# Management of children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both: a national clinical practice consensus guideline

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**Unexplained or idiopathic pituitary stalk thickening or central diabetes insipidus not only harbours rare occult malignancies in 40% of cases but can also reflect benign congenital defects. Between 2014 and 2019, a multidisciplinary, expert national guideline development group in the UK systematically developed a management flowchart and clinical practice guideline to inform specialist care and improve outcomes in children and young people (aged <19 years) with idiopathic pituitary stalk thickening, central diabetes insipidus, or both. All such cases of idiopathic pituitary stalk thickening and central diabetes insipidus require dynamic pituitary function testing, specialist pituitary imaging, measurement of serum β-human chorionic gonadotropin and alpha-fetoprotein concentrations, chest x-ray, abdominal ultrasonography, optometry, and skeletal survey for occult disease. Stalk thickening of 4 mm or more at the optic chiasm, 3 mm or more at pituitary insertion, or both, is potentially pathological, particularly if an endocrinopathy or visual impairment coexists. In this guideline, we define the role of surveillance, cerebrospinal fluid tumour markers, whole-body imaging, indications, timing and risks of stalk biopsy, and criteria for discharge. We encourage a registry of outcomes to validate the systematic approach described in this guideline and research to establish typical paediatric stalk sizes and the possible role of novel biomarkers, imaging techniques, or both, in diagnosis.**

## Introduction

Pituitary stalk thickening (PST) and central diabetes insipidus (CDI) are rare conditions (2–4 cases per 100 000 people for CDI)[1] that occur independently, synchronously, or metachronously. Children and young people (aged <19 years) with PST or CDI of indeterminate cause represent a diagnostic conundrum to differentiate the occult harmful, yet treatable, oncological, inflammatory, and infectious causes from benign congenital conditions.

Diagnostic criteria for defining PST are controversial, complicated by incidental findings, imprecise for stalk measurement at differing levels of the stalk, and do not have age-appropriate norms. There are few published clinical experiences, especially for children and young people. There are widely different prevalences of underlying causes in children and young people compared with adults,[2] and a paucity of high-quality studies or randomised trials in both age groups. This paucity in data, the rarity of the conditions, and their presentation to diverse specialties cause unacceptable inequalities in care. Under the auspice of the paediatric oncology society, Children's Cancer and Leukaemia Group (CCLG), and the paediatric endocrine society, British Society for Paediatric Endocrinology and Diabetes (BSPED), we aimed to develop a nationally endorsed clinical practice guideline for the investigation, management, and follow-up of children and young people with idiopathic PST, CDI, or both, to standardise service provision and to improve outcomes.

## Methods

A national guideline development group comprising clinical experts across the UK in adult and paediatric endocrinology, oncology, neuroradiology, neuropathology, and neurosurgery was convened in 2014. The guideline was developed with AGREE II methodology,[3] and its objectives were summarised in 64 population, intervention, comparison, and outcome clinical questions,[4] and reviewed by UK stakeholders before a systematic literature search was done (figure 1).

On Oct 8, 2014, we systematically searched Ovid MEDLINE, PubMed, EMBASE, and Cochrane Library databases, using the terms "thickened pituitary stalk", "pituitary stalk thickening", "pituitary stalk lesion", "central diabetes insipidus", "neurogenic diabetes insipidus", or "idiopathic diabetes insipidus", for papers published in English between Jan 1, 1990, and Oct 7, 2014. On July 14, 2019, we updated our search to include publications from Oct 8, 2014, to July 13, 2019 (figure 1). We included studies reporting on the epidemiology, clinical presentation, diagnosis, investigation, treatment, or follow-up of idiopathic PST, CDI, or both, in children and young people, and excluded animal studies and those reporting PST or CDI that was syndromic or associated with trauma, hypoxia, prematurity, pregnancy, or post partum. Selected papers were appraised with the Grading of Recommendations, Assessment, Development and Evaluation criteria.[5] High-quality evidence was scarce. Where there was little or no evidence in paediatric populations, the guideline development group considered adult studies, and downgraded the evidence level accordingly.

First, the guideline development group reviewed the likelihood of different occult causes underlying idiopathic PST or CDI in children and young people, and found that it differed considerably from adults.[2] After an average of 6 years (range 2–10) of surveillance across 11 studies,[6–16]

### Key messages

- The challenge posed by apparent idiopathic pituitary stalk thickening (PST) and central diabetes insipidus (CDI) in children and young people is to differentiate congenital variants from those with occult neoplasia. Unlike in adults, hypophysitis and neurosarcoidosis are exceptionally rare, whereas genetic CDI and congenital midline brain defects are a real possibility.
- The 39 recommendations and decision-making flowchart presented here aim to establish which cases are likely to suggest occult oncological disease (usually where PST or CDI and endocrinopathy or visual impairment coexist) and which patients might be discharged after stable pituitary MRI and clinical surveillance (usually mild or stable PST alone).
- To consider a pituitary stalk as thickened, the guideline development group defined cutoffs of 4 mm or more at the optic chiasm or 3 mm or more at pituitary insertion. However, without paediatric norms, size alone cannot distinguish physiological from pathological variants.
- Minimally invasive first-line investigations are strongly recommended in all cases:
  - Serum β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) to detect secreting germ-cell tumour
  - Chest x-ray, abdominal ultrasonography, and skeletal survey to detect signs of Langerhans' cell histiocytosis and possible sites for diagnostic biopsy
  - Dynamic anterior and posterior pituitary function to detect occult growth hormone and adrenocorticotropin deficiency or CDI
  - Optometry (visual acuity and field assessment), especially if PST encroaches on the optic chiasm
- Cerebrospinal fluid tumour markers (β-hCG and AFP) and whole-body imaging are second-line investigations recommended in cases where stalks are large (>6·5–7·0 mm), enlarging, pituitary or visual dysfunction is evolving, or a combination of all three.
- Pituitary stalk biopsy should only be done in specialist multidisciplinary centres in selected patients with endocrine or visual symptoms whose second-line investigations have been negative, and whose stalk thickening is sufficient (>6·5–7·0 mm) to yield a diagnostic biopsy without further visual or endocrine harm.
- More research is needed to further define normative criteria for pituitary stalks in children and young people and to establish the role of novel imaging techniques and biomarkers in securing a diagnosis, without resorting to a pituitary biopsy.

the evidence is summarised for the first time in the table. Neoplasia (46%)—either Langerhans' cell histiocytosis (LCH; 16%), germ-cell tumours (13%), or craniopharyngiomas (12%)—accounted for the majority of causes. Congenital lesions were the next largest group (19%), and a third (29%) of causes remained idiopathic. Only

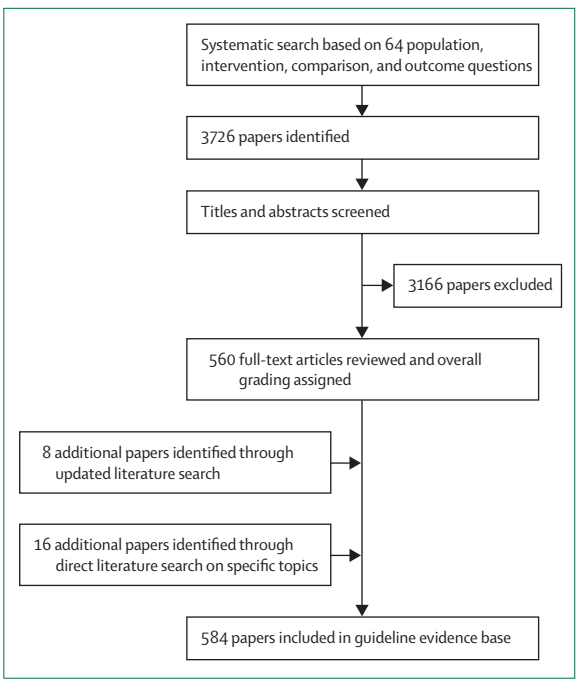


***Figure 1:*** **Literature search strategy**

a minority of children and young people had infectious and inflammatory or autoimmune causes, which were more common in adults.

39 recommendations were made. Where a moderate evidence base existed, the guideline development group made nine guideline recommendations. Where an evidence base was scarce, or to add support for moderate evidence, the guideline development group put forward recommendations to an independent international panel of 11–22 experts consulted in two rounds of a Delphi consensus process.[17] A recommendation was accepted if supported by over 70% of Delphi respondents with relevant specialty expertise to provide an opinion. 23 recommendations achieved over 75% agreement in the first round; nine of these were reformulated or separated on the basis of the panel's comments and then put to a second round. This process resulted in 29 consensus recommendations, and one further recommendation was made by the guideline development group consensus alone. Recommendations were all based on a trade-off between benefits and harms, the quality of evidence, stakeholder and user feedback, and two independent expert peer reviews.

