Rare endocrine tumour guidelines

Management of children and young people (CYP) with idiopathic thickened pituitary stalk (iTPS) and/or idiopathic central diabetes insipidus (iCDI): a national clinical practice consensus guideline

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Management of children and young people (CYP) with idiopathic thickened pituitary stalk (iTPS) and/or idiopathic central diabetes insipidus (iCDI): a national clinical practice guideline

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This is a summary version of the full guideline, ***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* which is available to download from www.cclg.org.uk/guidelines.

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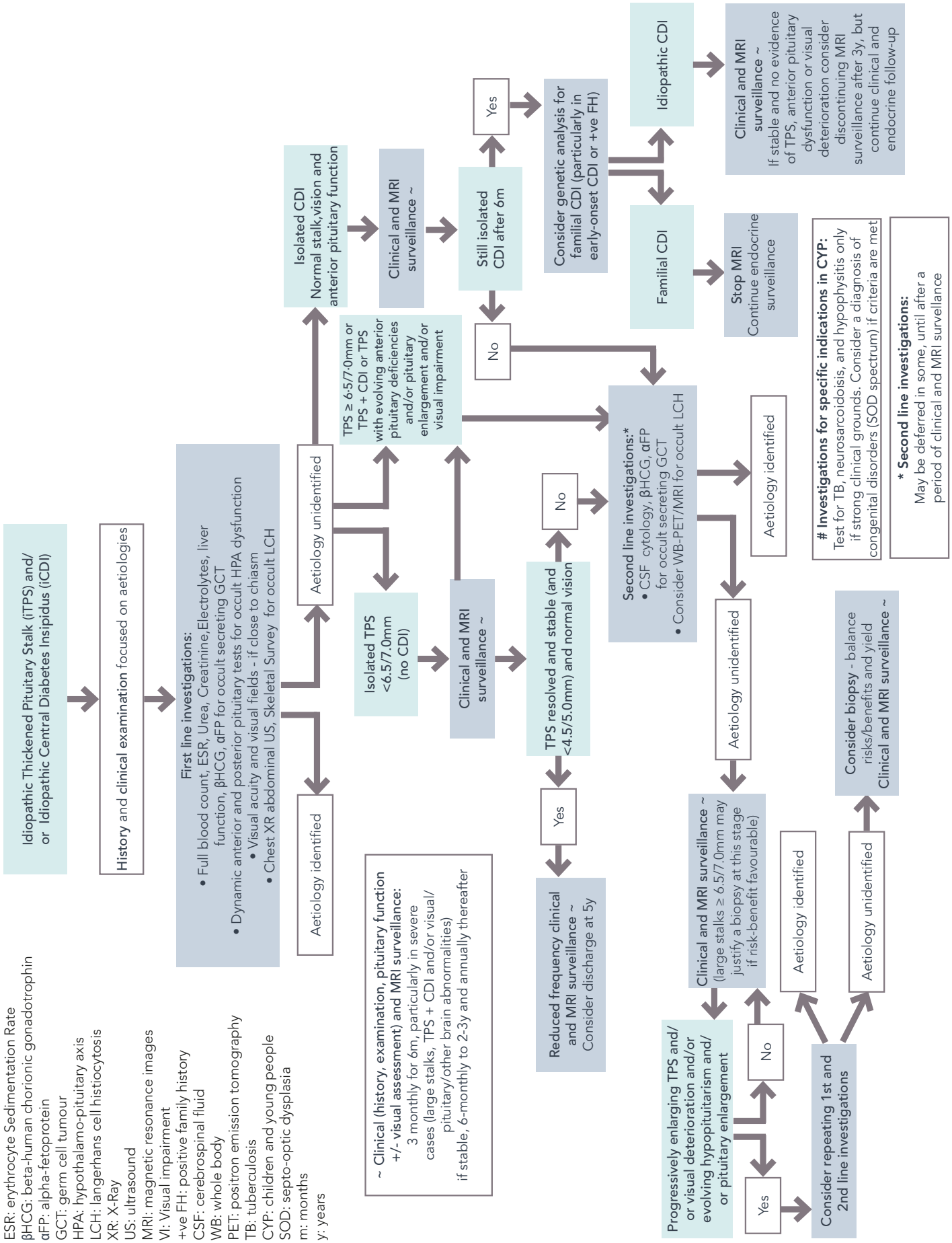
Summary

