontinuing the MRI surveillance after 3 years in CYP with isolated idiopathic CDI and no evidence of either TPS, anterior pituitary dysfunction or visual deterioration. *(Moderate quality of evidence)*

7.3.2.2. Offer continued regular endocrine and clinical surveillance to screen for a late presenting germ cell tumour or LCH to all patients with isolated idiopathic CDI. *(Moderate quality of evidence)*

8. Transition

8.1. All CYP with an endocrinopathy and those with TPS ≥ 4.5-5 mm or progressively enlarging TPS, whose growth and puberty are complete, should be transferred to receive on-going age-appropriate care in a specialist adult endocrine centre with experience in managing pituitary tumours for continued surveillance to detect late presenting germ cell tumour or LCH. *(Moderate quality evidence)*

Background to recommendations

1. Service provision

1.1. **Offer age-appropriate care, provided by an endocrinologist in a specialist centre with expertise in managing pituitary tumours, to all Children and Young People (CYP) with thickened pituitary stalk (TPS) or central diabetes insipidus (CDI).** *(Low/Moderate quality evidence, Delphi consensus 100%)*

1.2. **The endocrinologist providing care for those with TPS or CDI should liaise closely with a multidisciplinary team (MDT) representing expertise in pituitary tumours from paediatric and adult services, including endocrinology, pituitary surgery, neuroradiology, neuropathology and neuro-oncology.** *(Low/Moderate quality evidence, Delphi consensus 100%)*

The GDG favoured an endocrinologist in a specialist centre coordinating age-appropriate care from presentation of CDI and/or TPS to ensure effective assessment and treatment of potentially life-threatening endocrinopathies, whilst liaising closely with the pituitary and neurooncology MDT about investigation, surveillance and management. Cases of TPS diagnosed incidentally may not currently be referred to paediatric/adult endocrinology unless there is coexisting CDI, however, given that several longitudinal case series clearly report the evolution of progressive TPS and an association with evolving anterior and posterior pituitary dysfunction over a variable timeframe (12-15), the GDG recommend that patients with TPS should also be managed by an endocrinologist in close collaboration with the MDT.

Given the extreme rarity (2 to 4 per 100,000) (3) and the wide-ranging interdisciplinary aetiologies of CDI and TPS (Table 1 and 2), the extensive investigation and follow-up that may be required, and potential morbidity of underlying pathologies, the GDG felt that a coordinated interdisciplinary specialist discussion was required. This mandates involvement of members of the pituitary and the neurooncology MDT (including endocrinology, neuroradiology, surgeons experienced in transsphenoidal surgery (neurosurgery or ENT), neuropathology and oncology) to provide the opportunity for accurate decision making and diagnosis. The merits of any biopsy should be discussed on a case by case basis between all MDT members to minimise endocrine and visual morbidity. The surgical approach may vary depending on the specific skills of the local pituitary surgeon. Biopsies should be reported by a specialist neuropathologist.

1.3. **Given the rarity of pituitary tumours in CYP, a national clinical database and facilitated centralised review of images, histology and decision making process should be developed.** *(Delphi consensus 90%)*

1.4. **A centralised, national, pituitary MDT may require commissioning to facilitate review of complex cases.** *(Delphi consensus 90%)*

Data on rare diseases are often scarce, fragmented and biased. A national rare disease registry can change that by providing vital understanding of the condition's natural history and outcomes and by supporting the development of treatment protocols and research. The goals of such a registry would also include establishing a patient base for evaluating interventions (such as stalk biopsy in TPS), and facilitating connections among affected patients, families, and clinicians (16). The epidemiological data held in the registry would inform efforts to improve the quality of care and health outcomes, empower patients, inform further research and drive wider healthcare system improvements, for example commissioning of paediatric pituitary services specific to CDI and TPS. Centralised review of imaging, histology and decision making at a nationally commissioned MDT which interacts with a national database would facilitate this process, enhance consistent decision-making and standardise care.

1.5. **Offer all patients the opportunity to contribute to tissue banking and relevant ethically approved national and international biology and treatment studies.** *(Delphi consensus 100%)*

The availability of biological samples (e.g. biopsy material, blood and cerebrospinal fluid (CSF)) is essential to study the aetiology and develop potentially useful biomarkers for these conditions. Due to their rarity, single centre repositories are of limited value and national/international tissue-banking initiatives should be supported. There is a paucity of biology/treatment studies and national/international collaboration is required to undertake successful studies in these rare conditions. It is essential that patients are given the opportunity to participate in these studies.

2. Initial clinical assessment

2.1. Definition criteria for pituitary stalk thickening

2.1.1. **Consider that a pituitary stalk may be pathologically thickened and require further investigation and MRI surveillance if there is uniform/focal thickening (≥ 3 mm at the pituitary insertion and/or ≥ 4 mm at the level of optic chiasm) in the sagittal and/or coronal plane.** *(Low/moderate quality evidence, Delphi consensus 100%)*

2.1.2. **Consider further investigation and MRI surveillance for stalks measuring between 2 and 3 mm at the pituitary insertion and/or between 3 and 4 mm at the level of optic chiasm if associated with other clinical features increasing the risk of pathology (such as CDI, anterior pituitary or visual deficits).** *(Low/moderate quality evidence)*

2.1.3 **The interpretation of the stalk appearances requires neuroradiological expertise. The size criteria alone do not always allow differentiation between pathological thickening and physiological variants given the absence of normative data in children and the inter and intraindividual variability in the stalk measurements.** *(Low/Moderate quality evidence)*

In the absence of studies demonstrating the normal range for the size of the pituitary in young children and absence of information on how age may affect the size of the pituitary, the dimensions of a "normal" pituitary stalk were mainly derived from adolescent and adult radiological series. In a series of studies in healthy volunteers using a range of modalities including axial Computed Tomography (CT) (17), coronal 1.5T MRI (18, 19) and 3T MRI (T2 weighted images) in the sagittal and coronal planes (20), the upper normative limits have varied from between 2 mm and 4.5 mm depending on radiological technique, plane, cut and level of stalk measured (lower, mid or upper). Previously reported definitions for TPS in children are similarly inconsistent, ranging between > 2 mm to > 4 mm, most commonly > 3 mm (4, 5, 12, 14, 21).

The GDG considered the study of adults (mean age: 28 years, age range: 21-43 years) by Satogami et al (20) in which the stalk was measured at both the level of pituitary insertion and at the level of the optic chiasm, on T2-weighted oblique-axial fast spin-echo images, perpendicular to the long axis of the pituitary stalk, (see Figure 2) as the most accurate reporting normal dimensions for stalk size: 2.32 ± 0.39 mm (range: 1.65-3.17 mm) and 2.16 ± 0.37 mm (range: 1.56-3.04 mm) for the anterior-posterior and transverse diameters respectively at the pituitary insertion, and 3.25 ± 0.43 mm (range: 2.25-4.08 mm) and 3.35 ± 0.44 mm (range: 2.39-4.21 mm) respectively at the level of the optic chiasm.

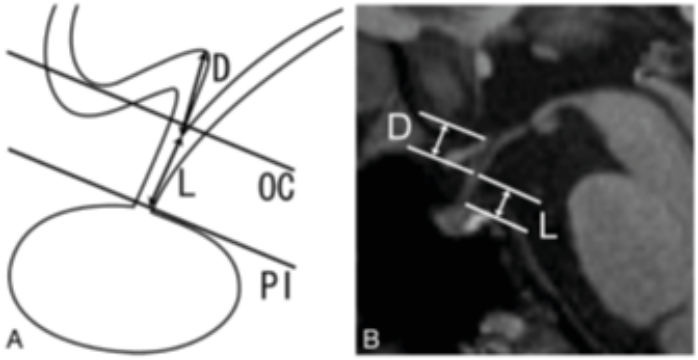


FIGURE 2 Pituitary stalk measurements
Schematic representation (A) with Magnetic Resonance Image comparison (B) of the physiological pituitary stalk shape and of the superior and inferior levels of measurement (from Satogami and colleagues).
D: Infundibular recess, L: Stalk length, OC: Optic chiasm, PI: Pituitary insertion

However, the GDG also took into consideration the data from one paediatric study by Godano et al (22), documenting smaller stalk sizes in children (mean size ranging between 2.35 and 2.82 mm at proximal level, between 1.79 and 2.45 mm at midpoint level and between 1.28 and 1.78 mm at distal level). This study provides measurements of the stalk size (T1 pre-contrast, T1 post-contrast, and T2-DRIVE images) in 102 children (aged 7.3-12 years) with various endocrine disorders (anterior and posterior pituitary deficits, precocious puberty, other conditions associated with short stature) but no reported TPS and eutopic posterior pituitary gland (22). Despite providing the only evidence of the stalk size in a paediatric population, the above study has the limitation of having been conducted in patients with endocrine disorders, possibly including patients with hypoplastic/threadlike stalks. Hence data about the normal stalk size in healthy subjects cannot be accurately extrapolated from this study.

On the basis of the above data and in order to increase its positive predictive value, the GDG agreed that for the purpose of this guideline a TPS will be defined as measuring ≥ 3 mm at the pituitary insertion and/or ≥ 4 mm at the level of optic chiasm just below the infundibular recess, either in the sagittal or coronal plane (taking the published upper limit of normal adult stalk measurements at the two defined points as its cut-offs) (see Figure 2). These are similar to most prior paediatric series, and hence unlikely to jeopardise sensitivity of detection of pathology. It remains, however, possible that the normal pituitary in children is smaller than in adults and these definitions may be set too high. For this reason, the GDG emphasized the importance of interpreting the stalk size in the context of the full clinical picture and pointed out that even smaller stalks (between 2 and 3 mm at the pituitary insertion and/or between 3 and 4 mm at the level of optic chiasm), particularly when associated with CDI and/or anterior pituitary deficits and/or visual disturbances, may have pathological significance and may deserve further investigation and MRI surveillance.

This definition does, however, benefit from delineating the exact level of measurement for the neuroradiologist and require careful future audit. It should also be considered that the stalk size might increase from birth to adolescence (23), hence age-appropriate cut-off criteria might be required. The GDG identified that urgent research to establish normative data in children is indicated (see section Research recommendations).

Interpretation of the pituitary stalk appearances requires specific neuroradiological expertise. The GDG recognises that size criteria alone may not always differentiate pathological thickening from physiological variants.

It is known that very large stalks (≥ 6.5-7 mm) are more likely to herald neoplasms (4, 12-15) and they usually clearly reveal themselves as tumours on the initial scan whilst they present less often as occult/idiopathic cases. However, for mildly/moderately enlarged stalks, little is known about the correlation between the degree of stalk thickening and the underlying pathology, its evolution overtime and the severity of pituitary/visual deficits. Previous papers have attempted some grading systems to score the severity of pituitary stalk thickening (12): minimal pituitary stalk thickness = 3.1–3.9 mm; moderate

pituitary stalk thickness = 4.0–6.5 mm; severe pituitary stalk thickness ≥6.5 mm. However these can be misleading. The degree of thickening depends on where the stalk is measured, particularly for mild forms, and there is always a measurement error to be taken into account, particularly for such a small structure. Generally, such grading systems can be used by the clinicians as a reference tool guide, but the GDG strongly believes that size criteria alone should not be used in isolation to guide the diagnostic and management pathway of these patients (See Figure 3 - Management Flow-Chart) and they would instead give the impression of false accuracy .

Finally, the shape of TPS has been described by Turcu and colleagues in 92 adults with stalk lesions and classified in: Uniform, Round/Diamond, Pyramid, and V-shaped (24). In this study round appearance was associated with congenital lesions, whilst uniform appearance was seen more in neurosarcoidosis. A correlation between the stalk morphology and the underlying aetiology in childhood has not been published. Hence, at the moment, there is not enough evidence to recommend that the stalk shape should guide the diagnostic and management pathway in CYP with idiopathic TPS. Our own data (13) showed that TPS due to germinomas more frequently present with upper stalk thickening, those due to LCH with upper and middle stalk thickening, whilst those cases remaining idiopathic despite extensive investigations can present with any type of focal (upper, middle, lower) or uniform thickening.

2.2. Dedicated pituitary MRI images to detect pituitary stalk thickening

Offer head and dedicated pituitary MRI to all CYP with suspected TPS and/or CDI. This should include uncontrasted 2D thinly sliced (<3mm) with no gap T1 and T2 weighted images in sagittal and coronal planes (and ideally at least one 3D highly weighted T2 sequence) to assess the possibility of uniform and/or focal thickening of the pituitary stalk in both planes. *(Moderate quality evidence, Delphi consensus 100%)*

The stalk tapers from its top level at the optic chiasm to its lower pituitary insertion; so, measurements at upper, middle and lower levels are required to capture its normal shape and size and the degree and shape of any abnormal thickening. As there are no differences between antero-posterior and transverse diameters at all levels of measurement, the thickening of the pituitary stalk can be assessed in any direction as long as the measurements are performed in the same plane and at the same level within a protocol applied in each single centre for stalk abnormalities.

Brain and dedicated pituitary MRI is essential to characterise the size and shape of the stalk and to detect congenital malformations possibly associated with CDI, such as absent posterior pituitary bright spot, anterior pituitary hypoplasia, midline brain and optic nerve abnormalities. The use of gadolinium-based contrast medium is indicated to rule out secondary brain metastases in cases where there is suspicion of a high-grade tumour such as a germinoma.

Children with congenital malformations of the suprasellar midline area and/or the optic nerves, termed SOD spectrum, are well recognised to have anomalies of the pituitary stalk (more frequently hypoplasia) and/or malposition of the posterior pituitary as well as hypoplasia of the corpus callosum and septum pellucidum which may be asymptomatic and diagnosed incidentally (27). These are often the milder spectrum which present outside the neonatal period and may develop evolving endocrinopathies over time (27).

Both head and dedicated pituitary MRI are essential to accurately characterise the stalk size and shape (22), avoid artefactual misinterpretation and detect any congenital malformations. Godano et al (22) favour high-resolution heavily T2-weighted sequences (such as sagittal T2 DRIVE which takes < 3 minutes to acquire, or CISS or FIESTA) to precisely measure the stalk in the sagittal plane and identify its abnormalities, without the addition of gadolinium contrast (22). Standard MR brain sequences must accompany the dedicated pituitary sequences to provide supporting information towards a diagnosis.

2.3. Additional MRI findings which increase suspicion of pathology

2.3.1.

The additional absence of a bright spot on the T1 non-contrasted scan and/or a significant reduction or enlargement of the pituitary, though not diagnostic, should increase suspicion of pathology. *(Moderate quality evidence, Delphi consensus 100%)*

2.3.2.

Consider a disease-tailored diagnostic approach if extra-pituitary MRI finding suggest a specific underlying aetiology (e.g. skull lesions for LCH or pineal lesions for bifocal germinoma or LCH). *(Moderate quality evidence)*

The presence/absence of associated structural pituitary abnormalities should also be taken into consideration, for example the absence of the posterior pituitary bright spot and anterior pituitary gland hypoplasia might increase suspicion of pathology (21), whilst in young children it is also important to assess for any possible congenital abnormality of the suprasellar midline structures, such as Septo-Optic Dysplasia (SOD). However, an absent posterior pituitary bright spot has also been observed in nephrogenic DI and in 4.1% of patients undergoing an MRI for non-endocrinological reasons.

Whilst its specific prevalence in CDI is unknown, pituitary hypoplasia has been described in 98% of patients with isolated hypopituitarism and 83.3% of those with associated midline brain defects and/or optic nerve hypoplasia. It has also been described in 24% of LCH cases, whilst hypophysitis and germinomas can present with pituitary enlargement.

Finally, it should be pointed out that the presence of additional extra-pituitary MRI findings might reveal the underlying aetiology (e.g. skull lesions suggestive of Langerhans Cell Histiocytosis (LCH) or pineal lesions suggestive of bifocal germinoma or LCH). Where the simultaneous presence of additional extra-pituitary MRI findings is suggestive of a specific underlying pathology, a disease-tailored diagnostic approach should be adopted. The stepwise decision-making approach recommended in these guidelines is intended for occult cases only (25, 26).