We consistently followed National Institute for Health and Care Excellence (NICE) terminology, using the verbs "offer" for strong and "consider" for less strong interventions or actions, and the verbs "should" for strong, "may" and "consider" for moderate, and "note" for weak recommendations. The evidence levels are shown as low (I) or medium (II) quality, or a combination (I–II), in addition to any Delphi or guideline development group consensus. Six strong consensus recommendations

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| | Werny et al, 2015[6] (n=147) | Richards et al, 2011[7] (n=105) | Di Iorgi et al, 2014[8] (n=78) | Maghnie et al, 2000[9] (n=73) | Cerbone et al, 2016[10] (n=53) | Santiprabhob et al, 2005[11] (n=50) | Liu et al, 2013[12] (n=48) | Bajpai et al, 2008[13] (n=46) | Catli et al, 2012[14] (n=34) | Jaruratanasirikul et al, 2002[15] (n=29) | Hamilton et al, 2007[16] (n=21) | Combined cohort (n=684) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Idiopathic | 18 (12%) | 12 (11%) | 43 (55%) | 41 (56%) | 28 (53%) | 7 (14%) | 5 (10%) | 19 (41%) | 10 (29%) | 16 (55%) | 0 (0%) | 199 (29%) |
| Neoplastic | 78 (53%) | 56 (53%) | 27 (34%) | 24 (33%) | 22 (42%) | 14 (28%) | 38 (79%) | 17 (37%) | 17 (50%) | 10 (35%) | 8 (38%) | 311 (46%) |
| Langerhans' cell histiocytosis | 18 (12%) | 20 (19%) | 12 (15%) | 12 (16%) | 11 (21%) | 3 (6%) | 12 (25%) | 11 (24%) | 4 (12%) | 3 (10%) | 4 (19%) | 110 (16%) |
| Germ-cell tumours | 15 (10%) | 11 (10%) | 9 (12%) | 6 (8%) | 9 (17%) | 8 (16%) | 20 (42%) | 2 (4%) | 4 (12%) | 4 (14%) | 2 (10%) | 90 (13%) |
| Craniopharyngioma | 37 (25%) | 19 (18%) | 6 (8%) | 6 (8%) | 1 (2%) | 3 (6%) | 1 (2%) | 3 (7%) | 7 (21%) | 1 (3%) | 0 (0%) | 84 (12%) |
| Other brain tumours* | 8 (5%) | 6 (6%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 5 (10%) | 1 (2%) | 2 (6%) | 2 (7%) | 1 (5%) | 26 (4%) |
| Metastatic disease† | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 1 (<1%) |
| Congenital or genetic | 46 (31%) | 21 (20%) | 6 (8%) | 5 (7%) | 3 (6%) | 20 (40%) | 3 (6%) | 8 (17%) | 4 (12%) | 2 (7%) | 13 (62%) | 131 (19%) |
| Rathke and pars intermedia cyst | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) | 0 (0%) | 3 (<1%) |
| Ectopic posterior pituitary | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (<1%) |
| Septo-optic dysplasia | 21 (14%) | 8 (8%) | 3 (4%) | 0 (0%) | 0 (0%) | 7 (14%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) | 40 (6%) |
| Holoprosencephaly | 8 (5%) | 11 (10%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4%) | 2 (4%) | 4 (9%) | 3 (9%) | 0 (0%) | 0 (0%) | 30 (4%) |
| Other congenital abnormalities‡ | 6 (4%) | 2 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (22%) | 0 (0%) | 4 (9%) | 0 (0%) | 1 (3%) | 13 (62%) | 37 (5%) |
| Genetic CDI§ | 11 (8%) | 0 (0%) | 3 (4%) | 5 (7%) | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (3%) |
| Infectious¶ | 0 (0%) | 4 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 4 (8%) | 2 (4%) | 2 (4%) | 0 (0%) | 1 (3%) | 0 (0%) | 13 (2%) |
| Post-traumatic | 2 (1%) | 0 (0%) | 2 (3%) | 2 (3%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (6%) | 0 (0%) | 0 (0%) | 8 (1%) |
| Inflammatory or autoimmune‖ | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) | 0 (0%) | 0 (0%) | 2 (<1%) |
| Other** | 3 (2%)†† | 12 (11%)‡‡ | 0 (0%) | 0 (0%) | 0 (0%) | 5 (10%)§§ | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 20 (3%) |

Data are n (%). From the initial combined cohort of 741 patients from the 11 paediatric studies, 57 cases with post-operative CDI were excluded. PST=pituitary stalk thickening. CDI=central diabetes insipidus. *Optic nerve glioma, neuroectodermal tumours, astrocytoma, lymphoma, pituitary adenoma, pinealoma, cavernous haemangioma, or unknown nature. †Glioblastoma multiforme. ‡Hydrocephalus, small anterior pituitary or empty sella, encephalocele, frontonasal dysplasia, absent septum pellucidum, hydranencephaly, schizencephaly, meningomyelocele, or arachnoid cyst. §Arginine vasopressin deficiency: autosomal dominant due to *AVP* gene mutation; Wolfram syndrome: autosomal recessive due to *WSF1* gene mutations. ¶Tuberculous or group B *Streptococcal* or *Escherichia coli* meningitis, encephalitis, ventriculoperitoneal shunt infection, or pituitary abscess. ‖Hypophysitis. **In some studies, different causes were combined and not specified; therefore, the prevalence of individual causes could not be extrapolated for such studies. ††Inflammatory or infectious. ‡‡Post-traumatic, metastatic, Rathke cyst, cerebral palsy, or congenital. §§Cerebral palsy of unknown origin.

***Table:*** **Prevalence of eventual causes responsible for initially unexplained PST, CDI, or both, in 11 paediatric studies**

***Panel 1*: Service provision**

- Offer age-appropriate care, provided by an endocrinologist in a specialist centre with expertise in managing pituitary tumours, to all children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both (I–II, Delphi 100%).
- The endocrinologist providing care should liaise closely with the specialist multidisciplinary team for pituitary tumours with mandated specialists from paediatric and adult endocrinology, pituitary surgery, neuroradiology, neuropathology, and neuro-oncology (I–II, Delphi 100%).
- Given the rarity of pituitary tumours in children and young people, a national clinical database and facilitated centralised review of images, histology, and the decision-making process should be developed (Delphi 90%).
- A centralised, national, pituitary multidisciplinary team may require commissioning to facilitate review of complex cases (Delphi 90%).
- Offer all patients the opportunity to contribute to tissue banking and relevant ethically approved national and international biology and treatment studies (Delphi 100%).

were felt clinically implicit or ethically necessary to avoid patient harm, and no evidence levels are reported for these.

Research recommendations are areas prioritised by the guideline development group for further research. The guideline was ultimately endorsed by the Quality Improvement Committee of the Royal College of Paediatrics and Child Health (RCPCH) and an update to the guideline and literature review is planned for 2026.

## Recommendations and explanations

### Service provision

Evolving pituitary dysfunction over a variable timeframe is well reported in children and young people with idiopathic PST with or without idiopathic CDI.[10,18–20] Hence, the guideline development group favoured early referral to a specialist pituitary centre with an endocrinologist coordinating age-appropriate care and ensuring anterior and posterior pituitary assessment, as well as timely diagnosis and treatment of occult life-threatening endocrinopathies that affect decision making (panel 1). These steps, and baseline optometric and radiological assessments, should be discussed within the pituitary and neuro-oncology multidisciplinary team to agree management.

The scarce evidence base and rarity of the conditions, with differing causes between children and adults, persuaded the guideline development group, Delphi panel, and peer experts that a centralised pituitary multidisciplinary team and a national registry would inform and help to standardise care. A national forum, which could form the basis of a national pituitary multidisciplinary team, has been operational for complex cases since 2010.[21] Such a multidisciplinary team could also facilitate participation in national or international biology (with tissue banking) and treatment studies.