Unexplained central diabetes insipidus (iCDI) or pituitary stalk thickening (iTPS) can harbour rare occult malignancies in 40% of children and young people under 19 years (CYP), but also benign congenital defects (Table 1). Between 2014 and 2019, a multidisciplinary expert national Guideline Development Group (GDG), using rigorous AGREE II methodology, developed a clinical practice guideline to inform specialist care and improve outcomes, endorsed by the Royal College of Paediatrics and Child Health (RCPCH). The 39 recommendations and management flowchart result from the GDG's critical appraisal of 584 systematically identified papers since 1990, and 2 Delphi consensus rounds amongst independent international experts, summarised below. Importantly our literature review highlighted a significant difference in occult aetiologies underlying this symptomatology in CYP as compared to adults (Table 1), hence demonstrating the need for a specific decision making flow chart for this age-group. The full guideline is available to download from www.cclg.org.uk/guidelines.

In brief all cases of iTPS and/or iCDI require optometry, dynamic pituitary function, specialist pituitary imaging, serum β-hCG/αFP levels, chest x-ray, abdominal ultrasound and skeletal survey for occult disease. Stalk thickening 4 mm or more at the optic chiasm and/or 3 mm or more at pituitary insertion is potentially pathological, particularly if endocrinopathy or visual impairment co-exist. The role of surveillance, CSF tumour markers and whole-body imaging, indications, timing and risks of stalk biopsy, and criteria for discharge, are defined. A registry of outcomes and research to determine paediatric normative stalk sizes and the role of novel biomarkers and/or imaging techniques in diagnosis is encouraged.

Management Flow Chart



Recommendations

Presented according to NICE terminology, using the verbs "offer" and "consider" respectively, for strong and less strong interventions/actions, and the verbs "should" for strong, "may" and "consider" for moderate, and "note" for weak recommendations

I: Low quality evidence, II: Moderate quality evidence

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 CYP with iTPS and/or iCDI. (I/II, Delphi 100%)

1.2. The endocrinologist providing care for those with iTPS and/or iCDI should liaise closely with the specialist Multidisciplinary Team (MDT) for pituitary tumours with mandated specialists from paediatric and adult endocrinology, pituitary surgery, neuroradiology, neuropathology and neuro-oncology. (I/II, Delphi 100%)

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 90%)

1.4. A centralised, national, pituitary MDT may require commissioning to facilitate review of complex cases. (Delphi 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 100%)

2. Initial clinical assessment

2.1. Definition criteria for pituitary stalk thickening

2.1.1. Consider that a pituitary stalk (assessed by dedicated pituitary imaging) may be pathologically thickened and require further investigation and MRI surveillance, if there is uniform or focal thickening, in the sagittal and/or coronal plane, measuring 3mm or more at pituitary insertion and/or 4mm or more at the optic chiasm. (I/II, Delphi 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 there are associated clinical features that increase the risk of pathology (such as CDI, anterior pituitary or visual deficits). (I/II)

2.1.3. The interpretation of the stalk appearances requires neuroradiological expertise. Given the absence of age-specific norms and the inter and intraindividual variability, size criteria alone do not always differentiate between pathological and physiological variants. (I/II)

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. (II, Delphi 100%)

2.3. Additional MRI findings which increase suspicion of pathology

2.3.1. The additional absence of a pituitary 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. (II, Delphi 100%)

2.3.2. Consider a disease-tailored diagnostic approach if extra-pituitary MRI findings suggest a specific underlying aetiology (e.g. skull lesions in LCH or pineal lesions in bifocal germinoma or LCH). (II)

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 the commonest causes 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 (Fig. 2). (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 FetoProtein (αFP) to all CYP with radiologically confirmed iTPS and/or iCDI. (II, Delphi 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 92%)

3.2. Endocrinology

Offer an early endocrine assessment of growth and pubertal status, posterior pituitary function (i.e. urinary concentrating capacity after fluid deprivation) and baseline and dynamic tests of anterior pituitary function, including growth hormone (GH) and cortisol reserve, to all CYP with iTPS and/or iCDI. (II, Delphi 100%)

3.3. Opthalmology

Offer a formal baseline assessment of visual acuity and, if child co-operative, visual fields by optometry, to all CYP with iTPS and/or iCDI, especially if the TPS is proximal to, or abutting the chiasm. (II, Delphi 100%)