2.4. Systematic history and clinical evaluation

If the aetiology for a confirmed TPS and/or CDI is not apparent at presentation and a systematic history and clinical evaluation assessing for the commonest causes in CYP (Table 1, 2 and 3) have failed to reveal a potential focus for testing, or if focussed testing has proved uninformative, a stepwise decision-making approach for investigation and surveillance should be adopted in all patients *(Management Flow-Chart, Figure 3). (GDG consensus)*

Pituitary stalk pathology can damage endocrine function, cause optic pathway compression and herald wider histiocytic neurological involvement or malignancy (germ cell tumours). Establishing a potentially treatable diagnosis is hence paramount, but this needs to be balanced against the likely diagnostic yield and potential hazards of the pituitary stalk biopsy (endocrine and visual). Uncertainty about what constitutes a TPS further increases the diagnostic challenge. The GDG thus proposes a stepwise approach to investigation and monitoring of these patients. Initial investigations require targeting to common differential diagnoses in CYP (Table 1 and 2). If a detailed history and clinical examination (Table 3) suggests a specific aetiology, age-appropriate guidelines for its diagnosis may confirm this. If the diagnosis remains occult, repeated interval surveillance for these symptoms and signs should be undertaken, as pituitary disease may precede involvement of other organs, as in LCH (28). In these occult cases the stepwise approach detailed in the Management Flow Chart (Figure 3) is recommended.

3. First line investigations

3.1. Serum tumour markers, haematology, liver and renal function

3.1.1. **Offer measurement of serum beta-human Chorionic Gonadotropin (β-hCG) and Alpha Feto-Protein (αFP) to all CYP with radiologically confirmed TPS and/or idiopathic CDI.** *(Moderate quality evidence, Delphi consensus 92%)*

3.1.2. **Although non-specific, consider performing Erythrocyte Sedimentation Rate (ESR), Full Blood Count (FBC), liver function, urea, creatinine, and electrolytes, to aid the diagnostic process.** *(Delphi consensus 92%)*

The sensitivity and specificity of plasma βHCG and αFP tumour markers in diagnosing occult secreting germinomas is unknown; however, their use is standard in the assessment of patients with potential germ cell tumours. Their detectability and predictive value increases over time on repeated sampling, often coupled with increased pituitary stalk thickening (12, 14, 29). Cut off values for marker positivity differ between studies (30, 31) with highly sensitive β-hCG assays increasing the sensitivity of disease detection (32, 33).

Additionally, the GDG considered that the initial panel of investigations should also include ESR, FBC, urea, creatinine, electrolytes and liver function tests to screen for LCH/inflammatory conditions and assess fluid and electrolyte homeostasis in possible posterior pituitary dysfunction. The GDG accepted the suggestion from the Delphi panelists that additional screening for autoimmune conditions and screening for tuberculosis with quantiferon measurement should be performed only in selected cases (see section 3.5 Investigations upon specific indications).

3.2. Endocrinology

Offer an early endocrine assessment of growth and pubertal status, posterior pituitary function (i.e. urinary concentrating capacity) and baseline as well as dynamic tests of anterior pituitary function, including growth hormone (GH) and cortisol reserve to all CYP with TPS and/or CDI. *(Moderate quality evidence, Delphi consensus 100%)*

There is robust evidence that anterior pituitary deficiencies are frequently encountered in children with TPS and/or CDI (4, 13, 15); their prevalence depends on the underlying aetiology and the testing undertaken (especially for GH deficiency).

Patients presenting with isolated TPS may have occult CDI, especially if there is additional cortisol deficiency. If they are not overtly hypernatraemic, they should undergo a water deprivation test to assess the possibility of inappropriately low urinary concentrating capacity in the face of a high plasma osmolality, responsive to desmopressin. Recent data suggest that the direct measurement of hypertonic saline-stimulated plasma copeptin has greater diagnostic accuracy than the water-deprivation test in patients with hypotonic polyuria (34). Although the above study was conducted in patients ages 16 years or older and the applicability of this test to children remains unclear, this approach might become in common use in the future, particularly in cases where the water deprivation test is inconclusive. Assessment of dynamic cortisol reserve should be undertaken at the same time as that of GH to ensure patients are not at risk of unrecognised adrenal insufficiency and to ensure timely replacement, which may, in turn, unmask co-existing CDI.

Early endocrine review following presentation is thus essential to allow timely diagnosis and replacement therapy of both life-threatening adrenocorticotropic hormone (ACTH) insufficiency and CDI and to ensure normal growth and pubertal development. Furthermore the constellation of endocrine deficits may help the distinction between "organic" vs "idiopathic" TPS and between "genetic" vs "non-genetic" CDI. Anterior pituitary deficiencies are more likely to indicate neoplastic or congenital TPS rather than idiopathic forms (13, 15). Genetic forms of CDI

do not usually cause anterior pituitary dysfunction (4).

3.3. Opthalmology

Offer a formal baseline assessment of visual acuity and, if child is able to co-operate, visual fields by optometry, to all CYP with TPS and/or CDI, especially if the TPS is proximal or abutting chiasm *(Moderate quality evidence, Delphi consensus 100%)*

Many pathologies causing TPS and/or CDI may extend to optic pathway involvement and later visual compromise through compression or infiltration by tumour (LCH, germinoma, optic glioma), autoimmune hypophysitis, infection (tuberculoma) or congenital SOD. These include reduced visual acuity/blindness, nystagmus, bitemporal or homonymous hemianopia, proptosis, diplopia or ophthalmoplegia. In a retrospective review of 54 children 10% with isolated TPS, 22% with isolated CDI and 8% with both TPS and CDI presented with visual symptoms and signs. This increased to 35% over time only in those with both TPS and CDI (13), suggesting that patients with both TPS and CDI need very close ophthalmology monitoring.

3.4. Imaging

Offer a skeletal survey, abdominal ultrasound and a chest x-ray (CXR) to all CYP with idiopathic TPS and/or CDI in whom initial blood tests have failed to reveal the aetiology *(Moderate quality evidence, Delphi consensus 87%)*

LCH is one of the most common neoplastic causes of TPS and/or CDI in CYP (Table 1 and 2). The rate of detection of LCH at other sites in patients presenting with idiopathic TPS and/or CDI, using different imaging modalities, is not known and investigating the diagnostic yield of the systematic investigation proposed has been highlighted as one of the research recommendations of these guideline (see the research recommendations section of these guidelines). The skeleton is involved in 76.8% and the liver in 7.7% of LCH cases in children (35). A skeletal survey and an abdominal ultrasound are therefore recommended as part of first line investigations in all CYP with TPS and/or CDI. If the skeletal survey identifies an abnormality suggestive of LCH more accessible to biopsy, this could provide an alternative to biopsy of the stalk. If the liver or spleen is enlarged, it will raise the suspicion of LCH or other multisystem disease and point to the need for further targeted investigations. In addition to the skeletal survey and abdominal ultrasound, a CXR is also recommended as part of the initial assessment of patients with LCH (25). Pulmonary involvement occurs in 7.6% of LCH cases (35). Tuberculosis, sarcoidosis and metastatic malignancy are much less likely aetiologies in children (Table 1 and 2) than in adults (24), but may also result in an abnormal CXR. TB meningitis may be associated with pulmonary involvement in 50% of the cases, hence British guidelines recommend CXR as first line investigation in this condition (36).

3.5. Investigations upon specific indications

3.5.1. Infectious and inflammatory/autoimmune disease

3.5.1.1. Consider testing for Tuberculosis (TB) or autoimmune disease, as per local practice, if indicated by history and clinical examination. *(Low-moderate quality evidence, Delphi consensus 92%)*

Infectious and systemic inflammatory/autoimmune diseases are rare causes of TPS and/or CDI in CYP (Table 1 and 2) .Thus screening tests for their detection are likely to have a very low yield and are recommended only in specific cases in which there is high probability of these conditions suggested by the symptoms and signs.

TB meningitis is suggested by a history of days to weeks of non-specific failure to thrive, irritability, vomiting, abdominal pain and sleep disturbances in the young (37) and headaches, fever, anorexia, and vomiting in older patients (38, 39). Pituitary tuberculomas may cause evolving pituitary deficiencies but be otherwise relatively asymptomatic (36, 40-42). Tuberculin skin test and plasma Interferon-Gamma Release Assays (IGRAs) may provide evidence of prior TB, but are insufficiently sensitive and specific to diagnose active tuberculous central nervous system (CNS) disease; in case of TB meningitis this requires cerebrospinal fluid (CSF) mycobacterial studies (38).

In adults, 96% of patients with hypophysitis have TPS and 72% CDI (43, 44). Autoimmune hypophysitis is, however, rare in CYP (45) (Table 1 and 2). The definitive diagnosis of primary lymphocytic hypophysitis relies on histology, since neuroimaging findings are non-discriminatory, and the anti-pituitary and anti-hypothalamic antibodies described (46, 47), are of too low sensitivity and specificity (45). IgG4-related hypophysitis is a recently described entity belonging to the group of IgG4-related disease, more frequent in older men but also described in young women. This condition can present with pituitary involvement (including TPS, CDI and anterior hypopituitarism), usually accompanied by multiorgan involvement (48). Paediatric cases have never been reported in the literature, hence the present guidelines do not recommend screening with IgG4 level in CYP presenting with idiopathic CDI and TPS. However, this is a newly emerging disease and this recommendation might change in the future.

3.5.1.2. **3.5.1.2. Serum Angiotensin-Converting Enzyme (ACE) to screen for neurosarcoidosis in CYP with TPS and/or CDI is not recommended.** *(Low-moderate quality evidence, Delphi consensus 100%)*

Although being reported as a frequent cause of TPS in adulthood (24), sarcoidosis is exceptionally rare in CYP with TPS and/or CDI (Table 1 and 2). Given the low sensitivity and specificity of serum ACE in detecting sarcoidosis (49, 50) and the insufficient experience of it by the Delphi participants, the GDG does not recommend its use as tool for diagnosing sarcoidosis in CYP with TPS and/or CDI.

3.5.2. Congenital midline brain abnormalities [also called Septo-optic dysplasia (SOD) spectrum]

Offer genetic counselling and, where appropriate, molecular genetic testing for SOD spectrum, if imaging (midline anomalies, optic nerve hypoplasia), age and ophthalmology are consistent with this diagnosis. *(Moderate quality evidence)*

Midline neuroimaging abnormalities and/or optic nerve hypoplasia in association with CDI in a young child should raise suspicion of SOD spectrum. This rare congenital disorder is diagnosed by the presence of at least two of either optic nerve hypoplasia, midline abnormalities or pituitary deficits (27). Causative mutations have been identified in less than 20% of cases (51, 52), but SOD may account for between 3.4%-14.3% of cases with CDI (Table 2). Thus genetic counselling, and if appropriate genetic testing, should be offered to CYP presenting with clinical SOD and to their families.

3.5.3. Familial CDI

Offer genetic counselling and genetic testing for inherited forms of CDI in CYP with isolated CDI and neither TPS nor other midline neuroimaging abnormalities suggestive of SOD, especially if there is a family history and/or early childhood presentation. *(Moderate quality evidence, Delphi consensus 100%)*

Familial forms of isolated CDI account for between 2% (13) and 7.5% (4) of CDI in CYP (Table 1 and 2) but these data are skewed by differing inclusion criteria and the availability of genetic testing. A presentation early in life (before 2-3 years of age) with isolated CDI and without other evolving endocrinopathy over time, a normal pituitary stalk and otherwise normal midline MRI appearances should prompt genetic counselling and analysis of the more common autosomal dominant mutation

in the AVP-NPII gene or the rarer autosomal recessive and X-linked recessive forms, particularly if there is a positive family history of polyuria and polydipsia (5, 53). The presence of the posterior pituitary bright spot, which may be present at diagnosis yet become invisible overtime (54), does not exclude a diagnosis of inherited familial CDI. PCSK1 mutations resulting in severe malabsorptive diarrhoea, growth hormone deficiency, central hypothyroidism, central hypogonadism and central hypocortisolism have also been recently associated with clinical CDI in 80% of these cases. In the rare X-linked form currently no known genes have been identified.

4. Second line investigations

4.1. Lumbar puncture

4.1.1. Indications

Consider a diagnostic lumbar puncture if, after initial blood tests and imaging, the aetiology is not apparent and the patient meets one or more of the following criteria a) TPS ≥ 6.5-7mm or progressive enlargement of TPS over time b) TPS associated with CDI c) TPS with evolving anterior pituitary deficiencies and/or pituitary enlargement and/or deteriorating visual function. ***(Moderate quality evidence, Delphi consensus 93%)***

CYP with TPS and/or CDI whose aetiology has not yet been identified from the above stepwise screening and whom, in addition, are causing concern by manifesting a TPS of 6.5-7 mm or more, multiple or evolving endocrinopathies and/or visual compromise, require CSF sampling as opposed to adopting a watch and wait strategy (See Figure 3 - Management Flow-Chart).

In two paediatric case series comprising 53 children followed for some four years, neoplasia (LCH or germinoma) was only later diagnosed in those cases initially presenting with TPS and CDI, and never in cases with isolated TPS (without CDI) (13, 14). By contrast, the data for later diagnosis of a neoplasm in patients presenting with isolated CDI in CYP is less clear. In one series LCH, germinoma, optic pathway glioma or craniopharyngioma developed in 40% of 38 cases 1.42 – 21.83 years after presenting with isolated CDI, but 45% of these had also developed TPS during the follow-up (13). In another series, 0/12 presenting with idiopathic isolated CDI and no TPS had neoplasia 0.6 to 15.3 years later, compared with 4/10 with CDI and TPS who developed germinoma (1) or LCH (3) over the same time period (4). Thus the GDG considered that the combination of CDI and TPS was more likely to indicate underlying evolving pathology requiring further investigation by lumbar puncture than TPS alone, whilst the evidence for isolated CDI was inconsistent. In these latter two series the presence of evolving anterior pituitary dysfunction in CYP presenting with idiopathic TPS and/or CDI was particularly likely to herald an underlying oncological diagnosis compared to those without: 85% vs 39% (4) and 67% vs 39% (13). It was also noted that visual deterioration was associated with neoplasia.

4.1.2. Markers of GCT and LCH

When a diagnostic lumbar puncture is undertaken, offer measurement of β-hCG and αFP in the CSF, together with CSF cytology. ***(Moderate quality of evidence, Delphi consensus 100%)***

Detecting germ cell tumours using CSF β-hCG, αFP and cytology is well established, though the sensitivity of these tests in detecting a GCT in patients with idiopathic TPS and/or CDI is not known. The GCT most common in the suprasellar region (germinoma) may be associated with mild elevation of βHCG in CSF in up to 38% of cases but is usually non-secretory. The majority of germinoma patients with raised CSF βHCG have normal serum βHCG (55). Significantly raised βHCG or raised αFP (in the context of TPS) indicates the presence of choriocarcinoma and yolk sac tumour respectively, or the presence of a mixed malignant germ cell tumour. The tumour marker levels at which the diagnosis of these conditions can be made is a matter of some debate and not the subject of this guideline (31). It is worth noting that slightly raised levels of β-hCG has been described in other conditions, including LCH and craniopharyngioma (56, 57). Additional biomarkers of germ cell tumours including microRNA are undergoing evaluation and may in future provide more accurate and specific means of detecting

germ cell tumours (see research recommendations below) (58).

Detecting central nervous system LCH in CSF has been less fruitful and the recent study demonstrating that osteopontin is a potentially helpful marker of LCH in the CSF, did not include patients with pituitary lesions (59). Potential CSF biomarkers of LCH in patients with pituitary disease require further investigation (see research recommendations below).

Several authors have recently explored novel disease markers in patients with brain tumours. Okamoto et al suggest Fluid-Placental Alkaline Phosphatase (PLAP) can differentiate intracranial germ cell tumours from other types of brain tumours and detect disease recurrence, whilst Murray et al highlight how microRNA quantification may assist the non-invasive diagnosis, prognostication and management of such patients. BRAF-V600E alterations have been identified in various types of primary brain tumours and their detection in the serum, plasma and CSF of children with brain tumours is under investigation; for example, whether its detection in the CSF of patients with LCH might indicate increased risk for LCH-associated neurodegeneration. These and other novel markers are recommended for further research.