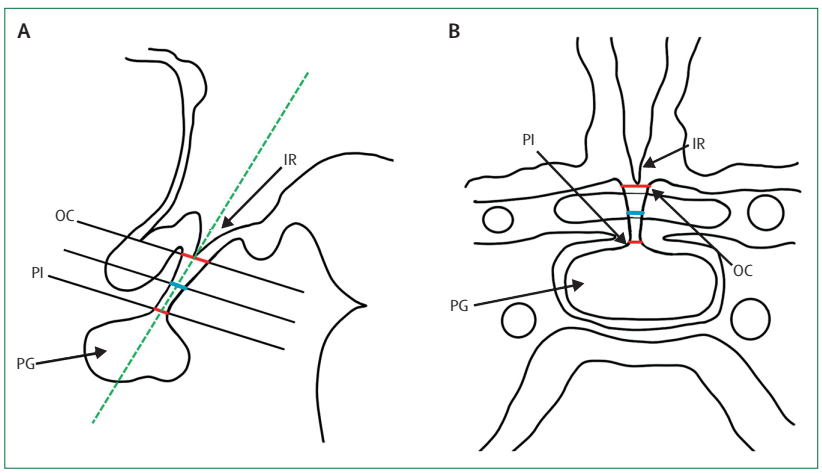


***Figure 2:*** **Measurement levels of a typical pituitary stalk on sagittal (A) and coronal (B) views**
Stalk measurements at upper level of OC and lower level of PI are shown in red. A further middle measurement (blue line) can also be taken. Coronal images (B) should be acquired in a plane parallel to the craniocaudal direction of the pituitary stalk, as shown by the green dashed line on sagittal views (A). OC=optic chiasm. IR=infundibular recess. PG=pituitary gland. PI=pituitary insertion.

### Diagnosis

Measurements at upper, middle, and lower levels of the puituary stalk are required to capture its typical shape and size (figure 2) and the degree and shape of any abnormal thickening (figures 3, 4). Because there are no differences between the anteroposterior and transverse diameters at all levels of measurement,[22–26] the thickening of the pituitary stalk can be assessed in any direction as long as the measurements are done in the same plane and at the same level within a protocol applied in each single centre for stalk abnormalities.

In the absence of such normative data in children, the guideline development group derived the dimensions of a typical pituitary stalk from dedicated pituitary imaging in healthy older adolescents and adult volunteers using CT,[22] 1·5 Tesla (T) MRI,[23,24] and 3·0 T MRI,[25] in which the upper normative limits ranged between 2·0 mm and 4·5 mm. Satogami and colleagues[25] measured the stalk at pituitary insertion and optic chiasm on T2-weighted, oblique axial, fast spin echo images in volunteers aged 21–43 years. This study reported typical dimensions of 2·32 mm (SD 0·39) at pituitary insertion and 3·25 mm (0·43) at the optic chiasm for anteroposterior diameters, and those of 2·16 mm (0·37) at pituitary insertion and 3·35 mm (0·44) at the optic chiasm for transverse diameters. However, in the only paediatric study involving 102 children aged 7–12 years, Godano and colleagues[26] reported smaller stalk sizes (2·35–2·82 mm proximally, 1·79–2·45 mm at midpoint, and 1·28–1·78 mm distally) on T1 pre-contrast, T1 post-contrast, and T2-DRIVE images than did other

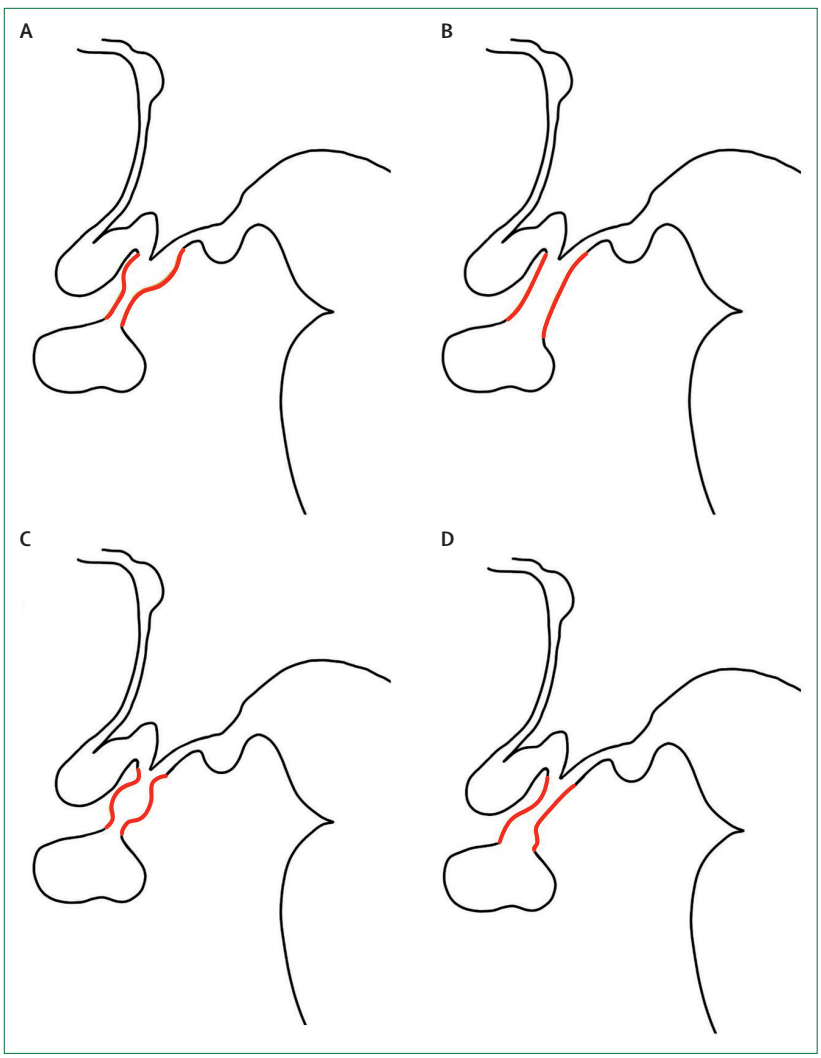


***Figure 3:*** **Different configurations of PST on a sagittal plane**
Different configurations of PST include upper (A), which is most usual in children and young people,[10] uniform (B), middle (C), and lower (D). PST=pituitary stalk thickening.

adult studies.[25] Nevertheless, the guideline development group considered these data to be flawed for the purpose of providing typical stalk size data in children, given that the healthy group included patients with congenital hypopituitarism who, despite not displaying major hypothalamic–pituitary abnormalities (without PST and with eutopic posterior pituitary), could still have pathological congenital hypoplastic or threadlike stalks. Therefore, this group cannot be considered representative of the healthy population and the measurements provided might err on the lower side.

Thus, to increase the positive predictive value, the consensus was to define PST in children and young people as measuring 3 mm or more at pituitary insertion, 4 mm or more at the optic chiasm, or both (panel 2), like most published paediatric pathological case series. However, in the presence of clinical signs, such as pituitary disturbance, visual disturbance, or both, even smaller stalk sizes (2–3 mm at pituitary insertion, 3–4 mm at the optic chiasm, or both) might have pathological significance.

To differentiate pathological thickening from physiological variants, interpretation requires dedicated imaging, neuroradiological expertise, and multidisciplinary assessment besides size criteria. Although large stalks (≥6·5–7·0 mm) are known to be more predictive of neoplasms than are mildly thickened stalks,[6,10,18–20] the predictive value of lesser degrees of thickening is less clear, and how this evolves over time and correlates with pituitary or visual deficits is unknown.

Both head and dedicated pituitary MRI are essential to accurately characterise the stalk size and shape,[26] avoid artefactual misinterpretation, and detect any congenital malformations.

Godano and collegaues[26] favour high-resolution, heavily T2-weighted sequences (eg, sagittal T2 DRIVE, which takes <3 mins to acquire, or constructive interference in steady state or fast imaging employing steady-state acquisition) to precisely measure the stalk in the sagittal plane and identify its abnormalities, without the addition of gadolinium contrast.[26] This method and the potential role of the so-called mismatch pattern (consisting of discrepancies between T2-DRIVE and post-contrast T1-weighted images of pituitary stalk thickness) as a prognostic marker for the likelihood of future anterior pituitary dysfunction or pituitary stalk stability in patients with CDI is promising, but requires confirmation in further studies.[27]

Standard MRI brain sequences must accompany the dedicated pituitary sequences to provide supporting information towards a diagnosis. Given the potential to deposit in the eloquent brain structures and other solid organs, use of gadolinium-based contrast medium is not routinely recommended in all children presenting with idiopathic PST or CDI. However, its use is specifically indicated to rule out secondary brain metastases in cases in which the clinical course is increasingly suspicious of a high-grade tumour, such as a germinoma (ie, additional precocious pseudopuberty, raised tumour markers, raised intracranial pressure, concomitant localisation in the pineal gland, basal ganglia calcification, visual abnormalities).