3.4. Imaging

Offer a skeletal survey, abdominal ultrasound and a chest x-ray (CXR) to all CYP with iTPS and/or iCDI in whom initial blood tests have failed to reveal the aetiology. (II, Delphi 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. (I/II, Delphi 92%)

3.5.1.2. Serum Angiotensin-Converting Enzyme (ACE) to screen for neurosarcoidosis in CYP with iTPS and/or iCDI is not recommended. (I/II, Delphi 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. (II)

3.5.3. Offer genetic counselling and genetic testing for inherited forms of CDI in CYP with isolated iCDI and neither TPS nor other midline neuroimaging abnormalities suggestive of SOD, especially if there is a family history and/or early childhood presentation. (II, Delphi 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) iTPS ≥6·5-7·0mm or progressively enlarging over time b) iTPS associated with iCDI c) iTPS associated with evolving anterior pituitary deficiencies and/or pituitary enlargement and/or deteriorating visual function. (II, Delphi 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 CSF, together with CSF cytology. (II, Delphi 100%)

4.1.3. Tuberculosis and neurosarcoidosis

4.1.3.1. Consider CSF analysis for TB only in those at risk. (II, Delphi 78%)

4.1.3.2. Consider CSF ACE only if neurosarcoidosis is strongly suspected. (I, Delphi 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. (i.e. TPS is ≥6·5-7·0mm, and/or is progressive, and/or is associated with CDI, changes in pituitary size, evolving endocrinopathy, or deteriorating visual function). (II, Delphi 90%)

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

5. Biopsy

5.1. In CYP who continue to pose a diagnostic dilemma after appropriate serial neuroimaging, whole body imaging and, if necessary, repeat CSF testing, consider a biopsy of the TPS if there is a very large (≥6·5-7·0mm) or progressively enlarging stalk and/or evolving hypopituitarism and/or visual deterioration. (I/II, Delphi 100%)

5.2. A biopsy should only be undertaken if the TPS 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 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. (I, Delphi 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 93%)

7. Surveillance

7.1. Surveillance for all CYP presenting with iTPS and/or iCDI

7.1.1. Offer regular surveillance including history, examination, endocrine +/- visual assessment and pituitary MRI to all CYP with iTPS and/or iCDI. (II, Delphi 100%)

7.1.2. In the absence of new symptoms or 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. (I, Delphi 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 (with/without biopsy). (II)

7.2. Reduced surveillance for CYP with stable isolated iTPS

Consider reducing the MRI surveillance frequency and/or discharging patients if, after 5 years of stable imaging, growth and puberty are complete in CYP who presented with isolated iTPS and have no anterior or posterior pituitary dysfunction and the TPS has either normalised or stabilised at under 4·5-5·0mm in maximal diameter. (I, Delphi 100%)

7.3. Reduced surveillance for CYP with stable isolated CDI

7.3.1. Familial CDI

7.3.1.1. In CYP with isolated CDI and a documented mutation responsible for familial CDI, MRI surveillance should be discontinued. (II)

7.3.2.	Isolated iCDI
7.3.2.1.	Consider discontinuing the MRI surveillance after three years, in CYP with isolated iCDI and no evidence of either TPS, anterior pituitary dysfunction or visual deterioration. (II)
7.3.2.2.	Offer continued regular endocrine and clinical surveillance screening for a late presenting GCT or LCH to all patients with isolated iCDI. (II)

8. Transition

8.1.	All CYP whose growth and puberty are complete but continue to have an endocrinopathy, iTPS ≥ 4·5-5·0mm or progressively enlarging iTPS, should be transferred for on-going age-appropriate, continued screening for late presenting GCT or LCH, to a specialist adult endocrine centre with experience in managing pituitary tumours. (II)

Estimated 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%)

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

Children's Cancer and Leukaemia Group (CCLG) is a leading national charity and expert voice for all childhood cancers.

Each week in the UK and Ireland, more than 30 children are diagnosed with cancer. Our network of dedicated professional members work together in treatment, care and research to help shape a future where all children with cancer survive and live happy, healthy and independent lives.

We fund and support innovative world-class research and collaborate, both nationally and internationally, to drive forward improvements in childhood cancer. Our award-winning information resources help lessen the anxiety, stress and loneliness commonly felt by families, giving support throughout the cancer journey.

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