4.1.3. Tuberculosis and neurosarcoidosis

4.1.3.1. **Consider CSF analysis for TB in those at risk.** ***(Moderate quality evidence, Delphi consensus 78%)***

Given the rarity of CNS tuberculous disease causing TPS/CDI in CYP (Table 1 and 2), routine examination of the CSF for this condition is not recommended.

Examination of the CSF for acid-fast bacilli (38) should be considered in those rare selected cases identified as high risk from the history, symptoms and signs. However, because the diagnostic yield is lower in infected children than adults (15-20% vs 80%) and critically dependent on the volume of CSF required (10% of the total), if TB meningitis is strongly suspected, repeated CSF examinations and commercial nucleic acid amplification assays on CSF are recommended. A tissue biopsy has a much higher yield specifically in tuberculoma (38)

4.1.3.2. **Consider CSF ACE if neurosarcoidosis is strongly suspected.** ***(Low quality evidence, Delphi consensus 78%)***

Neurosarcoidosis is unlikely to be the cause of TPS/CDI in CYP (Table 1 and 2). Published evidence regarding the clinical utility of CSF ACE in diagnosing neurosarcoidosis is inconsistent (49, 60) and its measurement is not recommended unless neurosarcoidosis is strongly suspected and it is part of a wider diagnostic process.

4.2. Imaging

4.2.1. **Consider whole body imaging to detect distant occult LCH lesions more amenable to biopsy, in CYP whose TPS and/or CDI remain idiopathic after initial blood tests, imaging and CSF screening but are nevertheless concerning for neoplasia (TPS is ≥ 6.5-7mm and/or the TPS is associated with CDI and/or changes in the pituitary size and/or the TPS is progressive and/or there is an evolving endocrinopathy and/or there is deteriorating visual function).** ***(Moderate quality evidence, Delphi consensus 90%)***

4.2.2. **Whole body imaging may consist of FluoroDeoxyGlucose Positron Emission Tomography MRI / CT (FDG PET MRI / FDG PET CT) or whole body MRI, depending on the local availability.** ***(Moderate quality evidence, Delphi consensus 90%)***

CDI (with or without TPS) due to LCH can occur years before the diagnosis of LCH is established histologically from a lesion elsewhere. Whole body imaging with FDG PET MRI/CT or whole body MRI are not yet routinely used as part of the staging process of patients with LCH but may detect LCH lesions not identified by routine imaging such as skeletal survey (25, 61-63). If abnormalities suggestive

of LCH are detected outside of the pituitary stalk, this may provide a more easily accessible target for biopsy. The rate at which these imaging modalities will identify such lesions in this context is not known but the potential it provides of expediting a diagnosis of LCH in a patient with CDI and/or avoiding the need for a pituitary stalk biopsy in those with TPS, makes this worth considering. The type of whole body imaging used will depend on local availability and individual circumstance of the patient.

5. Biopsy

5.1. **In CYP who continue to pose a diagnostic dilemma after appropriate repeat neuroimaging, whole body imaging and, if necessary, repeat CSF testing, consider a biopsy of the TPS if there is a very large (≥ 6.5-7mm) or progressively enlarging stalk and/or evolving hypopituitarism and/or there is visual deterioration.** *(Low-Moderate quality evidence, Delphi consensus 100%)*

5.2. **A biopsy should only be undertaken if it is judged by the MDT to be of sufficient size to yield a diagnostic sample and the benefits outweigh the risk of the procedure.** *(Delphi consensus 100%)*

5.3. **Pituitary surgery on CYP should be undertaken by a pituitary surgeon nominated by the MDT. There should be ready access to transsphenoidal, endoscopic and base of skull techniques and readily available age-appropriate endocrine support.** *(Low quality evidence, Delphi consensus 90%)*

There is insufficient evidence in the literature regarding indications for stalk biopsy in CYP with TPS. It is, however, known that very large stalks (≥ 6.5-7 mm) and an association with pituitary and visual deficits are more likely to herald neoplasm in these CYP (4, 12-15). The GDG therefore suggest that these criteria are taken into consideration in the MDT decision-making process regarding a biopsy in CYP with TPS. Studies reporting biopsies of TPS in children either via a transcranial or transphenoidal route have shown a good diagnostic yield with low morbidity with a diagnosis in 6 of 7 patients with no morbidity via a transcranial route (64) and diagnosis in 7 of 7 patients (1 required a second biopsy) via a transphenoidal route (65).

In order to ensure the highest possible diagnostic yield and the lowest morbidity (endocrine and visual), surgery should be undertaken by surgeons skilled in paediatric pituitary surgery with ready access to transphenoidal, endoscopic and base of skull techniques. Pituitary surgery may lead to severe peri-operative endocrine morbidity (caused by triphasic response / salt wasting) and immediate access to paediatric endocrine support is essential.

6. Treatment

6.1. **When an underlying aetiology is identified, the management should be dictated by this. Do not offer empiric disease-specific treatment without a confirmed aetiological diagnosis.** *(Delphi consensus 93%)*

Treatment of the underlying possible aetiologies differs markedly therefore disease specific treatment requires an established diagnosis. For instance, CNS germ cell tumours are treated with radiotherapy or a combination of chemotherapy and radiotherapy (66), while LCH is treated with prednisolone and chemotherapy (25). LCH induced CDI is not usually reversible and the possibility that systemic LCH directed treatment in these patients may reduce the risk of later developing anterior pituitary dysfunction or neurodegeneration is speculative and not proven (28).

Prospective studies have shown that only 19-20% of patients initially presenting with isolated

CDI are eventually diagnosed as LCH (5, 67, 68). This guideline therefore does not recommend empiric LCH treatment in the absence of a histological diagnosis. However, there is a great need for prospective randomised trials looking into strategies for the prevention of CNS complications in high risk LCH children (69)

7. Surveillance

7.1. Surveillance for all CYP presenting with TPS and/or CDI

7.1.1. Offer regular surveillance including history, examination, endocrine +/- visual assessment and pituitary MRI to all CYP with idiopathic TPS and/or CDI. *(Moderate quality of evidence, Delphi consensus 100%)*

7.1.2. In the absence of new symptoms/signs and if the MRI appearances are stable, consider the following frequency of surveillance: 3-monthly intervals for 6 months, 6-monthly intervals until 2-3 years and annually thereafter. *(Low quality evidence, Delphi consensus 100%)*

7.1.3. If surveillance reveals progressive endocrinopathies and/or evolving visual disturbance and/or progressively enlarging TPS, consider repeating first and second line investigations (+/- biopsy). *(Moderate quality of evidence)*

7.2. Reduced surveillance for CYP with stable isolated TPS

Consider reducing the MRI surveillance frequency and/or to discharge patients if, after 5 years of stable imaging appearances, growth and puberty are complete, in CYP presenting with isolated TPS and no evidence of any anterior or posterior pituitary dysfunction, in whom the TPS either normalises or remains stable at under 4.5-5 mm in maximal diameter. *(Low quality of evidence, Delphi consensus 100%)*

7.3. Reduced surveillance for CYP with stable isolated CDI

7.3.1. Familial CDI

In CYP with isolated CDI in whom a mutation responsible for familial CDI is documented, MRI surveillance should be discontinued. *(Moderate quality of evidence)*

7.3.2. Isolated idiopathic CDI

7.3.2.1. Consider discontinuing the MRI surveillance after three years in CYP with isolated idiopathic CDI and no evidence of either TPS, anterior pituitary dysfunction or visual deterioration. *(Moderate quality of evidence)*

7.3.2.2. Offer continued regular endocrine and clinical surveillance to screen for a late presenting germ cell tumour or LCH to all patients with isolated idiopathic CDI. *(Moderate quality of evidence)*

CYP with idiopathic TPS and/or CDI may harbour an occult neoplasm which manifests years later (4, 12, 13, 15, 68, 70). Where the aetiology is identified, it is usually identified in the first three years of surveillance (4, 12), though the occasional occult LCH and germ cell tumour have been detected up to 10 (12) and 20 years (70) after presentation, respectively (both these patients had CDI in addition to TPS at presentation). Significantly enlarged TPS and/or CDI are more likely to herald neoplasia than marginal stalk thickening or TPS alone (4, 12, 13, 15), whilst additional anterior pituitary deficits or visual disturbances increase the likelihood of pathological and possibly neoplastic disease (4, 5, 13, 14).

The optimal interval for surveillance imaging is unknown, but neuro-oncology surveillance intervals are typically 3 - 6 monthly initially. The GDG suggest 3-monthly scans for the first six months to ensure rapidly evolving disease is quickly identified, particularly in cases with a higher risk of heralding occult oncological conditions (TPS ≥ 4·5/5·0mm or TPS + CDI or TPS with evolving anterior pituitary deficiencies and/or pituitary enlargement and/or visual impairment or TPS with other concomitant brain MRI abnormalities suggesting an underlying oncological disease). Given rapid disease progression is unlikely after the first six months and most aetiologies come to light in the first three years of follow up, the GDG suggests that the interval is then increased to six months until two years and annually thereafter, provided MRI appearances continue to be stable or improve. The diagnosis of germinoma was made within the first 2.5 years with a systematic clinical/endocrine/imaging follow-up every six months in the first three years (67). If, on the other hand, surveillance identifies new or progressive clinical (endocrine and visual) or neuroimaging findings, closer monitoring and testing should be undertaken according to the stepwise approach summarized in the Management Flow-Chart (Figure 3).

In those cases of isolated TPS where thickening is marginal (under 4.5-5 mm), possibly incidental and/or a physiological variant, and the patient is otherwise entirely asymptomatic, discharge may be considered after five years of stable imaging appearances, once growth and puberty are complete. Though low (4, 12), CYP with isolated idiopathic CDI have a slightly higher potential for neoplasia. The GDG felt this justifies the requirement for continued clinical vigilance for, and patient awareness of, the symptoms and signs of possible underlying pathology during their endocrine follow up, even if surveillance neuroimaging is discontinued after 3 years (67).

8. Transition

8.1. **All CYP with an endocrinopathy and those with TPS ≥ 4.5-5 mm or progressively enlarging TPS, whose growth and puberty are complete, should be transferred to receive on-going age-appropriate care in a specialist adult endocrine centre with experience in managing pituitary tumours for continued surveillance to detect late presenting germ cell tumour or LCH.** *(Moderate quality evidence)*

In order to continue surveillance to detect late presenting germ cell tumours or LCH and provide appropriate endocrine care, CYP with idiopathic TPS greater than 4.5-5mm or a progressively enlarging TPS, and those with CDI or associated endocrinopathies, should transfer to receive ongoing age-appropriate care in a specialist adult endocrine centre with experience in managing pituitary tumours with ongoing involvement of the pituitary MDT, once they reach the age of 16 – 18 years and their growth and puberty are complete. Poorly managed transition/transfer can cause CYP to disengage from adult care and potentially suffer health consequences. The process ideally starts from age 13 years, with agreed, consistent monitoring pathways between paediatric and adult endocrine services and facilitated meeting(s) with members of the adult team prior to transfer (NICE transition guidance) (71).

Figure 3: Guideline Tool/Management Flow Chart

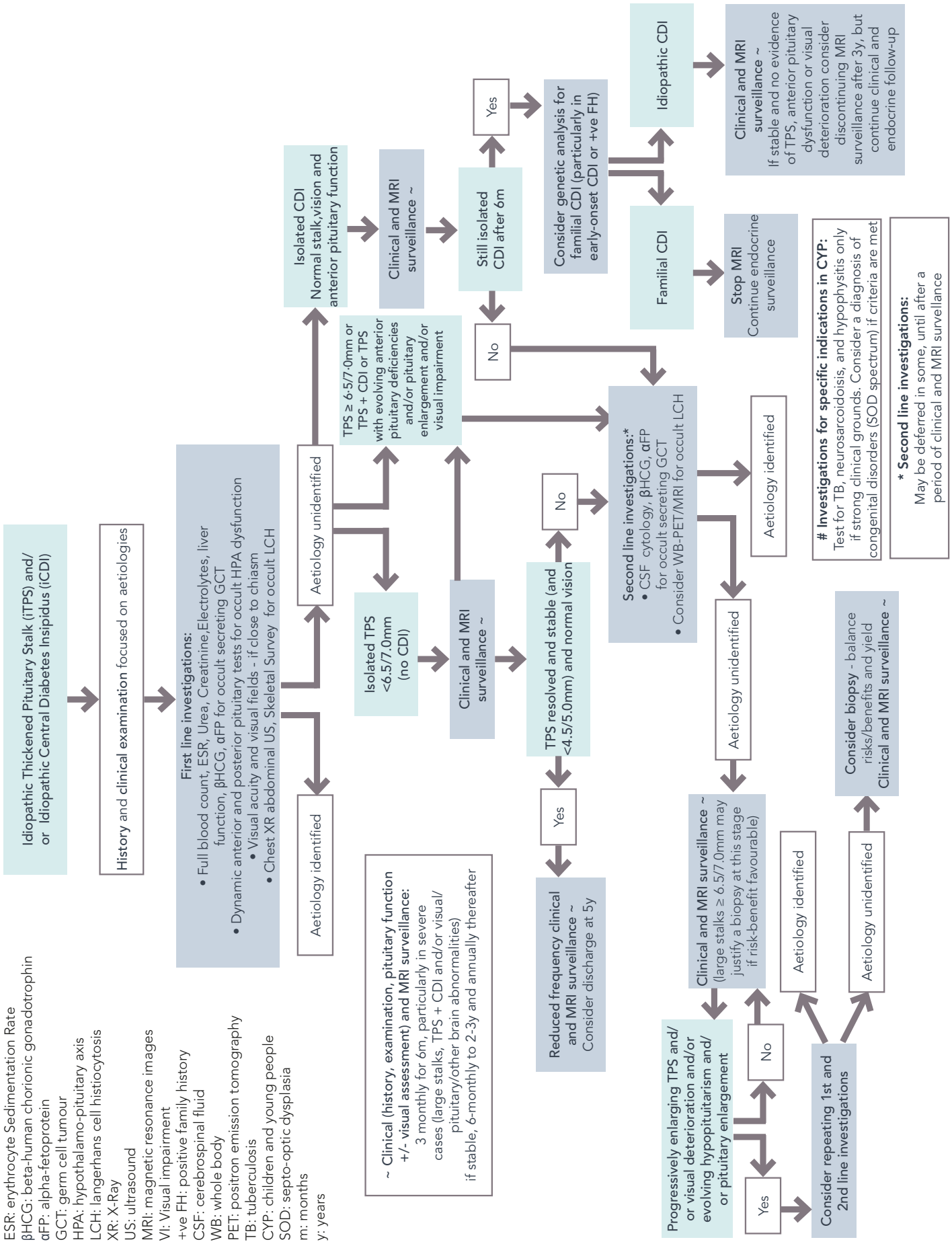


FIGURE 3

All CYP under 19 years of age with TPS (≥ 3 mm at the pituitary insertion and/or ≥ 4 mm at the level of the optic chiasm)* and/or CDI, in whom the aetiological diagnosis is not apparent at presentation, should undergo systematic evaluation designed to detect the common causes in this age group (Table 1 and 2).
** The stalk size should be interpreted in the context of the full clinical picture and it is recognised that smaller stalks (between 2 and 3 mm at the pituitary insertion and/or between 3 and 4 mm at the level of optic chiasm), particularly when associated with CDI and/or anterior pituitary deficits and/or visual disturbances, may have pathological significance and may deserve further investigation and MRI surveillance.*

The initial assessment is focused on:

a) detecting dysfunction of the hypothalamic-pituitary axis (by baseline and dynamic endocrine testing) and the optic pathway (visual acuity and visual fields) and

b) screening for LCH and secreting germ cell tumours by minimally invasive investigations [Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), liver function tests, serum beta-human Chorionic Gonadotropin (β-hCG) and Alpha Feto-Protein (αFP), chest x-ray (CXR), skeletal survey, abdominal ultrasound].