Additional pituitary and extra-pituitary abnormalities might aid diagnosis and should be noted (eg, skull lesions suggestive of LCH, or pineal lesions suggestive of bifocal germinoma or LCH). An absent posterior pituitary bright spot, anterior pituitary hypoplasia, or both, increase suspicion of pathology,[28] although the former finding has also been observed in nephrogenic diabetes insipidus[29] and in 4% of patients undergoing a brain MRI for non-endocrinological reasons.[30] Suprasellar midline anomalies might indicate developmental or syndromic conditions.[31] Although its specific prevalence in CDI is unknown, pituitary hypoplasia has been

described in 98% of patients with isolated hypopituitarism and in 83% of those with associated midline brain defects, optic nerve hypoplasia, or both.[31] Pituitary hypoplasia has also been described in 24% of cases of LCH,[32] whereas hypophysitis[33] and germinomas[34,35] can present with pituitary enlargement.

Systematic history and clinical examination, focused on the common differential diagnoses in children and young people (table, panel 3), should be done at diagnosis and repeatedly during follow-up. If the diagnosis remains occult, we recommend a stepwise decision-making and surveillance approach (panel 4; figure 5).

Although the sensitivity and specificity of plasma β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) in detecting secreting germinomas is unknown, these tumour markers are standard assessments in such patients. Their detectability and predictive value increases with repeated sampling over time and is often coupled with increased stalk thickening.[18,19,36] Cutoff values for marker positivity differ between studies,[37,38] and highly sensitive β-hCG assays increase the sensitivity of disease detection.[39,40] Baseline erythrocyte sedimentation rate, full blood count, urea, creatinine, electrolytes, and liver function tests are included as surrogate markers of disease severity (eg, LCH or inflammatory disease) and of fluid and electrolyte homeostasis in occult CDI.

Robust evidence supports frequent anterior pituitary deficits in children with idiopathic PST or CDI,[6,20] and timely, comprehensive endocrine assessment will aid diagnosis and replacement therapy of occult growth hormone deficiency, potentially life-threatening adrenocorticotropin insufficiency, and CDI, and will normalise growth and pubertal development. Patients with isolated PST might have occult CDI, especially if there is additional cortisol or thyroid deficiency that their replacement might unmask. The constellation and evolving hierarchy of endocrine deficits might assist differentiation of organic PST from idiopathic PST and of genetic CDI from non-genetic CDI (figure 2). Anterior pituitary deficits are more likely in cases with larger stalks[8] and in organic PST (*vs* idiopathic forms),[8,10,20] whereas genetic CDI is not usually associated with anterior pituitary deficits.[6] It is well known that secreting germ-cell tumours can present with precocious pseudopuberty.

Pathologies underlying PST or CDI might extend to the optic pathways and cause visual dysfunction. In a retrospective review of 53 children, 10% with isolated idiopathic PST, 22% with isolated idiopathic CDI, and 8% with both presented with visual symptoms.[10] This figure increased to 35% over time in children with both,[10] suggesting that all patients (especially those with both) need close ophthalmology monitoring.

The rate of detection of extra-pituitary LCH, by use of different imaging modalities in children and young people with idiopathic PST or CDI, is unknown. However, in children and young people with known LCH, 76·8% of children and 7·7% of young people have skeletal and hepatic disease.[41] A possible bony lesion in LCH is more accessible to diagnostic biopsy than is the pituitary stalk. Hepatomegaly or splenomegaly is suspicious of LCH or other multisystem diseases, and a chest x-ray might identify pulmonary involvement, which is seen in 7·6% of LCH cases[41,42] and in 50% of tuberculous meningitis cases, the latter being a rare cause of idiopathic PST or CDI.[43]

Unlike in adults, infectious, inflammatory, or autoimmune diseases are rare causes of idiopathic PST or CDI in children and young people (table). Thus, screening tests for their detection are likely to be of low yield, unless there are strong clinical indicators. Tuberculin skin testing and plasma interferon-γ release assays might provide evidence of previous tuberculosis; however, they are insensitive and non-specific in diagnosing active tuberculous CNS disease, which requires mycobacterial studies of the cerebrospinal fluid (CSF).[44]

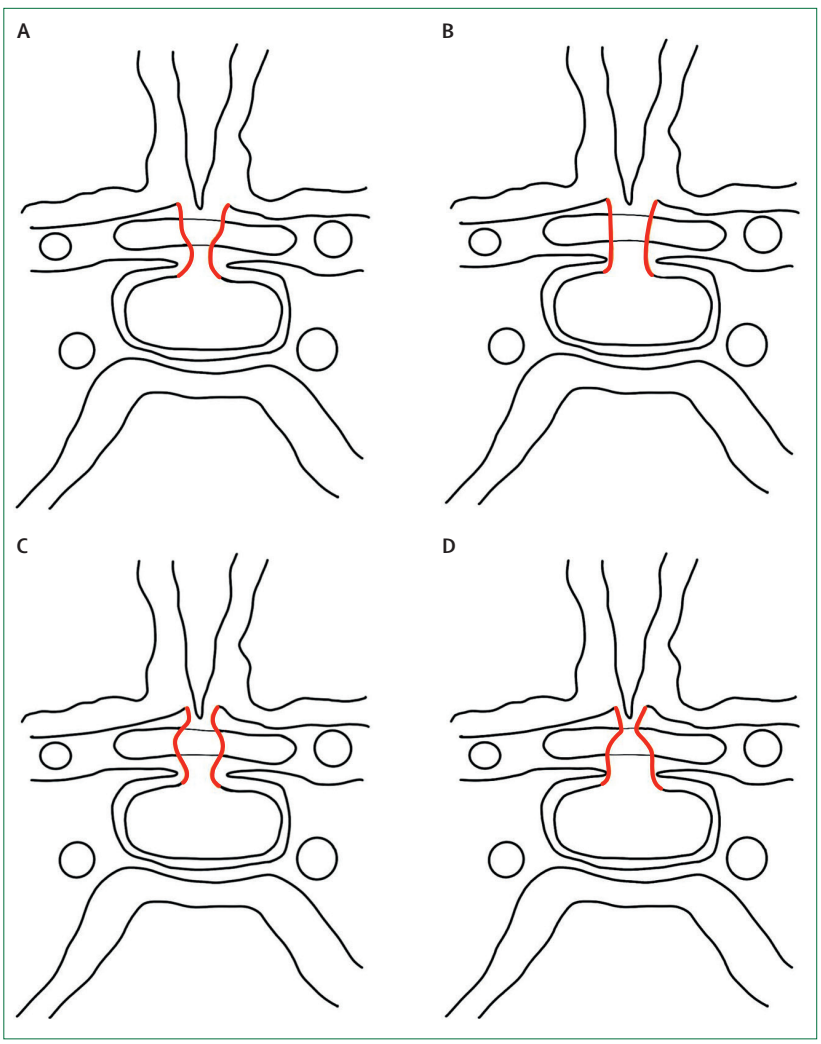


***Figure 4:*** **Different configurations of PST on a coronal plane**
Different configurations of PST include upper (A), which is most usual in children and young people,[10] uniform (B), middle (C), and lower (D). PST=pituitary stalk thickening.

### *Panel 2*: Initial imaging and clinical assessment

**Defining criteria for pituitary stalk thickening**

- 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 plane, coronal plane, or both, measuring 3 mm or more at pituitary insertion, 4 mm or more at the optic chiasm, or both (I–II, Delphi 100%).
- Consider further investigation and MRI surveillance for stalks measuring 2–3 mm at pituitary insertion, 3–4 mm at the optic chiasm, or both, if there are associated clinical features that increase the risk of pathology (eg, CDI, anterior pituitary dysfunction, or visual deficits; I–II).
- The interpretation of the stalk appearances requires neuroradiological expertise. Given the absence of age-specific norms and the variability between and within individuals, size criteria alone do not always differentiate between pathological and physiological variants (I–II).

**Dedicated pituitary MRI to detect pituitary stalk thickening**

- Offer head and dedicated pituitary MRI to all children and young people with suspected PST, CDI, or both, which should include non-contrasted, two dimensional, thinly sliced (<3 mm) weighted images with no T1 and T2 gap in sagittal and coronal planes (and ideally at least one three dimensional, highly weighted T2 sequence) to assess the possibility of uniform or focal thickening of the pituitary stalk in both planes (II, Delphi 100%).