If a specific aetiology is identified at any point, further investigation and management should follow disease-specific age-appropriate guidelines.

Otherwise, a systematic stepwise approach, taking into account the presentation (isolated TPS vs isolated CDI vs TPS+CDI), the degree of pituitary stalk thickening (if present), and the presence or absence of any anterior pituitary deficits or visual impairment should be followed (Figure 3)

The subsequent testing and surveillance of those in whom the aetiology remains unknown, is dependent on the presentation:

- PATIENTS WITH ISOLATED IDIOPATHIC CDI (and no TPS or other endocrine or visual compromise), should undergo clinical and MRI surveillance at three and six months. If the CDI remains isolated, and particularly if of early-onset with positive family history, with/without an absent posterior pituitary bright spot on MRI, a genetic analysis and counselling for familial CDI should be offered. If causative mutations are identified it will allow for MRI surveillance to be discontinued and patients treated appropriately with on-going endocrine follow-up.

  In the absence of a confirmed mutation or suggestive clinical history for familial CDI, we suggest six monthly clinical and MRI surveillance for two years and annually thereafter until at least three years

  If MRI and clinical signs remain unchanged after five years, imaging surveillance may be discontinued, but clinical and endocrine follow-up should continue to detect the rare case of late occult germ cell tumour or LCH.

  Patients with new concerning signs or symptoms developing during follow-up require active re-investigation.

- **PATIENTS WITH ISOLATED TPS < 6.5-7 mm** (and no associated CDI, endocrinopathy or visual compromise) should undergo clinical and MRI surveillance at three and six months. If the TPS normalises or remains stable at under 4.5-5 mm in maximal diameter, and the patient remains well and asymptomatic, the MRI frequency may be gradually reduced and then discontinued at five years.

- **PATIENTS WITH ISOLATED TPS ≥ 6.5-7 mm OR PATIENTS IN WHOM ANY TPS IS ASSOCIATED WITH CDI** require second line investigations, including CSF tumour markers, and whole body imaging to assess the possibility of peripheral /distant LCH. Decisions in this regard should be individualised and discussed in an age- and disease- specific neuro-oncology and/or pituitary MDT.

Patients in whom second line investigations reveal no underlying aetiology should continue on six monthly clinical and MRI surveillance for two-three years and then annually thereafter.

A biopsy of the pituitary stalk should only be considered if the stalk is large (over 6.5-7 mm) or progressively enlarging, especially if associated with CDI or rapidly evolving wider endocrinopathies and/or visual compromise, and if repeated re-investigation has proven negative and the MDT judges the benefits of the procedure to outweigh its risks.

For all three groups, the clinical assessment during surveillance should consistently include focused history and clinical examination to detect signs and symptoms of known possible aetiologies which might not be evident at presentation and only develop later during follow-up.

Research recommendations

Having reviewed the evidence and sought consensus opinion on areas where evidence is lacking or contradictory, the GDG has identified that research is needed to:

- Provide normative age-appropriate references ranges for pituitary stalk measurements at three levels in CYP and explore the potential value of stalk size/shape and other imaging characteristics in distinguishing between different underlying causes
- Study the true incidence of varying aetiologies and the natural history of idiopathic TPS/CDI - which remains occult despite systematic investigation and long term surveillance
- Investigate the value of novel blood, CSF and urine markers of disease (e.g. microRNA's, cell free BRAF V600E, PLAP), and/or new imaging techniques in establishing a diagnosis without a pituitary biopsy
- Measure the impact of a systematic diagnostic and surveillance program on diagnostic yield, outcome and quality of life
- Assess the impact of early diagnosis and treatment of LCH lesions associated with high risk of CNS disease (CDI, skull base lesions)

Implementation, evaluation and audit

In addition to publishing the electronic version of this guideline together with the other seven guidelines in this series on the main CCLG website, providing electronic cross references between them and linking all of these to the BSPED, we will also disseminate them widely to all the stakeholder groups and offer similar electronic links. The guidelines have been presented at the annual conference of BSPED, ESPE, HS, and the RCPCH. We plan for publication of peer reviewed summary guideline articles, either as a series or a supplement, in a high impact speciality journal.

This and each of the other seven guidelines in this series, will be subject to evaluation. CCLG will explore the possibility of an automated electronic link to the web-based guidelines, which would provide both a record of those using the guideline and facilitate a voluntary data retrieval system for evaluation of both professional experience and patient treatment outcomes, at 2 to 3 year intervals. The guidelines recommend the establishment of a national registry for these patients and CCLG is exploring ways in which this can be achieved. Such a registry would provide an additional resource for guideline evaluation and audit.

In the case of this guideline, it is proposed that the following outcomes form part of a longitudinal audit programme:

- Care led by an endocrinologist in a specialist centre with expertise in managing pituitary tumours
- Appropriate MDT involvement in care; discussed in national MDT
- Participation in clinical trials and tumour banking
- Application of 1st and 2nd line investigations, surveillance and transition in accordance with the guideline
- Indications for and outcomes of biopsies
- Diagnostic outcomes
- Event free survival, overall survival, endocrine and visual outcomes

Resource implications

The purpose of these recommendations is to improve a) understanding through audit and research and b) patient health outcomes by aiding healthcare professionals in the identification and treatment of idiopathic TPS and/or CDI which may herald important but occult neoplastic disease in CYP. In particular, we aim to enhance streamlined interdisciplinary referral which is currently outside standard cancer or endocrine pathways, for the highly specialised management strategies we recommend (neuroendocrine assessment, specialist neuroimaging and neurosurgical oncology services (pituitary biopsy). The rarity of the diseases they herald, and the lack of coordinated interdisciplinary decision-making dialogue have impeded timely care and registry outcome data for these patients. A facilitated national virtual interdisciplinary meeting has been piloted and welcomed but ultimately, referral to a nominated regional centre with both pituitary endocrine and neurosurgical oncology expertise is likely to be required.

Final considerations

The rarity of paediatric TPS and/or CDI makes their management challenging to the extent that the multidisciplinary professionals involved in their care have repeatedly called for these society-commissioned, evidence- and consensus- based guidelines, since our original 2005 consensus recommendations, which were well received by both users and patient groups. During the process for 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 and improve access to, and equity of, expertise in care, such a national register and centralised, advisory panel needs to be expedited alongside the development of tertiary, dedicated and age-appropriate, endocrine oncology multidisciplinary teams and services.

Appendix 1: PICO clinical questions

1. Epidemiology
2. Presenting features
3. Diagnosis/investigations
4. Treatment
5. Follow-up/surveillance

P: population I: interventions C: comparison O: outcome T: time-course

1. Epidemiology

a. Incidence	P In Children <19 years of age O what is the incidence of -isolated pituitary stalk thickening -isolated CDI - pituitary stalk thickening and CDI T per year?
b. Age-specific incidence	P In children <19 years of age do I children aged: • 0-5y • 5-10y • 10-15y • 15-19y C compared with children in other age groups O have a higher age specific incidence of pituitary stalk thickening/ CDI?
c. Sex specific incidence	P In children <19 years of age I do boys C compared with girls O have a higher sex-specific incidence of pituitary stalk thickening/ CDI?
d. Ethnicity-specific incidence	P In children <19 years of age I do non-white populations C compared with white populations O have a higher ethnicity specific incidence of pituitary stalk thickening/ CDI?

2. Presenting features

a. Time to diagnosis	P In Children <19 years of age O what is the average time to diagnosis from first symptoms in pituitary stalk thickening/ CDI
b. Age-specific presenting features	P In children <19 years of age with pituitary stalk thickening/ CDI I do children aged: • 0-5y • 5-10y • 10-15y • 15-19y C compared with children in other age groups O have different age specific presenting features?

c. Presenting symptoms and signs	P In children <19 years of age with pituitary stalk thickening/ CDI? O what is the frequency of the following symptoms/signs: • Symptoms/signs of anterior pituitary dysfunction • Symptoms/signs of posterior pituitary dysfunction • Symptoms/signs of visual impairment • Neurological symptoms or signs • No symptoms/signs (Incidental) • Distant symptoms/signs of LCH T At diagnosis; at 1 year post diagnosis; at 5 years post diagnosis; at 10 years post diagnosis.
d. Aetiology 1	P In children <19 years of age with pituitary stalk thickening/ CDI O What proportion of patients had an identifiable • Congenital • Inflammatory • Neoplastic • LCH • Autoimmune Underlying pathology (need to record what each individual diagnosis was within each subgroup) T at diagnosis; at 1 year post diagnosis; at 5 years post diagnosis; at 10 years post diagnosis; at any time during follow up
e. Aetiology 2	P In children <19 years of age with pituitary stalk thickening/ CDI O what was the time to identification of an underlying aetiology T from initial identification of pituitary stalk thickening/ CDI
f. Genetics	P In children <19 years of age with pituitary stalk thickening/ CDI O Which genetic mutations/syndromes have been described as being associated?

3. Diagnosis/investigations

a. Definition	P In Children <19 years of age with pituitary stalk thickening O Is diagnosis based on radiological findings of • Transverse diameter at pituitary insertion>2mm • Transverse diameter at the level of the optic chiasm>3mm • other T at time of diagnosis?
b. Radiological features	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing MRI O what proportions will have the following pattern - normal - uniform thickening - v-shaped - round/diamond shape - pyramid shape T at time of diagnosis?
c. Radiology	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing MRI (T1 scan) O what proportion will have an ectopic posterior pituitary gland? T at time of diagnosis?
d. Mode of imaging	P In children <19 years of age with pituitary stalk thickening/ CDI I how does CT scanning in addition to MRI C compare to MRI alone O In terms of sensitivity and specificity for diagnosis of thickened pituitary stalk?

e. Vision 1	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion are tested for visual dysfunction T at diagnosis; at any time during follow up
f. Vision 2	P In children <19 years of age with pituitary stalk thickening/ CDI I who undergo formal visual assessment O what proportion have which type of vision abnormality T at diagnosis; at any time during follow up
g. Vision 3	P In children <19 years of age with pituitary stalk thickening/ CDI I/C which of the following visual tests (in combination or alone) • Formal field testing • Informal field testing • Goldmann perimetry • Visual acuity • (?other) O are most sensitive and specific at detecting visual dysfunction T at diagnosis; at any time during follow up
h. Anterior pituiary dysfunction 1	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion are tested for anterior pituitary dysfunction T at diagnosis; at any time during follow up
i. Anterior pituitary dysfunction 2	P In children <19 years of age with pituitary stalk thickening/ CDI O what is the incidence of the following based on biochemical testing • GH deficiency/insufficiency (on stimulation testing) • Delayed/arrested puberty (on LHRH testing or basal testing) • Precocious puberty (on LHRH testing or basal testing) • Central hypothyroidism (TFTs) • ACTH deficiency (standard synacthen test/low dose synacthen/glucagon/ insulin tolerance test) • Hyperprolactinaemia (serum prolactin) T at diagnosis; at any time during follow up
j. Posterior pituitary dysfunction 1	P In children <19 years of age with pituitary stalk thickening O what is the incidence Posterior pituitary dysfunction (on water deprivation or other) T at diagnosis; at any time during follow up
k. Posterior pituitary dysfunction 2	P In children <19 years of age with pituitary stalk thickening/ CDI I how do the following (in combination or alone) • Paired early morning urine/plasma osmolalities • Urine specific gravity • Polyuria >5ml/kg/h • Absence of a posterior pituitary bright spot C compare to a water deprivation test O in terms of specificity and sensitivity for detecting DI T at diagnosis
l. Anterior/posterior pituitary dysfunction	P In children <19 years of age with pituitary stalk thickening CDI O what proportion of patients had an identifiable pituitary endocrinopathy T when an underlying diagnosis of each of • Idiopathic • Congenital • Inflammatory • Neoplastic • LCH • Autoimmune was present? T at diagnosis

m. Serum tumour markers 1	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion of patients are undergoing serum β-hCG and αFP analysis T at diagnosis; at any time during follow up
n. Serum tumours markers 2	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing serum β-hCG and αFP analysis O how sensitive is this for detecting underlying pathology? T at diagnosis; at any time during follow up
o. CSF analysis 1	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion of patients undergo CSF β-hCG and αFP analysis T at diagnosis; at any time during follow up
p. CSF analysis 2	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing CSF β-hCG and αFP analysis O how sensitive is this for detecting underlying pathology? T at diagnosis; at any time during follow up
q. CSF cytology 1	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion of patients undergo CSF cytology T at diagnosis; at any time during follow up
r. CSF cytology 2	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing CSF cytology O how sensitive is this for detecting underlying pathology? T at diagnosis; at any time during follow up
s. Neurosarcoidosis	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients are investigated for neurosarcoidosis and when undergoing (alone or in combination) • CXR • CT chest • Bone scan • Serum ACE • Respiratory evaluation • Renal evaluation O have abnormal findings? T at diagnosis; at any time during follow up
t. LCH	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients are investigated for systemic LCH and when undergoing (alone or in combination) • CXR • Skeletal survey x-ray • FBC, LFT • MRI head • Bone scan • PET scan • Abdominal ultrasound • Skin examination • CD1a scan O have abnormal findings? T at diagnosis; at any time during follow up
u. Autoimmunity 1	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients undergo autoantibody testing (AVPcAb) T at diagnosis; at any time during follow up

v. Autoimmunity 2	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients undergoing autoantibody testing (AVPcAb) O have abnormal findings? T at diagnosis; at any time during follow up
w. Autoimmunity 3	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing autoantibody testing (AVPcAb) O how specific is this for the diagnosis of hypophysitis?
x. Tuberculosis 1	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients undergo testing for TB and in particular • Contact history • CXR • Microscopy, culture, nucleic acid amplification tests of sputum/gastric washings • Tuberculin skins tests • interferon-gamma release assay (IGRA) tests • other T at diagnosis
y. Tuberculosis 2	P In children <19 years of age with pituitary stalk thickening/ CDI I What proportion of patients undergoing testing for TB O have abnormal findings? T at diagnosis; at any time during follow up
z. Biopsy 1	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing biopsy O what are the indications for this?
aa. Biopsy 2	P In children <19 years of age with pituitary stalk thickening/ CDI I who do NOT undergo biopsy O what are the indications for this? (i.e. what are the contraindications for biopsy)
bb. Biopsy 3	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing biopsy O/T what is the timing from diagnosis to biopsy?
cc. Biopsy 4	P In children <19 years of age with pituitary stalk thickening/ CDI I what proportion of patients undergoing PS biopsy O have abnormal findings?
dd. Biopsy/Histology 5	P In children <19 years of age with pituitary stalk thickening/ CDI O what are these abnormal histological findings; T at biopsy?
ee. Biopsy 6	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing biopsy O What proportion experience complications?
ff. Biopsy 7	P In children <19 years of age with pituitary stalk thickening/ CDI I undergoing biopsy O What are the complications that arise from this procedure?
gg. Biopsy 8	P In children <19 years of age with pituitary stalk thickening/ CDI undergoing biopsy I does endoscopic biopsy C compared with open biopsy O have fewer complications?

hh. Biopsy & radiology	P In children <19 years of age pituitary stalk thickening/ CDI I do histological findings O correlate with pattern of radiological: • enhancement or • size of lesion or • course of enlargement?
ii. PET scanning	P In children <19 years of age pituitary stalk thickening/ CDI I does PET scanning O sensitively and specifically differentiate between malignancies and autoimmune disease?