**Additional MRI findings that increase suspicion of pathology**

- Although not diagnostic, the additional absence of a pituitary bright spot on the T1 non-contrasted scan, a clinically significant reduction or enlargement of the pituitary, or both, should increase suspicion of pathology (II, Delphi 100%).
- Consider a disease-tailored diagnostic approach if extra-pituitary MRI findings suggest a specific underlying cause (eg, skull lesions in LCH and pineal lesions in bifocal germinoma or LCH; II).

**Systematic history and clinical evaluation**

- If the cause for a confirmed PST, CDI, or both, is not apparent at presentation and a systematic history and clinical evaluation assessing the most common causes have failed to reveal a potential focus for testing, or if focused testing has proven uninformative, a stepwise decision-making approach for investigation and surveillance should be adopted in all patients (figure 5; guideline development group consensus).

PST=pituitary stalk thickening. CDI=central diabetes insipidus. LCH=Langerhans' cell histiocytosis.

In adults with autoimmune hypophysitis, 96% have PST and 72% have CDI;[45,46] however, hypophysitis itself is rare in children and young people (table).[47] A definitive diagnosis relies on histology because neuroimaging findings are non-discriminatory and because anti-pituitary and anti-hypothalamic antibodies[48,49] do not have high sensitivity or specificity.[47]

IgG4-related hypophysitis is a new entity of pituitary dysfunction and PST, usually presenting with multiorgan involvement.[50] To date, only one of 76 described cases affected a child or young person (a patient aged 16 years),[51] hence routine measurement of IgG4 concentrations are not currently recommended.

Although frequently reported in adults with idiopathic PST,[2] sarcoidosis is exceptionally rare in the paediatric population, and serum angiotensin-converting enzyme (ACE) does not have the sensitivity or specificity to detect neurosarcoidosis.[52,53] Therefore, we do not recommend its routine use in children and young people.

Midline neuroimaging abnormalities, optic nerve hypoplasia associated with CDI, or both, in a young child should raise suspicion of septo-optic dysplasia spectrum.[10,54] Causative mutations are identified in under 20% of such cases,[55,56] but septo-optic dysplasia might account for 3·4–14·3% of patients with CDI (table). Thus, genetic counselling with appropriate testing should be offered in these cases.

Familial CDI accounts for 2·0–7·5% of CDI in children and young people (table).[6,10] Isolated and early presenting cases should prompt a careful family history, genetic counselling, and a targeted genetic analysis for a dominant or, rarely, recessive variant in the *AVP* gene, particularly if symptoms are familial.[9,57] Wolfram syndrome due to biallelic mutations in the *WSF1* gene can also cause familial CDI.[57] *PCSK1* mutations resulting in severe malabsorptive diarrhoea, growth hormone deficiency, and central hypothyroidism, hypogonadism, and hypocortisolism have also been associated with clinical CDI in 80% of these cases.[57] In the rare X-linked form of CDI, no known genes have yet been identified.

Children and young people with idiopathic PST, CDI, or both, might harbour neoplasia if the cause remains occult after diagnostic tests and if they manifest with a progressive or clinically significant PST (ie, evolving endocrinopathies or visual compromise). In two case series comprising 53 children followed up for 4 years, only those with both idiopathic PST and CDI had neoplasia, which was detected later.[10,19] In cases of isolated idiopathic CDI, the risk of neoplasia is less clear, not least because idiopathic PST might additionally evolve. In one series, 40% of 38 cases with isolated idiopathic CDI developed neoplasia 1·42–21·83 years later; however, 45% of these also developed idiopathic PST during surveillance.[10] Another series did not report any cases of neoplasia in 12 children with isolated idiopathic CDI, compared with four cases in ten children with idiopathic CDI and PST after 0·6–15·3 years.[6] Thus, the guideline development group considered idiopathic CDI with idiopathic PST as more indicative of an underlying pathology requiring a lumbar puncture than idiopathic PST alone, while the evidence for isolated idiopathic CDI is inconsistent.

Nevertheless, because both series report evolving anterior pituitary dysfunction more commonly in patients with neoplastic disease than in those without (85% *vs* 39% and 67% *vs* 39%),[4,10] and visual deterioration also tracks with neoplasia,[10] the presence of these signs with idiopathic PST decreases the threshold for CSF sampling.

Use of CSF β-hCG and AFP concentrations and cytology to detect germ-cell tumour is well established, but their sensitivity and specificity in idiopathic PST or

***Panel 3*: Presenting signs and symptoms associated with the main causes of PST, CDI, or both, in children and young people**

**General**

*Central or hypothalamic*

- Headaches (even without increased intracranial pressure), weight loss, vomiting, anorexia, change in school performance, drowsiness, bulging fontanelle, lethargy, behaviour or mood change, seizures, fever, or temperature instability

*Pituitary deficits*

- Growth hormone: 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
- Adrenocorticotropin: fatigue, hypoglycaemia, hypotension, hyponatraemia, hyperkalaemia, muscle weakness, loss of appetite and weight loss, nausea, vomiting, behaviour or mood change, acute collapse (especially during intercurrent illness or procedure)
- Thyroid-stimulating hormone: 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 or thinning, prolonged reflexes
- Gonadotropins: absent or delayed puberty, primary or secondary amenorrhoea in girls (paradoxical precocious pseudopuberty in children with hCG-secreting germ-cell tumour, despite luteinising hormone or follicle-stimulating hormone deficiency), reduced bone mineral density
- Vasopressin: polyuria (particularly nocturia in childhood or adolescence), polydipsia (particularly night thirst, sometimes manifests as inconsolable crying or sleep disturbance in infants), weight loss or failure to thrive (from occult dehydration), hypernatraemia, dehydration, delayed growth

*Visual disturbances*

- Reduced vision (visual acuity) and visual fields (occult in younger children), diplopia, or squint

**Specific**

*Langerhans' cell histiocytosis*

- Skin: dermatitis (can mimic so-called cradle cap and fungal infection), vesicles, ulcerative lesions, petechiae, nodules
- Bones (single or multiple sites): pain, lumps, fracture, limp, decreased mobility
- Bone marrow: pallor, fatigue, increased susceptibility to infections, bruising, bleeding
- Gastrointestinal tract: diarrhoea, rectal bleeding, weight loss, failure to thrive, malabsorption
- Liver: hepatomegaly (usually occurs with splenomegaly), jaundice, ascites, coagulopathy
- Spleen: splenomegaly (usually occurs with hepatomegaly)
- Lungs: shortness of breath, cough
- CNS
  - Neurodegeneration: dysmetria; tremor; ataxia; dysarthria; behavioural disturbances; cognitive disorders, psychosis, or both
  - Tumorous lesions: raised intracranial pressure, seizures, site-specific symptoms and signs (eg, hypothalamus involvement might present with temperature instability, abnormal eating patterns with weight gain, behavioural problems, or both)
- Mouth, jaw, or gums: pain and swelling of face, loosening or loss of teeth, mouth ulcers, swollen or bleeding gums
- Ears: persistent or recurrent discharge, hearing loss
- Eyes: proptosis, vision loss (extremely rare)
- Lymph nodes: enlargement, soft or hard, can be matted

*Germinoma*

- Precocious pseudopuberty (if secreting hCG)

*Optic pathway gliomas*

- Association with neurocutaneous and occasionally hormonal (growth hormone excess) manifestations from neurofibromatosis type 1

*Congenital midline brain defects*

- Variable association of optic nerve, hypothalamic–pituitary axis, and corpus callosum congenital abnormalities

*Familial CDI*

- Early-onset forms, family history of CDI

*Tuberculosis (contact history)*

- Meningitis: prolonged fever, vague CNS symptoms, encephalopathy, anorexia, failure to thrive, poor appetite, nausea, vomiting and abdominal pain, sleep disturbances
- Tuberculoma: often asymptomatic

*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

*Autoimmune polyglandular syndrome type 1*

- Frequently presents with mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency
- Rarely associated with CDI

PST=pituitary stalk thickening. CDI=central diabetes insipidus. hCG=human chorionic gonadotropin.

CDI is unknown. Mildly elevated CSF β-hCG is detected in up to 38% of patients with suprasellar germinomas, whereas most of these patients have normal serum β-hCG concentrations.[58] Significantly raised β-hCG or AFP (in the context of PST) indicates the presence of choriocarcinoma and yolk sac tumour, respectively, or the presence of a mixed malignant germ-cell tumour. The tumour marker concentrations at which the diagnosis of these conditions can be made is still debated.[38] It is of note that mildly elevated CSF β-hCG

### *Panel 4*: Subsequent stepwise approach

#### First-line investigations

*Serum tumour markers, haematology, and liver and renal function*

- Offer measurement of serum β-hCG and AFP to all children and young people with radiologically confirmed idiopathic PST, CDI, or both (II, Delphi 92%).
- Although non-specific, consider assessing erythrocyte sedimentation rate, full blood count, liver function, urea, creatinine, and electrolytes to aid the diagnostic process (Delphi 92%).

*Endocrinology*

- Offer an early endocrine assessment of growth and pubertal status, posterior pituitary function, and baseline and dynamic tests of anterior pituitary function (including growth hormone and adrenocorticotropin reserve) to all children and young people with idiopathic PST, CDI, or both (II, Delphi 100%).

*Ophthalmology*

- Offer a formal baseline assessment of visual acuity and, if the child is able to cooperate, visual fields by optometry to all children and young people with idiopathic PST, CDI, or both, especially if the PST is proximal to or abutting the chiasm (II, Delphi 100%).

*Imaging*

- Offer a skeletal survey, abdominal ultrasonography, and chest x-ray to all children and young people with idiopathic PST, CDI, or both, in whom initial blood tests have not indicated the cause (II, Delphi 87%).

*Investigations of specific conditions as clinically indicated*

Infectious, inflammatory, or autoimmune disease

- Consider testing for tuberculosis or autoimmune disease as per local practice, if indicated by history and clinical examination (I–II, Delphi 92%).
- Screening for neurosarcoidosis with serum ACE in children and young people with idiopathic PST, CDI, or both, is not recommended (I–II, Delphi 100%).

Congenital midline brain abnormalities (also called septo-optic dysplasia spectrum)

- Offer genetic counselling and, when appropriate, molecular genetic testing for septo-optic dysplasia spectrum, if imaging (eg, midline anomalies or optic nerve hypoplasia), age, and ophthalmology are consistent with this diagnosis (II).

Familial CDI

- Offer genetic counselling and genetic testing for inherited forms of CDI in children and young people with isolated CDI and neither PST nor other midline neuroimaging abnormalities suggestive of septo-optic dysplasia, especially if there is a family history, early childhood presentation, or both (II, Delphi 100%).

#### Second-line investigations

*Lumbar puncture*

Indications

- Consider a diagnostic lumbar puncture if, after initial blood tests and imaging, the cause is not apparent and the patient meets one or more of the following criteria: idiopathic PST of at least 6·5–7·0 mm or progressively enlarging over time; idiopathic PST associated with idiopathic CDI; or idiopathic PST associated with evolving anterior pituitary deficiencies, pituitary enlargement, deteriorating visual function, or a combination of all three (II, Delphi 93%).

Markers of germ-cell tumour and LCH

- When a diagnostic lumbar puncture is done, offer measurement of β-hCG and AFP in the CSF, together with CSF cytology (II, Delphi 100%).

Tuberculosis and neurosarcoidosis

- Consider CSF analysis for tuberculosis in patients at risk only (II, Delphi 78%).
- Consider CSF ACE only if neurosarcoidosis is strongly suspected (I, Delphi 78%).

*Imaging*

- Consider whole-body imaging to detect distant and occult lesions in LCH that are more amenable to biopsy in children and young people whose PST, CDI, or both, remain idiopathic after initial blood tests, imaging, and CSF screening, but are still concerning for neoplasia (ie, PST is ≥6·5–7·0 mm, progressive, or associated with CDI, changes in pituitary size, evolving endocrinopathy, or deteriorating visual function [II, Delphi 90%]).
- Whole-body imaging may consist of MRI, $^{18}$FDG-PET-MRI, or $^{18}$FDG-PET-CT, depending on local availability (II, Delphi 90%).

#### Biopsy

- In children and young people 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 PST if there is a very large (≥6·5–7·0 mm) or progressively enlarging stalk, evolving hypopituitarism, visual deterioration, or combination of all three (I –II, Delphi 100%).
- A biopsy should only be done if the PST is judged by the multidisciplinary team to be of sufficient size to yield a diagnostic sample and the benefits outweigh the risks of the procedure (Delphi 100%).
- Pituitary surgery in children and young people should be done by a pituitary surgeon nominated by the multidisciplinary team. There should be ready access to trans-sphenoidal, endoscopic, and base of skull techniques, and readily available age-appropriate endocrine support (I, Delphi 90%).

β-hCG=β-human chorionic gonadotropin. AFP=alpha-fetoprotein. PST=pituitary stalk thickening. CDI=central diabetes insipidus. ACE=angiotensin-converting enzyme. LCH=Langerhans' cell histiocytosis. CSF=cerebrospinal fluid. $^{18}$FDG=$^{18}$F-fluorodeoxyglucose.