4. Treatment

a. Treatment 1	P In children <19 years of age with pituitary stalk thickening/CDI WITHOUT established etiological diagnosis O what treatment (if any) T is used?
b. Treatment 2	P In children <19 years of age with pituitary stalk thickening/CDI WITHOUT established etiological diagnosis O what indications for treatment (if any) T are used?
c. Diagnostic value of treatments	P In children <19 years of age with pituitary stalk thickening/CDI WITHOUT established etiological diagnosis I is radiotherapy/chemotherapy/steroids O useful in determining the etiological diagnosis
d. Surgery	P In Children <19 years of age with pituitary stalk thickening/ CDI I does surgery prevent progression to/of O • Anterior pituitary dysfunction • Posterior pituitary dysfunction • Visual deficits • LCH neurodegeneration
e. Chemotherapy 1	P In children <19 years of age with pituitary stalk thickening/ CDI I Is systemic chemotherapy T used in the absence of a histological diagnosis of malignancy or LCH?
f. Chemotherapy 2	P In children <19 years of age with pituitary stalk thickening/CDI WITHOUT established etiological diagnosis I Does chemotherapy O reverse or prevent • Anterior pituitary dysfunction • Posterior pituitary dysfunction • Visual deficits • LCH neurodegeneration • progression of malignancy
g. Chemotherapy 3	P In children <19 years of age with pituitary stalk thickening/ CDI WITHOUT established etiological diagnosis I receiving chemotherapy O what are the risks T during treatment and follow-up?
h. Radiotherapy 1	P In children <19 years of age with pituitary stalk thickening/ CDI I Is radiotherapy T used in the absence of either a histological diagnosis of malignancy or LCH?

i. Radiotherapy 2	P In children <19 years of age with pituitary stalk thickening/ CDI WITHOUT established etiological diagnosis I Does radiotherapy O reverse or prevent • Anterior pituitary dysfunction • Posterior pituitary dysfunction • Visual deficits • LCH neurodegeneration • malignancy In the different diagnostic groups
j. Steroids 1	P In children <19 years of age with pituitary stalk thickening/ CDI I Are steroids T used WITHOUT established etiological diagnosis?
k. Steroids 2	P In children <19 years of age with pituitary stalk thickening/ CDI WITHOUT established etiological diagnosis I Does steroids O reverse or prevent • Anterior pituitary dysfunction • Posterior pituitary dysfunction • Visual deficits • LCH neurodegeneration • malignancy
l. Steroids 3	P In children <19 years of age with pituitary stalk thickening/ CDI WITHOUT established etiological diagnosis I receiving steroids O what are the risks T during treatment and follow-up?
m. Growth hormone (GH) replacement in the growth hormone deficient patient	P In children <19 years of age with pituitary stalk thickening/ CDI I given prompt GH replacement O is there evidence of progression/regression of Underlying aetiology • Inflammatory • Neoplastic • LCH • Autoimmune Stalk thickening Dysfunction • Anterior pituitary dysfunction • Posterior pituitary dysfunction • Visual deficits

5. Follow-up and surveillance

a. Radiological definition of progress of TPS	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing follow up MRI C compared to size at diagnosis what is considered progression of thickness of pituitary stalk

b. Overall & progression-free survival	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing follow up O What is the overall and progression-free (enlarging pituitary stalk) survival and is this different for the different diagnostic groups • Idiopathic • Congenital • Inflammatory • Neoplastic • LCH • Autoimmune T at 1, 5,10,15 and 20 years from diagnosis?
c. Late effects 1	P In Children <19 years of age with pituitary stalk thickening/ CDI What proportion develop • Vision • Anterior pituitary dysfunction • Posterior pituitary dysfunction • LCH neurodegeneration • Obesity • Developmental delay • Neurological deficits T at 1, 5,10,15 and 20 years from diagnosis?
d. Late effects 2	P In Children <19 years of age with pituitary stalk thickening/ CDI who develop 1 or more of: • Visual impairment • Anterior pituitary dysfunction • Posterior pituitary dysfunction • LCH neurodegeneration • Obesity • Developmental delay • Neurological deficits I is this detected clinically C or through follow-up investigations T at 1, 5,10,15 and 20 years from diagnosis?
3. Late effects 3	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing late effects follow up C are the proportion of the patients developing the different late effects different in the different diagnostic groups • Idiopathic • Congenital • Inflammatory • Neoplastic • LCH • Autoimmune
f. Clinical	P In children <19 years of age with pituitary stalk thickening <6.5mm and normal pituitary function and vision I is 6 monthly clinical follow-up for • 5, 10, 15, 20, years or lifelong O sufficient to detect signs of disease progression?
g. MRI follow-up 1	P In children <19 years of age with pituitary stalk thickening <6.5mm and normal pituitary function and vision I is 6 monthly MRI follow-up for • 5, 10, 15, 20, years or lifelong O sufficient to detect signs of disease progression?

h. MRI follow-up 2	P In children <19 years of age with pituitary stalk thickening <6.5mm and some pituitary/visual dysfunction I is 6 monthly MRI follow-up for • 5, 10, 15, 20, years or lifelong O sufficient to detect signs of disease progression?
i. Transition	P In Children <19 years of age with pituitary stalk thickening/ CDI I undergoing surveillance C is there an optimal time/process to transfer surveillance to adult teams O to ensure optimal compliance

Appendix 2: Literature Search

The PICO questions formed the starting point for systematic reviews of relevant evidence. A focused search was carried out on Ovid Medline and Ovid Embase databases. A search strategy was developed by the GDG to ensure that all studies identified met the pre-defined inclusion and exclusion criteria. Searches were limited to English language and there was no hand searching of journals. The process was completed in October 2014.

Full search strategy

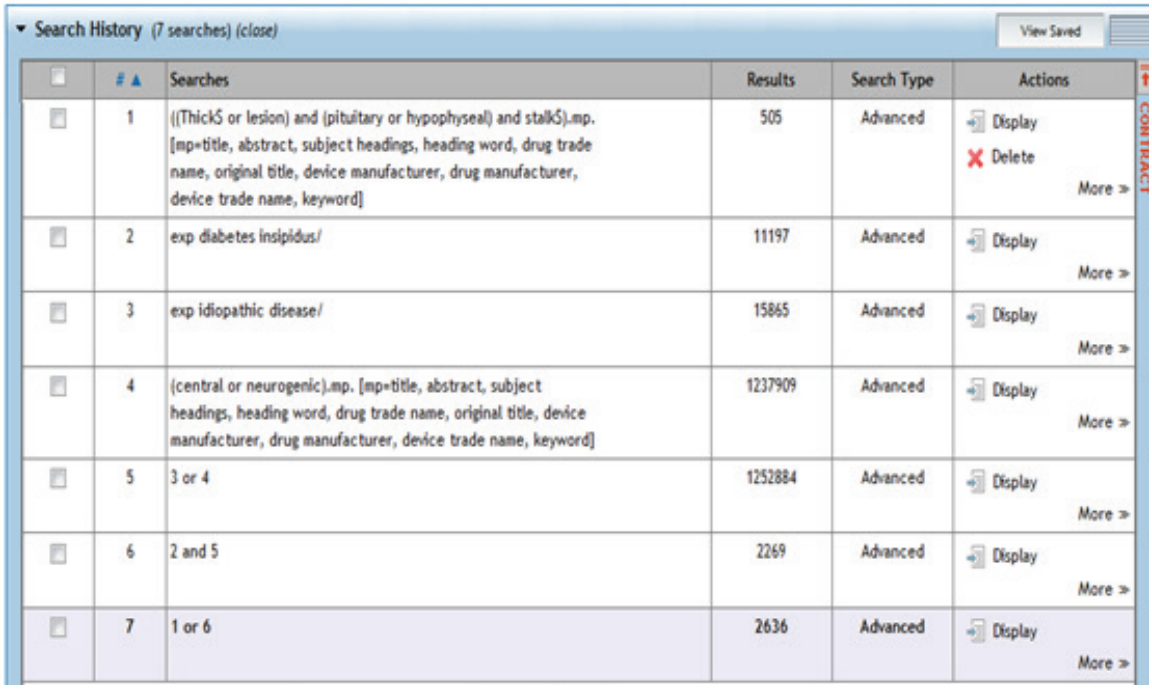
Text words

- Thickened pituitary stalk
- Pituitary stalk thickening
- Pituitary stalk lesion
- Central diabetes insipidus
- Neurogenic diabetes insipidus
- Idiopathic diabetes insipidus

Synonyms/truncation of text words

- Hypophysial
- Pituitary
- Stalk$
- Thick$
- Diabetes Insipidus (exp)
- Idiopathic (exp – Embase only)
- Central
- Neurogenic

Embase Classic + Embase 1974 to October 07, 2014

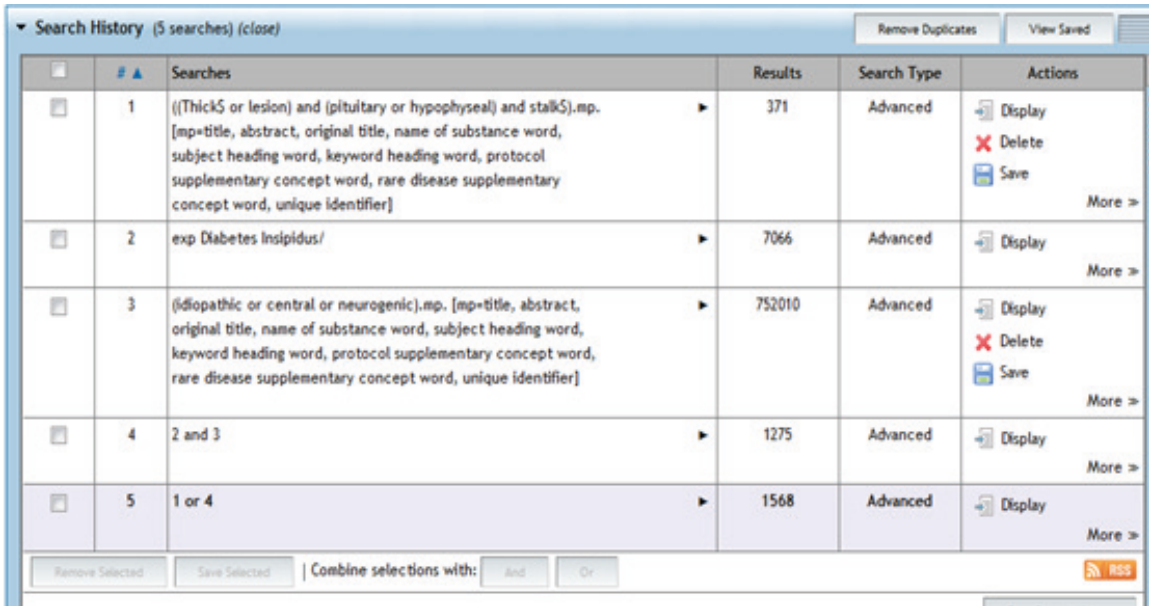


Search History (7 searches) (close) — View Saved

# ▲	Searches	Results	Search Type	Actions
1	((Thick$ or lesion) and (pituitary or hypophyseal) and stalk$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	505	Advanced	Display, Delete, More »
2	exp diabetes insipidus/	11197	Advanced	Display, More »
3	exp idiopathic disease/	15865	Advanced	Display, More »
4	(central or neurogenic).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1237909	Advanced	Display, More »
5	3 or 4	1252884	Advanced	Display, More »
6	2 and 5	2269	Advanced	Display, More »
7	1 or 6	2636	Advanced	Display, More »

Search Returned: 2636 text results

Ovid MEDLINE® Daily Update October 07, 2014, Ovid MEDL®(R) In-Process & Other Non-Indexed Citations and Ovid M®INE(R) 1946 to Present



Search History (5 searches) (close) — Remove Duplicates — View Saved

	# ▲	Searches	Results	Search Type	Actions
☐	1	((Thick$ or lesion) and (pituitary or hypophyseal) and stalk$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	371	Advanced	Display, Delete, Save, More »
☐	2	exp Diabetes Insipidus/	7066	Advanced	Display, More »
☐	3	(idiopathic or central or neurogenic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	752010	Advanced	Display, Delete, Save, More »
☐	4	2 and 3	1275	Advanced	Display, More »
☐	5	1 or 4	1568	Advanced	Display, More »

Remove Selected | Save Selected | Combine selections with: And Or | RSS

Search Returned: 1568 text results

Total results from all databases = 4202
Duplicates disregarded = 476 (11%)
Final total = 4202-476 = 3726 abstracts

Inclusion criteria

Studies were considered for inclusion if they were primary studies (case reports, case series or observational studies) or reviews reporting on the epidemiology, clinical presentation, diagnosis, investigation, treatment or follow-up of TPS and/or CDI in CYP <19 years of age.

Exclusion criteria

Publications were excluded if:

- Pre-1990 publication
- Syndromic associations (e.g. DIDMOAD, SOD) in view of the fact that the CDI would no longer be classified as 'idiopathic'.
- Association with trauma/hypoxia/prematurity – as CDI could no longer be classified as 'idiopathic'.
- Association with pregnancy/postpartum – considered to be a separate entity not specifically being addressed within this guideline.
- Animal studies – evidence considered too distant from clinical questions being posed. Papers on molecular mechanisms included when relating to genetic causes of CDI.
- Articles published in languages other than English.

Identification and review of the evidence

Titles and abstracts were screened for inclusion by two GDG members independently based on whether they fitted within the scope as defined in October 2014 and/or addressed any of the PICO questions as stated in September 2014. Where there was any disagreement, the abstracts were screened by the lead for the GDG. The total number of abstracts selected for full text review was 560. Full articles were then obtained and full papers were reviewed against prespecified inclusion and exclusion criteria to identify studies that addressed the PICO questions in the appropriate population and reported outcomes

of interest. The GDG lead was asked to resolve any queried articles by making a final decision.

Papers were reviewed and key information about the study's population, methods and results were extracted and recorded in an excel spreadsheet designed for this process. In assessing the quality of the evidence, each study was classified based on the GRADE criteria. The process of reviewing and grading the evidence was undertaken between November 2014 and June 2016. Where the evidence found in this review did not meet the inclusion criteria for the clinical questions, the GDG formulated guidelines statements (July 2016) and undertook a Delphi consensus process (August-November 2016).

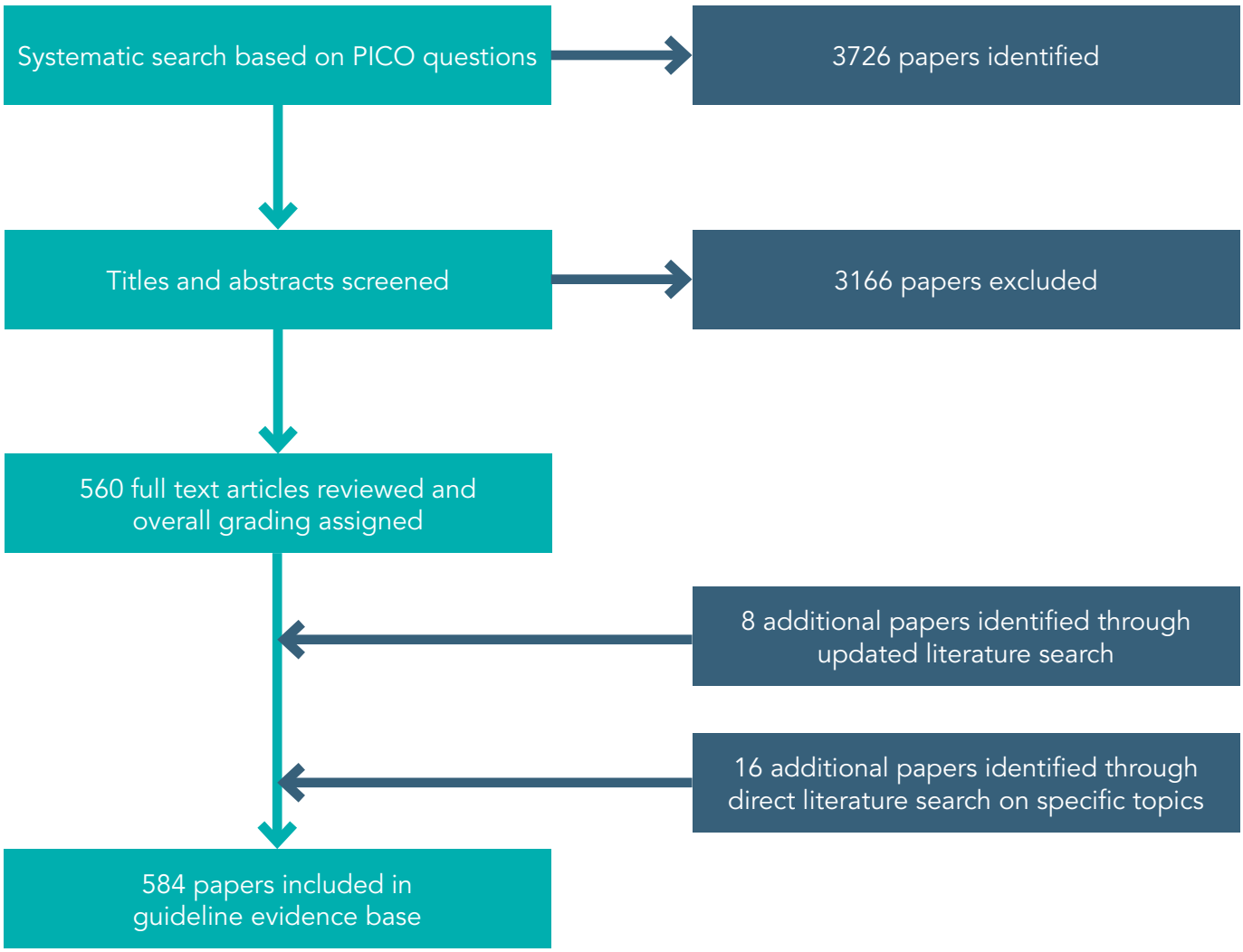
Additional 15 papers were identified through direct search of the Pubmed database for specific topics where the initial search strategy did not identify the evidence needed.

An updated literature search was performed in order not to miss recent relevant papers. The terms "central diabetes insipidus", "pituitary stalk thickening", and "thickened pituitary stalk" were searched with the following filters: "dates: 18/11/2014-13/07/2019", "ages: birth-18 years". Case reports were not graded on this round as likely to provide very low grade evidence. Following the above search and selection criteria, 8 further papers were graded.

References and grading of papers which provided evidence that informed the guidelines are presented in Appendix 4.

A summary of the literature review process is shown in Figure 4.

Figure 4: Literature review



Appendix 3: Evidence tables

The tables below provide the grading of the references selected for citing in the guidelines.

1. General

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Juul et al. National Surveillance of Central Diabetes Insipidus (CDI) in Denmark: results from 5 years registration of 9309 prescriptions of desmopressin to 1285 CDI patients. JCEM. 2014	Drug utilisation and patient registry study Observational	Moderate	Not serious	Not serious	serious	Not serious	Not serious	1285 patients with CDI were recorded in the observation period and given 9309 prescriptions for desmopressin in the nasal formulation, orodispersible tablet, or conventional tablet. 5-year period from 2007 to 2011.
Di Iorgi et al. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clinical Endocrinology 2015	Review Clinical question	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Leger et al. Thickened Pituitary Stalk on Magnetic Resonance Imaging in Children with Central Diabetes Insipidus. JCEM. 1999	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	26 patients with TPS. Mean age 8 years (2.5-18.6 years).
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Robison NJ et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer. 2013	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	69 patients presenting with isolated TPS. Mean age 13.6 years; age range 0.8–19.7 years. Of 4 germinoma cases: • One had increased CSF αFP at presentation, the other 3 had normal serum CSF markers. During follow-up: one case had slightly positive CSF βHCG another case had marked positive serum and plasma αFP
Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcome': A User's Guide. Volume 1: Page 7. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 20, Rare Disease Registries	User's Guide	Low	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	A reference for establishing, maintaining, and evaluating the success of registries created to collect data about patient outcomes produced by the agency for Healthcare Research and Quality (AHRQ) in USA. Methods: recommendations from a range of stakeholders, including government agencies, industry groups, medical professional societies, and other experts in the field; review of the literature

2. Initial clinical assessment

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Werny et al. Pediatric Central Diabetes Insipidus: Brain Malformations Are Common and Few Patients Have Idiopathic Disease. JCEM. 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	147 patients with CDI. Average follow-up 6.2 years.

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Di Iorgi et al. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clinical Endocrinology 2015	Review Clinical question	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Robison NJ et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer. 2013	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	69 patients presenting with isolated TPS. Mean age 13.6 years; age range 0.8–19.7 years. Of 4 germinoma cases: • One had increased CSF αFP at presentation, the other 3 had normal serum CSF markers. During follow-up: one case had slightly positive CSF βHCG another case had marked positive serum and plasma αFP
Maghnie et al. Central Diabetes Insipidus in children and young adults. NEJM. 2000	Retrospective Longitudinal	Moderate	Not serious	Serious	Not serious	Not applicable	Not applicable	79 patients with CDI. Mean age 7 years; age range 0.1–24.8 years.
Peyster RG et al. CT of the normal pituitary stalk. Am J Neuroradiol, 1984	Retrospective	Moderate	Not serious	Not serious	Serious	Serious	Not serious	184 patients (9-84 years).
Tien RD et al. Thickened Pituitary Stalk on MR Images in Patients with Diabetes Insipidus and Langerhans Cell Histiocytosis AJNR Am J Neuroradiol 1990	Retrospective	Low	Not serious	Serious	Serious	Serious	Not serious	4 females with CDI and LCH compared with 20 controls (ages not reported).
Simmons GE et al. MR Imaging of the Pituitary Stalk: Size, Shape, and Enhancement Pattern. AJR 1992	Retrospective	Low	Not serious	Serious	Serious	Serious	Not serious	58 patients (17 men, 41 women), 19-71 years old (mean 40 years).

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
N. Satogami et al. Normal Pituitary Stalk: High-Resolution MR Imaging at 3T, AJNR Am J Neuroradiol 2010	Prospective, Cross-sectional	Moderate	Not serious	Not serious	Serious	Serious	Not serious	Mean age: 28 years; age range: 21–43 years
Sbardella et al. Pituitary stalk thickening: the role of an innovative MRI imaging analysis which may assist in determining clinical management. EJE 2016	Retrospective	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	36 patients (mean age 37 years, range: 4–83)
Abla O, Weitzman S, Minkov M, McClain KL, Visser J, Filipovich A, Grois N. Diabetes insipidus in Langerhans cell histiocytosis: When is treatment indicated? Pediatr Blood Cancer. 2009 May;52(5):555-6.	Review	Low	Serious	Not serious	Not serious	Serious	Not serious	Summarises the published evidence relating to DI in children with LCH
Sebahattin Sari, Erkan Sari*, Veysel Akgun, Emrah Ozcan, Selami Ince, Mehmet Saldir, Oguzhan Babacan, Cengizhan Acikel, Gokalp Basbozkurt, Salim Ozenc, Sirzat Yesilkaya, Cenk Kilic, Kemal Kara, Sebahattin Vurucu, Murat Kocaoglu and Ediz Yesilkaya. Measures of pituitary gland and stalk: from neonate to adolescence. J Pediatr Endocr Met 2014; 27(11-12): 1071–1076	Retrospective Prospective	Moderate	Not serious	Not serious	Serious	Serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Elisabetta Godano, Giovanni Morana, Natascia Di Iorgi, Angela Pistorio, Anna Elsa Maria Allegri, Flavia Napoli, Roberto Gastaldi, Annalisa Calcagno, Giuseppa Patti, Annalisa Gallizia, Sara Notarnicola, Marta Giaccardi, Serena Noli, Mariasavina Severino, Domenico Tortora, Andrea Rossi and Mohamad Maghnie. Role of MRI T2-DRIVE in the assessment of pituitary stalk abnormalities without gadolinium in pituitary diseases. EJE 2018	Restrospective	Moderate	Not serious	Not serious	Serious	Serious	Not serious	102 children (aged 7.3-12 years) with various endocrine but no reported pituitary stalk thickening and eutopic posterior pituitary gland

3. First line investigations

3.1 Serum tumour markers, haematology, liver and renal function

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Di Iorgi et al. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clinical Endocrinology 2015	Review Clinical question	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Robison NJ et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer. 2013	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	69 patients presenting with isolated TPS. Mean age 13.6 years; age range 0.8–19.7 years. Of 4 germinoma cases: • One had increased CSF αFP at presentation, the other 3 had normal serum CSF markers. During follow-up: one case had slightly positive CSF βHCG another case had marked positive serum and plasma αFP

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Hu et al. An update on the clinical diagnostic value of β-hCG and αFP for intracranial germ cell tumors. Eur J Med Res. 2016	Retrospective	Low	Not serious	Serious	Not serious	Serious	Not serious	
Zhang et al. Determining an Optimal Cut off of Serum βHumanChorionicGonadotropin for Assisting the Diagnosis of Intracranial Germinomas. Plos One. 2016	Retrospective	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	
Sethi et al. Delayed diagnosis in children with intracranial germ cell tumours. The Journal of Pediatrics. 2013	Retrospective Longitudinal	Low	Not serious	Not serious	Serious	Serious	Not serious	70 patients with intracranial germ cell tumors. All had negative plasma and CSF markers at presentation. In two patients with germinoma CSF β-hCG raised during follow-up, after progressive growth of the infundibulum. In another patient with germinoma both serum and plasma αFP raised shortly before chemotherapy.
Yoshizawa et al Elevated levels of human chorionic gonadotropin-beta, a marker of active neurohypophyseal germinoma, detected by immune complex transfer enzyme immunoassay. Pituitary. 2004	Case report	Very low	Serious	Serious	Serious	Serious	Not serious	
Fukuoka et al Human chorionic gonadotropin detection in cerebrospinal fluid of patients with a germinoma and its prognostic significance: assessment by using a highly sensitive enzyme immunoassay. J Neurosurg Pediatr. 2016	Prospective Longitudinal	Moderate	Not serious	Not serious	Serious	Serious	Not serious	

3.2 Endocrinology

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Leger et al. Thickened Pituitary Stalk on Magnetic Resonance Imaging in Children with Central Diabetes Insipidus. JCEM. 1999	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	26 patients with TPS. Mean age 8 years (2.5-18.6 years).
Werny et al. Pediatric Central Diabetes Insipidus: Brain Malformations Are Common and Few Patients Have Idiopathic Disease. JCEM. 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	147 patients with CDI. Average follow-up 6.2 years.
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED. 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.

3.3 Opthalmology

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.

3.4 Imaging

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Rigaud C1,2, Barkaoui MA1, Thomas C3, Bertrand Y4, Lambilliotte A5, Miron J1, Aladjidi N6, Plat G7, Jeziorski E8, Galambrun C9, Mansuy L10, Lutz P11, Deville A12, Armari-Alla C13, Reguerre Y14, Fraitag S15, Coulomb A16, Gandemer V17, Leboulanger N18, Moshous D19, Hoang-Xuan K20, Tazi A21, Heritier S1, Emile JF22, Donadieu Langerhans cell histiocytosis: therapeutic strategy and outcome in a 30-year nationwide cohort of 1478 patients under 18 years of age. J1.Br J Haematol. 2016 Sep;174(6):887-98.	Prospective nationwide registry	High	Not serious	Not serious	Not serious	Not serious	Not serious	The largest comprehensive LCH cohort published
Haupt et al. Langerhans Cell Histiocytosis (LCH): Guidelines for Diagnosis, Clinical Work-Up, and Treatment for Patients Till the Age of 18 Years. Pediatric Blood Cancer. 2012	Guidelines	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Curless et al. Central nervous system tuberculosis in children. Pediatr Neurol. 1991	Retrospective	Low	Not serious	Not serious	Not serious	Serious	Not serious	
Farinha et al. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect, 2000	Retrospective	Low	Not serious	Not serious	Not serious	Serious	Not serious	
Thwaites et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. Journal of Infection. 2009	Guidelines	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Stalldecker et al. Pituitary stalk tuberculoma. Pituitary. 2002	Case report	Low	Serious	Not serious	Serious	Serious	Not serious	
Jain et al. Suprasellar tuberculoma presenting with diabetes insipidus and hypothyroidism-a case report. Neurology India. 2001	Case report	Low	Serious	Not serious	Serious	Serious	Not serious	
Sinha et al. Hypophyseal tuberculoma: direct radiosurgery is contraindicated for a lesion with a thickened pituitary stalk: case report. Neurosurgery. 2000	Case report	Low	Serious	Not serious	Serious	Serious	Not serious	
Turcu et al. Pituitary stalk lesions: The Mayo Clinic Experience. JCEM 2013	Retrospective review	Moderate	Not serious	Not serious	Serious	Not serious	Not serious	152 adults, mean age 44 years (2-82 years). 17 patients younger than 21 years.

3.5 Investigations upon specific conditions

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Thwaites et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. Journal of Infection. 2009	Guidelines	Moderate	Not serious	Not serious	Serious	Not serious	Not serious	
Caturegli P et al. Autoimmune Hypophysitis. Endocrine Reviews. 2005.	Review	Moderate	Not serious	Serious	Serious	Not serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Wang et al, Primary lymphocytic hypophysitis: Clinical characteristics and treatment of 50 cases in a single centre in China over 18 years. Clin Endocrinology. 2017.	Retrospective	Moderate	Not serious	Serious	Serious	Not serious	Not serious	50 cases, mean age 37.2 y (age range 18-60y). 28 histologically confirmed, 20 not confirmed
Honegger et al. Diagnosis of Primary Hypophysitis in Germany. JCE. 2015.	Retrospective cross-sectional	Moderate	Not serious	Serious	Serious	Not serious	Not serious	76 cases, mean age 41 y (age range 16-81y). 36 histologically confirmed, 40 not confirmed
De Bellis et al. Involvement of hypothalamus autoimmunity in patients with autoimmune hypopituitarism: role of antibodies to hypothalamic cells. JCEM, 2012	Cross-sectional cohort	Moderate	Not serious	Not serious	Serious	Serious	Not serious	
Ricciuti et al. Detection of pituitary antibodies by immunofluorescence: approach and results in patients with pituitary diseases. JCEM. 2014	Cross-sectional	Moderate	Not serious	Not serious	Serious	Not serious	Not serious	
Turcu et al. Pituitary stalk lesions: The Mayo Clinic Experience. JCEM. 2013.	Retrospective review	Moderate	Not serious	Not serious	Serious	Not serious	Not serious	152 adults, mean age 44 years (2-82 years). 17 patients younger than 21 years.
Marangoni S et al. Neurosarcoidosis. Clinical description of 7 cases with a proposal for a new diagnostic strategy. J neurol. 2006	Retrospective Small case series	Low	Not serious	Serious	Serious	Serious	Not serious	7 cases with neurosarcoidosis. All of them had normal serum ACE.
Hoitsma et al, A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. Curr Op Pulm Med. 2010	Review	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Webb et al. Septo-optic dysplasia. Eur J Hum Genet. 2010	Review	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	
McCabe et al. Novel FGF8 mutations associated with recessive holoprosencephaly, craniofacial defects, and hypothalamo-pituitary dysfunction. JCEM. 2011	Prospective, Genetic study	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Fang et al. Genetics of Combined Pituitary Hormone Deficiency: Roadmap into the Genome Era. Endocr Rev. 2016	Review	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Werny et al. Pediatric Central Diabetes Insipidus: Brain Malformations Are Common and Few Patients Have Idiopathic Disease. JCEM,. 2015	Retrospecitve longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	147 patients with CDI. Average follow-up 6.2 years.
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospecitve longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.
Maghnie et al. Central Diabetes Insipidus in children and young adults. NEJM. 2000	Retrospecitve longitudinal	Moderate	Not serious	Serious	Not serious	Not applicable	Not applicable	79 patients with CDI. Mean age 7 years; age range 0.1–24.8 years.
Maghnie et al. Disorders of salt and water balance in children. Hormone Research. 2007	Review	Moderate	Not serious	Not serious	Not serious	Not serious	Serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Turkkahraman et al. Pituitary, 2015. AVP-NPII gene mutations and clinical characteristics of the patients with autosomal dominant familial central diabetes insipidus	Small case series (two families)	Low	Serious	Serious	Not serious	Serious	Not serious	Two Turkish families with AD AVP-NPII mutations.