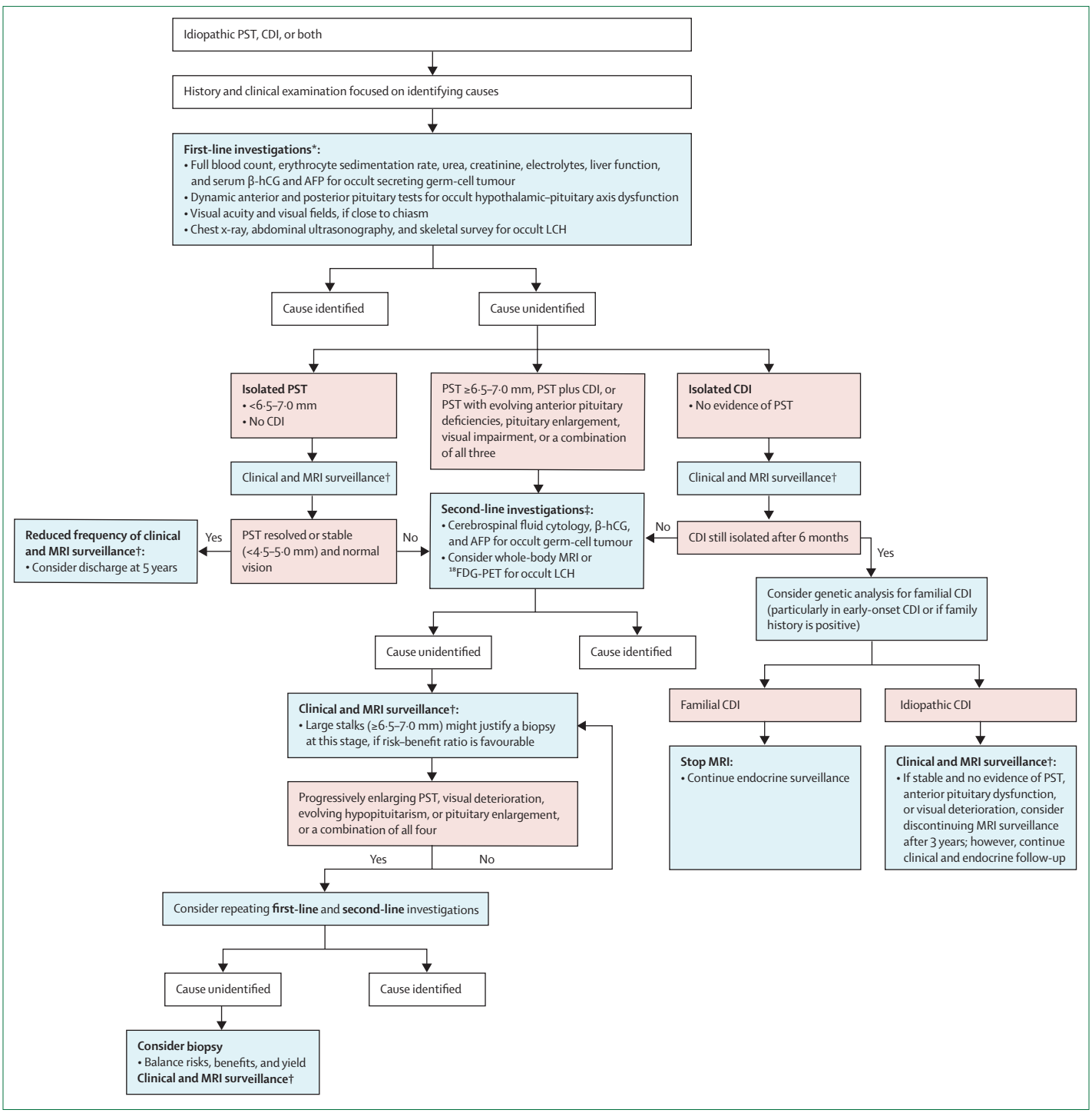


***Figure 5:*** **Management flowchart for the investigation and surveillance of children and young people with idiopathic PST, CDI, or both**
¹⁸FDG=¹⁸F-fluorodeoxyglucose. β-hCG=β-human chorionic gonadotropin. AFP=alpha-fetoprotein. CDI=central diabetes insipidus. LCH=Langerhans' cell histiocytosis. PST=pituitary stalk thickening. *Investigations for specific indications in children and young people: only test for tuberculosis, neurosarcoidosis, and hypophysitis in cases with specific clinical concerns; consider a diagnosis of congenital disorders (eg, septo-optic dysplasia) if criteria are met. †Clinical (history, examination, and pituitary function with or without visual assessment) and MRI surveillance every 3 months for the first 6 months, particularly in severe cases (large stalks; PST plus CDI; visual, pituitary, or other brain abnormalities); if stable, every 6 months for 2–3 years and annually thereafter. ‡Investigations might be deferred in some patients until after a period of clinical and MRI surveillance.

concentrations have also been described in LCH and craniopharyngioma.[59,60]

Several investigators have explored novel disease markers in patients with brain tumours. Okamoto and colleagues[61] suggest that fluid-placental alkaline phosphatase can differentiate intracranial germ-cell tumours from other types of brain tumours and can detect disease recurrence, whereas Murray and colleagues[62] highlight how microRNA quantification might assist the non-invasive diagnosis, prognostication, and management of such patients. *BRAF*$^{V600E}$ (ie, Val600Glu) alterations have been identified in various types of primary brain tumours.[63] Furthermore, detection of such alterations in the serum, plasma, and CSF of children with brain tumours is under investigation;[64] for example, whether its detection in the CSF of patients with LCH might indicate increased risk of neurodegeneration associated with the condition.[65] These novel markers, among others, are recommended for further research.

Given the rarity of CNS tuberculous disease causing idiopathic PST, CDI, or both, in children and young people, routine CSF examination for acid-fast bacilli is not recommended,[44] but should be considered in exposed patients or those at high risk. Because the diagnostic yield is lower in children than in adults (15–20% *vs* 80%) and is crucially dependent on CSF volume, repeated CSF examinations and commercial nucleic acid amplification assays might be needed to confirm the diagnosis where there is a high index of suspicion, whereas a tissue biopsy from a tuberculoma has a higher diagnostic yield.[44]

Neurosarcoidosis is unlikely to be the cause of idiopathic PST or CDI in children and young people, and given the inconsistent reports on the clinical utility of ACE measurement in the CSF,[52,66] this is not recommended unless neurosarcoidosis is strongly suspected.

Whole-body imaging with MRI, $^{18}$F-fluorodeoxyglucose ($^{18}$FDG)-PET-MRI, or $^{18}$FDG-PET-CT is not routinely used to stage patients with LCH, but it might detect extracranial lesions not otherwise identified.[42,67–69] If abnormalities outside the PST are detected and are suspicious, these might be easier targets for diagnostic biopsy. The accuracy of these imaging modalities to identify such lesions in this context is uncertain, and which whole-body imaging modality will have the highest yield is not known. Nevertheless, because of the potential to expedite a diagnosis of LCH in a patient with idiopathic CDI, while avoiding stalk biopsy in those with idiopathic PST, it is worth consideration. Early data suggest that both whole-body MRI[63] and $^{18}$FDG-PET-CT[71,72] might be more sensitive and accurate in detecting LCH lesions than is conventional imaging; however, their availability and the higher radiation dose for PET-CT limit their use. In the absence of data showing the superiority of one technique over another, the choice of whole-body imaging depends on local availability and patient circumstances (eg, age).

Although there is inadequate evidence regarding the safety, indications for, and diagnostic yield of PST biopsy in children and young people, PST that is very large (≥6·5–7·0 mm) or associated with pituitary or visual deficits is more likely to suggest neoplasms than mild, isolated PST.[4,22–25] Hence, these criteria are considered in the multidisciplinary team decision-making process regarding a biopsy of high diagnostic yield and low morbidity. For example, a transcranial biopsy was diagnostic without morbidity in six of seven children in one study,[71] as was a trans-sphenoidal biopsy in all seven children (although one required a repeat procedure).[73]

For patient safety and the best risk–benefit outcome, there was consensus that surgery should only be done by a skilled pituitary surgeon. Pituitary surgery might cause perioperative endocrine morbidity, including a triphasic response, salt wasting, and acute dehydration implicated in cerebrovascular accidents, especially in young children. Preoperative and perioperative paediatric endocrine support on site is essential, hence the need for multiprofessional, specialist centre care.

## Treatment and surveillance

Treatment of the potential underlying causes differs markedly and the side-effects of inappropriate therapy can be harmful and might potentially mask an alternative diagnosis. CNS germ-cell tumours require radiotherapy with or without chemotherapy,[74] whereas LCH requires prednisolone and chemotherapy.[42] CDI induced by LCH is usually permanent and the possibility that timely systemic LCH therapy might avoid a later risk of anterior pituitary dysfunction or neurodegeneration is not yet proven.[75] Therefore, in the absence of evidence of benefit and to avoid harm, the guideline development group felt strongly that empiric therapy for LCH should not be offered without a previous histological diagnosis (panel 5).

Where a cause is identified, this is usually within 3 years of surveillance.[6,18] Nevertheless, occasionally, occult LCH has been detected up to 10 years[18] after presentation and germ-cell tumour up to 20 years after.[62] Clinically significantly enlarged idiopathic PST with or without idiopathic CDI is more concerning than marginal stalk thickening or persistently isolated idiopathic PST,[6,10,18,20] but additional anterior pituitary deficits or visual disturbances increase the likelihood of neoplasia.[6,9,10,19]

The optimal interval for surveillance imaging is unknown; however, typically, initial neuro-oncology

***Panel 5*: Treatment**

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

surveillance is every 3–6 months. In one study, the diagnosis of germinoma was made within 2·5 years of a systematic follow-up every 6 months over 3 years.[8] Scans every 3 months for the first 6 months would ensure detection of rapidly evolving disease and should be considered, particularly in cases with a high risk of having occult oncological conditions (PST ≥4·5–5·0 mm; PST and CDI; PST with evolving anterior pituitary deficiencies, pituitary enlargement, visual impairment, or a combination of all three; or PST with other concomitant brain MRI abnormalities, all of which could suggest an underlying oncological disease). Subsequently, provided that MRI appearances are stable or improve, we suggest MRI every 6 months for 2–3 years and annually thereafter (panel 6).

In asymptomatic patients with marginal (<4·5–5·0 mm) isolated idiopathic PST that remains stable after 5 years of imaging, thickening might be incidental or a physiological variant. Discharge may be considered when growth and puberty are complete. By contrast, children and young people with isolated idiopathic CDI have a slightly increased risk of neoplasia,[6,10] for which continued clinical vigilance was felt justified, although surveillance neuroimaging can be discontinued after 3 years.[8]

To detect occult, late presenting germ-cell tumour or LCH and to provide ongoing endocrine care, children and young people with idiopathic PST greater than 4·5–5·0 mm, idiopathic PST that is enlarging, or idiopathic CDI or other endocrinopathies should be transferred to adult endocrine care once they are aged 16–18 years, and growth and puberty are complete. The centre should have experience in managing pituitary tumours and have a pituitary multidisciplinary team for case review. The transition process should ideally start with consistent monitoring and facilitated meeting(s) between paediatric and adult service teams from the age of 13 years, before transfer to adult services (NICE transition guidance).[77]

***Panel 6*: Surveillance and transition to adult care**

**Surveillance for all children and young people presenting with idiopathic PST, CDI, or both**

- Offer regular surveillance, including history, examination, endocrine (with or without visual assessment) and pituitary MRI, to all children and young people with idiopathic PST, CDI, or both (II, Delphi 100%).
- In the absence of new symptoms or signs, and if the MRI appearances are stable, consider the following frequency of surveillance: 3 month intervals for 6 months or 6 month intervals for 2–3 years and annually thereafter (I, Delphi 100%).
- If surveillance shows progressive endocrinopathies, evolving visual disturbance, progressively enlarging PST, or a combination of all three, consider repeating first-line and second-line investigations, with or without biopsy (II).