4. Second line investigations

4.1 Lumbar puncture

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Maghnie et al. Central Diabetes Insipidus in children and young adults. NEJM. 2000	Retrospective Longitudinal	Moderate	Not serious	Serious	Not serious	Not applicable	Not applicable	79 patients with CDI. Mean age 7 years; age range 0.1–24.8 years
Di Iorgi et al. Diabetes insipidus-diagnosis and management. Horm Res Pediatr, 2012	Mini review	Moderate	Not serious	Serious	Not serious	Not applicable	Not applicable	
Leger et al. Thickened Pituitary Stalk on Magnetic Resonance Imaging in Children with Central Diabetes Insipidus. JCEM. 1999	Retrospecitve Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	26 patients with TPS. Mean age 8 years (2.5-18.6 years).
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Robison NJ et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer. 2013	Retrospecitve Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	69 patients presenting with isolated TPS. Mean age 13.6 years; age range 0.8–19.7 years. Of 4 germinoma cases: • One had increased CSF αFP at presentation, the other 3 had normal serum CSF markers. During follow-up: one case had slightly positive CSF β-HCG another case had marked positive serum and plasma αFP
Werny et al. Pediatric Central Diabetes Insipidus: Brain Malformations Are Common and Few Patients Have Idiopathic Disease. JCEM. 2015	Retrospecitve Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	147 patients with CDI. Average follow-up 6.2 years.
Thwaites et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. Journal of Infection. 2009	Guidelines	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	
Marangoni et al. Neurosarcoidosis. Clinical description of 7 cases with a proposal for a new diagnostic strategy. J Neurol. 2006	Retrospecitve Small Case Series	Low	Not serious	Serious	Serious	Serious	Not serious	7 cases with neurosarcoidosis. All of them had normal serum ACE.
Bridel et al. Cerebrospinal fluid angiotensin-converting enzyme for diagnosis of neurosarcoidosis. J Neuroimmunol. 2015	Retrospecitve Small Case Series	Low	Not serious	Serious	Serious	Serious	Not serious	9 cases diagnosed with neurosarcoidosis on tissue biopsy.
McClain et al. CNS Langerhans cell histiocytosis: Common hematopoietic origin for LCH-associated neurodegeneration and mass lesions. Cancer. 2018	Case series	Low	Serious	Not serious	Serious	Not serious	Not serious	

4.2 Second line imaging

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Haupt et al. Langerhans Cell Histiocytosis (LCH): Guidelines for Diagnosis, Clinical Work-Up, and Treatment for Patients Till the Age of 18 Years. Pediatr Blood Cancer. 2013	Consensus guidelines	Very low	Not serious	Not serious	Not serious	Not serious	Not serious	Consensus guidelines developed by international Histiocyte Society members
Sher AC et al. PET/MR in the Assessment of Pediatric Histiocytoses: A Comparison to PET/CT. Clin Nucl Med. 2017	Case series	Low	Serious	Not serious	Not serious	Not serious	Serious	
Phillips et al. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2009	Case series	Low	Serious	Not serious	Not serious	Not serious	Serious	
Goo HW et al. Whole-body MRI of Langerhans cell histiocytosis: comparison with radiography and bone scintigraphy. Pediatr Radiol. 2006	Case series	Very low	Serious	Not serious	Not serious	Not serious	Serious	Very small number of cases

5. Biopsy

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospecitve Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Beni-Adani L, Sainte-Rose C, Zerah M, Brunelle F, Constantini S, Renier D, Lellouch-Tubiana A, Leger J, Pierre-Kahn A. Surgical implications of the thickened pituitary stalk accompanied by central diabetes insipidus. J Neurosurg. 2005 Aug;103 (2 Suppl):142-7	Retrospective Longitudinal	Low	Not serious	Not serious	Not serious	Serious	Not serious	
Sudha I. Mootha, Anthony J. Barkovich, Melvin M. Grumbach, Michael S. Edwards, Stephen E. Gitelman, Selna I. Kaplan, and Felix A. Conte. Idiopathic Hypothalamic Diabetes Insipidus, Pituitary Stalk Thickening, and the Occult Intracranial Germinoma in Children and Adolescents. Journal of Clinical Endocrinology and Metabolism. 1997	Retrospective Longitudinal	Low	Not serious	Not serious	Not serious	Serious	Not serious	

6. Treatment

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Calaminus G et al. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. Neuro Oncol. 2013	Multinational non-randomized trial for children and adults	Low	Not serious	Not serious	Serious	Not serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Haupt et al. Langerhans Cell Histiocytosis (LCH): Guidelines for Diagnosis, Clinical Work-Up, and Treatment for Patients Until the Age of 18 Years. Pediatr Blood Cancer. 2013	Consensus guidelines	Very low	Not serious	Not serious	Not serious	Not serious	Not serious	Consensus guidelines developed by international Histiocyte Society members
Abla O et al. Diabetes insipidus in LCH: When is treatment indicated? Pediatr Blood Cancer. 2009	Review of literature and expert opinion	Very low	Serious	Serious	Serious	Serious	Serious	

7. Surveillance

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Cerbone et al. Neuroradiological features in a cohort of 53 children with Thickened Pituitary Stalk (TPS) and/or Idiopathic Central Diabetes Insipidus (ICDI). Free Communication. BSPED 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	53 children presenting with TPS/CDI over a 30 years period. Median age at diagnosis TPS: 9.02 years, CDI 8.3 years, TPS+CDI 3.8 years. Median follow-up: TPS: 2.45 years, CDI 5.12 years, TPS+CDI: 3.11 years.
Werny et al. Pediatric Central Diabetes Insipidus: Brain Malformations Are Common and Few Patients Have Idiopathic Disease. JCEM. 2015	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	147 patients with CDI. Average follow-up 6.2 years.
Di Iorgi et al. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clinical Endocrinology 2015	Review Clincal Question	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Leger et al. Thickened Pituitary Stalk on Magnetic Resonance Imaging in Children with Central Diabetes Insipidus. JCEM. 1999	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Serious	Not serious	26 patients with TPS. Mean age 8 years (2.5-18.6 years).
Richards et al. Natural history of idiopathic diabetes insipidus. The Journal of Pediatrics. 2011	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not applicable	Not applicable	105 patients with CDI. Age at DI diagnosis 8.5 years (5 months – 15 years). Median follow-up 7 years.
Charmandari et al. 20 years of experience in idiopathic central diabetes insipidus. Lancet. 1999	Retrospective Longitudinal	Moderate	Serious	Not serious	Not serious	Not serious	Not serious	16 patients with idiopathic CDI. Age at presentation 6 months-17 years.
Robison NJ et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer. 2013	Retrospective Longitudinal	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	69 patients presenting with isolated TPS. Mean age 13.6 years; age range 0.8–19.7 years.
Maghnie et al. Central Diabetes Insipidus in children and young adults. NEJM. 2000.	Retrospective Longitudinal	Moderate	Not serious	Serious	Not serious	Not applicable	Not applicable	79 patients with CDI. Mean age 7 years; age range 0.1–24.8 years.

8. Transition

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Willis et al. Transition from children's to adults' services for young people using health or social care services (NICE Guideline NG43). Arch Dis Child Educ Pract Ed. 2017	Guideline	Moderate	Not serious	Not serious	Not serious	Not serious	Not serious	

Reference	Study design	Final grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Comments
Campbell et al. Transition of care for adolescents from paediatric services to adult health services. Cochrane Database Syst Rev. 2016	Systematic review	Moderate	Not serious	Serious	Not serious	Not serious	Not serious	

Appendix 4: The Delphi Consensus Process

Recommendations that the GDG wished to make for which there was no evidence or in which the identified evidence was contradictory, were evaluated using up to two rounds of a Delphi consensus process (11), conducted through an electronic survey.

The Delphi participants selected one of the following options for each statement:
- 'I support the statement'
- 'I would support the statement with modification'
- 'I do not support the statement'
- 'I do not have the expertise in this area to be able to comment'

Experts were alerted to the forthcoming survey before the summer of 2016 and their email addresses provided by the GDG, verified individually by the PB. The 1st round of the survey was run in September 2016 for at least 3 weeks, with two reminders. A recommendation was deemed to have reached consensus if 70% or more of the Delphi participants who responded and felt they had the expertise to comment on the recommendation, supported the statement or indicated that they would support it with modification. All Delphi participants were offered the opportunity to comment on recommendations. Both the PB and the GDG reviewed comments from the Delphi panellists. Those recommendations in which modifications were likely to achieve consensus were modified and reviewed in a second Delphi consensus round. This was run in November 2016 for at least 2 weeks.

The Delphi process for the guideline on the management of TPS/CDI is summarised in the text and tables below.

Seventy-eight potential Delphi consensus process participants from across the UK, Europe and the USA were nominated by GDG members. They were chosen for their recognised expertise in the management of patients with TPS/CDI and to be representative of the multidisciplinary knowledge required. 22 took part in the first round of the Delphi process and 18 in the second round. 10 participated in both rounds. The 30 responders were made up of 2 adult endocrinologists, 2 paediatric endocrinologists, 1 neuropathologist, 8 neuroradiologists, 12 paediatric oncologists and 5 neurosurgeons.

All 23 statements achieved consensus in the first round. However, following 'round 1' the GDG revised a number of statements in order to improve their clarity or to take account of Delphi panel comments. 9 statements were put to a second round of consensus and achieved consensus. The Delphi panel voting is summarised in the table below. All statements were supported by > 75% of the Delphi group participants who felt they had the expertise to comment on the recommendation.

The names of participants who took part in respective rounds of Delphi surveys are listed below.

1st round (22 participants) – Ruth Batty, Kling Chong, Daniel Warren, Carlos Rodriguez-Galindo, Shivaram Avula, Eric Bouffet, Didier Frappaz, Peter Clayton, Daniel Connolly, Mohamad Maghnie, Ajay Sinha, Ryo Nishikawa, Jeffrey Allen, Saurabh Sinha, Niki Karavitaki, Kevin Windebank, Matthew Murray, Claire Higham, Daniela Prayer, Sheila Weitzman, Jean Donadieu, Kathreena Kurian

2nd round (18 participants) – Maria Luisa Garre, Mohamad Maghnie, Saurabh Sinha, Stavros Stivaros, Sheila Weitzman, Claire Higham, Ryo Nishikawa, Donald Macarthur, Shivaram Avula, Niki Karavitaki, Neil Stoodley, Milen Minkov, Matthew Murray, Didier Frappaz, Kling Chong, Scott Macfarlane, Thomas Czech, James Nicholson

Both rounds (10 participants) - Mohamad Maghnie, Saurabh Sinha, Sheila Weitzman, Claire Higham, Ryo Nishikawa, Shivaram Avula, Niki Karavitaki, Matthew Murray, Didier Frappaz, Kling Chong

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
All CYP with suspected thickened pituitary stalk and/ or central diabetes insipidus should be managed in a tertiary paediatric endocrine centre by a nominated lead consultant paediatric endocrinologist with an interest/experience in pituitary tumours, in liaison with the designated tertiary paediatric neuroncology service/team.	22	86.36	4.55	0	9.09	100.0	1st
The treatment of all CYP with suspected pituitary tumours should be discussed in the nominated age-appropriate pituitary MDT, with paediatric and adult pituitary specialists (endocrinologists,transphenoidal and base of skull surgeons) as well as at the neuroncology MDT.	22	86.36	9.09	0	4.55	100.0	1st
Any pituitary surgery should be attempted only by the adult pituitary or paediatric neurosurgeon nominated by the MDT with ready access to transphenoidal, endoscopic and base of skull techniques and readily available paediatric endocrine support.	22	77.27	4.5	9.09	9.09	90.0	1st
Given the rarity of pituitary tumours in CYP, a national registry should be developed and centralised review of images, histology and decision making process facilitated.	20	75	15	10	0	90.0	1st
The registry should provide the means by which the outcomes of patients managed with these guidelines can be monitored.	21	90.48	9.52	0	0	100.0	1st
Patients should be offered the opportunity to contribute to tissue banking and relevant ethically approved national and international biology and treatment studies.	22	100	0	0	0	100.0	1st

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
To establish if patient has TPS, all patients should have appropriate, dedicated MRI imaging of the pituitary as well as head MR · Including dedicated uncontrasted T1 weighted MRI imaging (sagittal and coronal planes) of the pituitary to allow for the evaluation of the pituitary stalk for uniform or focal thickening in both planes.	21	76.19	19.05	0	4.76	100.0	1st
In the absence of congenital midline defects and/or a septo-optic dysplasia spectrum, a pituitary stalk should be considered pathologically thickened and requiring further investigation if, in the sagittal or coronal plane a) it is uniformly thickened (measures > 3mm in diameter), or b) there is focal (non-uniform) expansion along its length.	20	85	10	0	5	100.0	1st
If congenital midline defects and/or a septo-optic dysplasia spectrum are absent on MRI, a pituitary stalk should be considered pathologically thickened and requiring further investigation if, there is in the sagittal or coronal plane, either:a) uniform thickening along its length (>3mm in diameter) OR b) focal (non-uniform) expansion >5mm at upper part or >3mm at its proximal part. The additional absence of a bright spot on the T1 non-contrasted scan, though not diagnostic, increases suspicion of pathology. [Revised Q8 from 1st round DELPHI]	15	60	13.3	0	26.67	100.0	2nd

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
All patients deemed to have TPS and/or central DI should have a) assessment of growth and pubertal status b) assessment of posterior pituitary function (ie urinary concentrating capacity) c) baseline anterior pituitary function tests, including urgent prolactin d) dynamic anterior pituitary function testing (including assessment of growth hormone and cortisol reserve) e) regular endocrine follow-up.	16	72.73	9.09	0	18.18	100.0	1st
All patients with TPS should have baseline assessment of visual acuity and, if child is able to co-operate, visual fields by optometry.	22	72.73	4.55	0	22.73	100.0	1st
Only CYP with proximal TPS or abutting chiasm requires baseline assessment of visual acuity and, if the child is able to cooperate, visual fields by optometry.	18	27.78	22.22	5.56	44.44	90.0	2nd
All CYP with idiopathic TPS and /or central DI should have blood taken for · β-HCG and αFP (for germ cell tumour) · ESR· Quantiferon (for TB) · Autoimmune screen.	22	59.09	13.64	0	27.27	100.0	1st
Initial basal blood sampling in all CYP with idiopathic TPS and/or central DI should include measurement of beta-human chorionic gonadotropin (β-hCG) and alpha feto-protein (αFP) for germ cell tumour at a minimum. Additional assessment of erythrocyte sedimentation rate (ESR) and Quantiferon for tuberculosis, and an autoimmune screen should be undertaken if a detailed family or travel history indicates a potentially high clinical risk.	18	50	11.11	5.56	33.33	91.7	2nd

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
Serum ACE is not helpful in the diagnosis or exclusion of neurosarcoidosis in patients with TPS and /or central DI and should not be measured.	22	27.27	9.1	0	63.64	100.0	1st
All CYP with idiopathic TPS and/or central DI in whom initial blood tests above fail to reveal the aetiology, should have the following imaging a) CXR (detect pulmonary TB, sarcoidosis, LCH, metastatic malignancy) b) Abdominal ultrasound scan for hepatosplenomegaly (multisystem LCH) c) Skeletal survey (relative radiation exposure 1.5x that of CXR)	21	57.4	9.52	9.52	23.81	87.5	1st
If the etiological diagnosis for central DI is not apparent at presentation, the stalk is not thickened and there are no other midline anomalies suggestive of SOD on MR, molecular genetics for inherited forms of central DI is recommended (especially if there is a family history).	22	54.55	9.09	0	36.36	100.0	1st
A diagnostic lumbar puncture should be undertaken in CYP with TPS and/or central DI if, after initial blood (for β-HCG, αFP, ESR, autoimmune screen and Quantiferon), and imaging (CXR, abdominal US and skeletal survey), the etiological diagnosis is not apparent and the patient falls into one of the following categories a) TPS and central DI or b) progressive enlargement of TPS or c) TPS and evolving endocrinopathy or d) TPS and evolving visual dysfunction.	22	59.09	4.55	4.55	31.82	93.3	1st

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
If a diagnostic LP is undertaken in CYP with TPS, CSF should be analysed for : ·β-HCG and αFP (for germ cell tumour) ·ACE (for sarcoidosis) · cytospin and microscopy to detect cells · if cells obtained, immunohistochemistry stain for LCH (CD1a or CD207) · culture · PCR for TB	22	54.55	9.09	4.55	31.82	93.3	1st
If a diagnostic lumbar puncture is undertaken, cerebrospinal fluid (CSF) should always be analysed for β-hCG and αFP (for germ cell tumour), cytospin and microscopy to detect cells and if cells obtained, immunohistochemistry stain for Langerhans' cell histiocytosis (LCH) CD1a or CD207, at a minimum.	18	55.56	11.12	0	33.33	100.0	2nd
In CYP undergoing diagnostic lumbar puncture, additional CSF analysis for angiotensin converting enzyme (ACE) for sarcoidosis, culture and PCR for tuberculosis should be undertaken in patients considered at risk.	18	33.33	5.56	11.11	50	77.8	2nd
In CYP who pose a diagnostic dilemma and are undergoing a lumbar puncture for TPS +/- DI and, the following clinical trials need prioritising : · test for known LCH mutations if · cells obtained (e.g. BRAF, V600E, MAP2K) · to test for known LCH mutations (e.g. BRAF V600E, MAP2K) in cell free DNA	22	31.8	13.64	9.09	45.45	83.3	1st

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
For those CYP continuing to pose a diagnostic dilemma, BRAF V600E and MAP2K mutations testing in either CSF cells or cell free DNA is currently of unknown sensitivity and specificity in differentiating LCH from other disease (e.g. glioma) and requires further study before either can be recommended.	17	47.06	11.76	0	41.18	100.0	2nd
In CYP with TPS and central DI, or progressive thickening, endocrinopathy or visual disturbance, who still pose a diagnostic dilemma after initial blood, imaging and CSF screens (above), whole body imaging is recommended to detect distant occult LCH lesions which may be more amenable to biopsy by: a) FDG PET CT scan or b) Whole body MRI.	22	50	27.27	9.09	13.64	89.6	1st
A biopsy of the thickened stalk should be considered if the initial blood tests, imaging, LP and whole body imaging did not reveal the aetiology in the following situations a) associated anterior pituitary dysfunction or b) there is progressive enlargement of the TPS or c) very large TPS d) risk to optic pathway	22	45.45	31.82	0	22.73	100.0	1st
In CYP who continue to pose a diagnostic dilemma after whole body imaging and (if necessary) repeat CSF testing, a biopsy of the thickened stalk should be considered if there is a very large or progressively enlarging (TPS >6.5-7mm) hypothalamo-chiasmatic or 3rd ventricular involvement with/without anterior pituitary enlargement.	18	66.67	11.11	0	22.22	100.0	2nd

Statement	Respondents (N)	I would support the statement (%)	I would support the statement with modifications (%)	I do not support the statement (%)	I do not have the experience in this area to be able to comment	% of agreement	Round of Delphi (1st/2nd)
A biopsy of the stalk should only be considered if it is judged by the MDT to be of sufficient size to ensure that it is likely that a diagnostic sample will be obtained and the benefit outweighs the risk of the procedure.	22	81.82	0	0	18.18	100.0	1st
Disease specific treatment should not be initiated until an aetiological diagnosis has been made.	21	61.9	9.52	0	28.57	100.0	1st
All CYP without an established etiological diagnosis for TPS and/or central DI should have on-going endocrine review and serial pituitary MRI at 3 months, at 9 months and then every year.	22	68.18	18.18	4.55	9.09	95.0	1st
All CYP without an established etiological diagnosis for TPS and/or central DI should have on-going endocrine review and regular pituitary MRI surveillance at initial 3-monthly intervals to 6 months and, if stable, 6-monthly intervals to 2 years and annually thereafter.	18	77.78	16.67	0	5.56	100.0	2nd
If there is no progression of TPS and no endocrinopathy or visual problems, consider discharge after 5 years as long as growth and puberty are complete.	22	59.09	9.09	9.09	22.73	88.2	1st
If there is either a) normalisation of TPS, OR b) absence of TPS progression (<5mm) AND no evidence of DI or endocrinopathy (after dynamic testing), consider discharge after 5 years as long as growth and puberty have completed.	18	61.11	11.11	0	5	100.0	2nd

Appendix 5: Tables

Table 1. Estimated prevalence of aetiologies

TABLE 1. ESTIMATED PREVALENCE OF EVENTUAL AETOIOLOGIES RESPONSIBLE FOR INITIALLY UNEXPLAINED THICKENED PITUITARY STALK AND/OR CENTRAL DIABETES INSIPIDUS IN CYP <19Y
NEOPLASTIC (45.5%) 1. Langerhans cells histiocytosis (16.1%) 2. Germ cell tumours (13.1%) 3. Craniopharingioma (12.3%) 4. Other brain tumours (3.8%) 5. Metastatic diseases (0.1%)
IDIOPATHIC (29.1%)
CONGENITAL/GENETIC (19.1%) 1. Septo-optic dysplasia (5.8%) 2. Other congenital abnormalities (5.4%) 3. Holoprosencephaly (4.4%) 4. Genetic CDI (2.9%) 5. Rathke and pars intermedia cyst (0.4%) 6. Ectopic posterior pituitary (0.1%)
INFECTIOUS (1.9%)
POST-TRAUMATIC (1.2%)
INFLAMMATORY/AUTOIMMUNE CONDITIONS (0.9%)
OTHER (NOT SPECIFIED) (2.9%)

TABLE 2. PREVALENCE OF EVENTUAL AETIOLOGIES RESPONSIBLE FOR INITIALLY UNEXPLAINED TPS AND/OR CDI IN 11 PAEDIATRIC STUDIES (n: 684)

	Werny et al 2015	Richards et al 2011	Di Iorgi et all 2014	Maghnie et all 2000	Cerbone et al 2015	Santi-prabhob et all 2005	Liu et al 2013	Bajpai et all 2008	Catli et al 2012	Jaru-ratanasiri-kul et al 2002	Hamilton et al 2007	Conbined Cohort
	(n: 147)	(n: 1-5)	(n: 78)	(n: 73)	(n: 53)	(n: 50)	(n:48)	(n: 46)	(n: 34)	(n: 29)	(n: 21)	(n: 684)
IDIOPATHIC n (5)	18 (12.2)	12 (11.0)	43 (55.1)	41 (56.2)	28 (52.8)	7 (14.0)	5 (10.4)	19 (41.3)	10 (29.4)	16 (55.2)		**199 (29.1)**
NEOPLASTIC n (%)	78 (53.1)	56 (53.3)	27 (34.6)	24 (32.9)	22 (41.5)	14 (28.0)	38 (79.2)	17 (36.9)	17 (50.0)	10 (34.5)	8 (38.1)	**311 (45.5)**
1. Langerhans cell histiocytosis	18 (12.2)	20 (19.0)	12 (15.4)	12 (16.4)	11 (20.7)	3 (6.0)	12 (25.0)	11 (23.9)	4 (11.8)	3 (10.3)	4 (19.0)	110 (16.1)
2. Germ cell tumours	15 (10.2)	11 (10.0)	9 (11.5)	6 (8.2)	9 (17.0)	8 (16.0)	20 (41.7)	2 (4.3)	4 (11.8)	4 (13.7)	2 (9.5)	90 (13.1)
3. Craniopharingioma	37 (25.2)	19 (18.0)	6 (7.7)	6 (8.2)	1 (1.9)	3 (6.0)	1 (2.1)	3 (6.5)	7 (20.6)	1 (3.4)		84 (12.3)
4. Other brain tumours [a]	8 (5.4)	6 (6.0)			1 (1.9)		5 (10.4)	1 (2.2)	2 (5.9)	2 (6.9)	1 (4.8)	26 (3.8)
5. Metastic disease [b]											1 (4.8)	1 (0.1)
CONGENITAL/GENETIC n (%)	46 (31.3)	21 (20.0)	6 (7.7)	5 (6.8)	3 (5.7)	20 (40.0)	3 (6.2)	8 (17.4)	4 (11.8)	2 (6.9)	13 (61.9)	**131 (19.1)**
1. Rathke and pars intermedia cyst					2 (3.8)				1 (2.9)			3 (0.4)
2. Ectopic posterior pituitary							1 (2.1)					1 (0.1)
3. Septo-optic dysplasia	21 (14.3)	8 (8.0)	3 (3.8)			7 (14.0)				1 (3.4)		40 (5.8)
4. Holoprosencephaly	8 (5.4)	11 (10.0)				2 (4.0)	2 (4.2)	4 (8.7)	3 (8.8)			30 (4.4)
5. Other congenital abnormalities [c]	6 (4.1)	2 (2.0)				11 (22.0)		4 (8.7)		1 (3.4)	13 (61.9)	37 (5.4)
6. Genetic CDI	11 (7.5)		3 (3.8)	5 (6.8)	1 (1.9)							20 (2.9)
INFECTIOUS [d] n (%)		4 (4.0)				4 (8.0)	2 (4.2)	2 (4.3)	2 (5.9)	1 (3.4)		**13 (1.9)**
POST-TRAUMATIC n (%)	2 (1.3)		2 (2.6)	2 (2.7)					1 (2.9)			**8 (1.2)**
INFLAMMATORY/AUTOIMMUNE [e] n (%)				1 (1.4)								**2 (0.3)**
OTHER [f] n (%)	3 (2.0) ¶	12 (11.4) *				5 (10.0) #						**20 (2.9)**

Note: from the initial combined cohort of 741 patients from the 11 paediatric studies, 57 cases with post-operative CDI were excluded

[a] Optic nerve glioma, neuroectodermal tumours, astrocytoma, lymphoma, pituitary adenoma, pinealoma, cavernous hemangioma, unknown nature
[b] Glioblastoma multiforme
[c] Hydrocephalus, small anterior pituitary/empty sella, encephalocele, fronto-nasal dysplasia, absent septum pellucidum, hydrancephaly, schizencephaly, meningomyelocele, arachnoid cyst
[d] Tuberculous, Group B Streptococcal, E-coli meningitis/encephalitis/ventriculo-peritoneal shunt infection, pituitary abscess
[e] Hypophysitis
[f] In some studies different aetiologies were combined and not specified, hence the prevalence of individual causes could not be extrapolated for those studies
¶ Inflammatory/infectious
* Post-traumatic, metastatic, Rathke cyst, cerebral palsy, congenital
# Cerebral palsy of unknown origin

Table 3. Signs, symptoms and associated conditions

TABLE 3: PRESENTING SIGNS AND SYMPTOMS ASSOCIATED WITH THE MAIN AETIOLOGIES OF THICKENED PITUITARY STALK (TPS) AND/OR CENTRAL DIABETES INSIPIDUS (CDI) IN CYP <19Y

GENERAL

1. **Central/hypothalamic:** headaches (even without increased intracranial pressure), weight loss, vomiting, anorexia, change in school performance, drowsiness, bulging fontanelle, lethargy, behaviour/mood change, seizures, fever or temperature instability
2. **Pituitary deficits:**
   - *GH:* short stature, growth deceleration with bone age delay, immature appearance compared to peers, infantile hypoglycaemia, fatigue, reduced muscular tone and increased adipose tissue, reduced bone mineral density
   - *ACTH:* fatigue, hypoglycaemia, hypotension, hyponatraemia, hyperkalaemia, muscle weakness, loss of appetite and weight loss, nausea, vomiting, behaviour/mood change, acute collapse (especially during intercurrent illness/procedure)
   - *TSH:* reduced school performances, growth failure, weight gain, bone age delay, neurodevelopmental delay, constipation, neonatal prolonged jaundice, tiredness, cold intolerance, puffiness around the eyes, impaired memory, depression, hoarse voice, delayed puberty, dry skin, hair loss/thinning, prolonged reflexes
   - *FSH/LH:* absent or delayed puberty, primary or secondary amenorhorrea (females) (NB. paradoxical precocious pseudopuberty in children with HCG-secreting GCT despite LH/FSH deficiency), reduced bone mineral density
   - *AVP:* polyuria (particularly nocturia in childhood or adolescence), polydipsia (particularly night thirst, sometimes manifest as inconsolable crying or sleep disturbance in infants), weight loss or failure to thrive (from occult dehydration), hypernatraemia, dehydration, delayed growth
3. **Visual disturbances:** reduced vision (visual acuity) and visual fields (occult in younger children), diplopia/squint

SPECIFIC

1. LCH:
   - *Skin:* scaly, waxy rash or lesions (seen under Woods light), hair loss, oozing, tenderness
   - *Bones (Single or Multiple Sites):* pain, lumps, fracture, limp, decreased mobility, XR lesions
   - *Bone Marrow:* pallor, fatigue, increased susceptibility to infections, bruising, bleeding
   - *Gastro-intestinal Tract:* abdominal pain, vomiting, diarrhoea, haematemesis, rectal bleeding, weight loss, jaundice, hepatomegaly, ascites
   - *Lungs:* chest pain, shortness of breath, difficulty breathing, cough, haemoptysis, Chest XR shadowing
   - *Central nervous system:* headaches, dizziness, seizures, weakness, dysphasia, dysphagia, fever or temperature instability
   - *Mouth/Jaw/Gums:* pain and swelling of face, loosening or loss of teeth, "floating" teeth, mouth ulcers, swollen or bleeding gums, jaw cysts on XR
   - *Ears:* hearing loss, discharge, cysts
   - *Eyes:* visual loss, proptosis
   - *Lymph Nodes:* enlargement, tenderness
   - *Ovaries:* pelvic pain, amenorrhoea
2. **Germinoma:** precocious pseudopuberty (if HCG secreting)
3. **Optic pathway gliomas:** association with neurocutaneous manifestations from NF1
4. **Congenital midline brain defects:** variable association of optic nerve, hypothalamo-pituitary and corpus callosum congenital abnormalities
5. **Familial CDI:** early onset forms, family history of CDI
6. **Tubercolosis:** contact history
   - *Meningitis:* prolonged fever, vague central nervous system symptoms, encephalopathy, anorexia, failure to thrive, poor appetite, nausea, vomiting and abdominal pain, sleep disturbances
   - *Tuberculoma:* often asymptomatic
7. **Hypophysitis:** family history and association with autoimmune conditions (eg. Polyglandular autoimmune syndrome). A definitive diagnosis of this condition (extremely rare in childhood) can only be made obtaining histology from neurosurgical biopsy
8. **APS-1:** more frequently presenting with mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency, it can also be rarely associated with CDI

Appendix 6: Conflicts of interest

Dr Johannes Visser (Group lead)	None
Dr Manuela Cerbone (Group Co-Lead)	None
Dr Chloe Bulwer	None
Dr Ash Ederies	None
Kirtana Vallabhaneni	None
Prof Stephen Ball	None
Prof Ian Kamaly-Asl	• Member of the NHS England Paediatric Neurosciences Clinical Reference Group 2013 onwards • Member of Council of the Society of British Neurological Surgeons 2018 onwards • Chairman of the British Paediatric Neurosurgical Group 2016 to 2018
Prof Ashley Grossman	None
Dr Helena Gleeson	None
Prof Marta Korbonits	None
Dr Vasanta Nanduri	None
Dr Vaitza Tziaferi	None
Prof Tom Jacques	I have no direct conflict of interest but the followed are declared for transparency: • I am a director and shareholder in two private limited companies, Repath Ltd and Neuropath Ltd and I am company secretary at Repath Ltd. My wife is a director and shareholder at Neuropath Ltd. These companies handle my non-NHS work. • I am an editor in chief of the journal, Neuropathology and Applied Neurobiology. • I am the lead for the childhood solid tumour domain Genomes Clinical Interpretation Partnership (GeCIP) for Genomes England and the 100,000 genomes projects
Dr Helen Spoudeas	• Chair of the Project Board for all 8 PAED endocrine tumours being developed • Project Board Lead for Pituitary Adenomas, Craniopharyngiomas and idiopathic thickening of pituitary stalk and /or idiopathic central diabetes Insipidus • Responsible for raising grants to fund wider endeavour • Initiator and founder of group with wider involvement across all guidelines

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