**Reduced surveillance for children and young people with stable isolated idiopathic PST**

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

**Reduced surveillance for children and young people with stable isolated CDI**

*Familial CDI*

- In children and young people with isolated CDI and a documented mutation responsible for familial CDI, MRI surveillance should be discontinued (II).

*Isolated idiopathic CDI*

- Consider discontinuing the MRI surveillance after 3 years in children and young people with isolated idiopathic CDI and no evidence of either PST, anterior pituitary dysfunction, or visual deterioration (II).
- Offer continued regular endocrine and clinical surveillance screening for a late presenting germ-cell tumour or LCH in all patients with isolated idiopathic CDI (II).

**Transition to adult care**

- All children and young people whose growth and puberty are complete but continue to have an endocrinopathy, idiopathic PST of at least 4·5–5·0 mm, or progressively enlarging idiopathic PST should be transferred to a specialist adult endocrine centre with experience in managing pituitary tumours for ongoing, age-appropriate, continued screening for late presenting germ-cell tumour or LCH (II).

PST=pituitary stalk thickening. CDI=central diabetes insipidus. LCH=Langerhans' cell histiocytosis.

## Discussion

These guidelines were jointly commissioned by the paediatric societies in endocrinology (BSPED) and oncology (CCLG), and were endorsed by the RCPCH. They were deemed vital to clarify service provision for rare paediatric pituitary disease in the UK, not least because of growing concerns to differentiate occult malignancy from normal or congenitally abnormal midline variants[31] against an increasing background of referrals to tertiary endocrine centres from various (and sometimes age-inappropriate) disciplines. Our Review has highlighted, for the first time, the difference in underlying causes between children and adults, supporting a role for pituitary-specific multidisciplinary teams for children and young people. The guideline development group and Delphi panels agreed that, to avoid harm, services should manage patients in specialist paediatric endocrine centres associated with age-appropriate pituitary and neuro-oncological services, ideally associated with a centrally commissioned outcome registry and virtual multidisciplinary team for complex cases.[21]

Given the scarcity of age-dependent radiological norms and high-quality evidence, the guideline development group's first dilemma was to define a PST, allowing for differing shapes, techniques, and measurement error. After two consensus rounds and reconsideration of cutoff specificity, the guideline development group eventually defined a PST in children and young people as 4 mm or more at the optic chiasm, or 3 mm or more at the pituitary insertion (figures 3, 4). However, unlike in adults, children and young people with even smaller stalk cutoffs (3 mm at the optic chasm and 2 mm at the pituitary insertion) might warrant investigation and surveillance, if associated with pituitary or visual dysfunction. While normative data still

need to be collected in children and young people, size criteria alone cannot discriminate between physiological and pathological variants.

To decide mandatory baseline investigations and to inform the subsequent decision-making tree that the guideline development group devised (figure 2), the group first reviewed prevalence and time to detection of underlying causes in the 11 published paediatric series (684 cases) of idiopathic PST or CDI (table), with an average follow-up of 6 years. The recommended panel of minimally invasive tests include blood tests (eg, β-hCG and AFP) and imaging (eg, chest x-ray, abdominal ultrasonography, and skeletal survey), which are simple and safe respective screens for germ-cell tumour and LCH, the two most common and worrying occult causes of idiopathic PST or CDI in children and young people. Dynamic anterior and posterior pituitary function testing and optometry (especially if encroaching on the chiasm) are important to diagnose occult CDI, growth hormone and adrenocorticotropin deficiency, and visual deficits, the presence of which increases concern for malignancy and alters the decision-making tree (figure 2), especially in the youngest children who otherwise present late. By contrast, we were able to recommend against routine screening for tuberculosis, neurosarcoidosis, and hypophysitis (as in adults), unless there are specific clinical concerns and target genetic testing for familial CDI in early-onset, isolated CDI with family history.

We also advised against masked treatment and we deferred CSF sampling and whole-body imaging to second-line investigations as suspicion increases of occult neoplasia (figure 2), recognising that in this cohort there is uncertainty about the sensitivity of CSF tumour markers to detect germ-cell tumour and about the ability of whole-body imaging to detect LCH at other sites more amenable to biopsy. Given that, for some young children, these procedures require general anaesthesia and that some of the whole-body imaging modalities involve ionising radiation, the value of this approach requires auditing.

The indications for and timing of endoscopic pituitary biopsy in children and young people are controversial. After reviewing two childhood series, the guideline development group perceived that the risk–benefit of trans-sphenoidal or transcranial biopsy could be optimised if done in a specialist pituitary neurosurgical unit with endocrine perioperative support on site, with the decision to proceed being taken on an individual basis with a specialist multidisciplinary pituitary and neuro-oncological team. Considering a biopsy only in markedly thickened (≥6·5 mm) or enlarging stalks with additional visual or endocrine deficits, which continue to pose a worrying diagnostic dilemma after repeated tests, is more likely to give a diagnostic yield without additional harm.

Furthermore, the guideline development group identified which cases of idiopathic PST, CDI, or both, required ongoing surveillance, which required transition to adult endocrine services, and which could be safely discharged. The decision-making flowchart aimed to facilitate the lead paediatric endocrinologist's surveillance (figure 5) and the detection of occult neoplasia in specific subgroups at high risk, alongside monitoring of growth, development, and vision. The initial surveillance every 3 months needed in the cases at high risk may be decreased gradually over time, depending on clinical stability and the subgroup risk. Cases of isolated idiopathic PST under 4·5–5·0 mm could be discharged following completion of growth and puberty, and 5 years of stable surveillance. However, we recommend continued clinical surveillance and adult transition in cases of stable isolated idiopathic CDI, despite discontinuation of MRI surveillance after 3 years. Any idiopathic PST and CDI combination with additional pituitary dysfunction not thought to be congenital, as well as non-familial cases of isolated idiopathic CDI, are potentially at risk of occult oncological disease and require adult transition in accordance with NICE guidelines for transition, for surveillance in the longer term.

It is hoped this first consensus guideline will aid service configuration, reduce morbidity and late diagnosis of occult oncological disease, and provide a best practice framework in this complex and niche area of childhood pituitary disease for endocrine, radiology, oncology, and neurosurgery professionals. A nationally commissioned, virtual, paediatric, pituitary multidisciplinary team and registry to audit outcomes would further improve care and inform future updates. Research to clarify normative stalk size criteria in growing children and young people and to study the accuracy of novel disease biomarkers and imaging techniques in making a diagnosis, without the need for a pituitary biopsy, should be encouraged.

**Contributors**

HAS chaired the project board, obtained the funding, and coordinated the guideline development group. JV with MC led the guideline development group. MC, JV, and HAS were responsible for the study concept and design and drafted the manuscript. CB and KV did the literature search. All authors took part in the grading process, interpreted the data, revised the manuscript critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

**Declaration of interests**

IK-A has been a member of the National Health Service England Paediatric Neurosciences Clinical Reference Group from 2013 onwards, member of Council of the Society of British Neurological Surgeons from 2018 onwards, and was chairman of the British Paediatric Neurosurgical Group from 2016 to 2018. TJ reports grants from Brain Tumour Charity, Children with Cancer UK, Cancer Research UK, Great Ormond Street Hospital Children's Charity, Olivia Hodson Cancer Fund, and National Institute of Health Research; and personal fees from Bayer, outside of the submitted work. TJ is also a director and shareholder in Repath and Neuropath; the company secretary at Repath; the editor in chief of *Neuropathology and Applied Neurobiology*; and the lead for the childhood solid tumour domain Genomes Clinical Interpretation Partnership for Genomes England and the 100 000 genomes projects. HAS is chair of the Project Board for all eight paediatric endocrine tumours in simultaneous development; Project Board Lead for pituitary adenomas, craniopharyngiomas, and idiopathic PST, CDI, or both; responsible for raising grants to fund wider endeavour; initiator and founder of group with wider involvement

across all guidelines; non-renumerated, voluntary trustee, founder, and chair of Success Charity–Life After Cure (RCN 1188298); and is a stakeholder in this guideline and donated (like other charity stakeholders Association of Multiple Endocrine Neoplastic Disorders, Pituitary Foundation, BSPED, British Neurological Surgeons, RCPCH, and CCLG) between £1000 and £3000 either in kind or in a restricted grant to the CCLG charity to support its administrative expenses only for this and seven other endocrine tumour childhood guidelines. All other authors declare no competing interests.

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