Pituitary stalk thickening in patients under 18 years of age – the most common causes and diagnostic procedures

Pogrubienie szypuły przysadki u pacjentów poniżej 18. roku życia – najczęstsze przyczyny i postępowanie diagnostyczne

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Abstract

Introduction: Pituitary stalk thickening (PST) is a rare abnormality in children, and it may be challenging due to its diverse clinical picture.

The aim of the study is to summarize the data on the causes and diagnostic procedures of PST.

Material and methods: Papers were searched in the PubMed database identifying published randomized clinical trials, reviews, systematic reviews, meta-analyses, and case reports.

Results: The most common causes of a thickened pituitary stalk in children are germ cell tumours (GCTs), Langerhans cell histiocytosis (LCH), and lymphocytic infundibulo-neurohypophysitis (LINH). Neurosarcoidosis, pituitary tuberculosis, granulomatosis, or specific inflammations were only reported in the pediatric population as case studies. PST mainly affects teenagers and is often detected with brain magnetic resonance imaging (MRI) in patients with central diabetes insipidus (CDI). It is not possible to differentiate the causes of PST with the use of the MRI image alone. Although various biochemical and oncological markers and other imaging tests are used, the diagnosis of PST remains a significant diagnostic challenge for clinicians. The final diagnosis is made based on histopathological examination. The indications for a biopsy are not uniform. Most experts, including the authors of the 2021 British consensus, recommend biopsy in the case of PST with a stalk lesion diameter ≥ 6.5–7 mm.

Conclusions: The differential diagnosis of PST is a challenge. The diagnostic and treatment strategy should be individually adapted. Patients should be diagnosed in large clinical centres with experience in this field.

Key words: children, diabetes insipidus, histiocytosis, germinoma, pituitary stalk thickening.

Streszczenie

Wstęp: Pogrubienie szypuły przysadki (PST) jest rzadką nieprawidłowością u dzieci i trudnym problemem diagnostycznym ze względu na zróżnicowany obraz kliniczny.

Cel pracy: Podsumowanie danych dotyczących etiologii i diagnostyki PST.

Materiały i metody: Przegląd publikacji bazy PubMed obejmujący badania kliniczne z randomizacją, przeglądy systematyczne, metaanalizy, opinie przypadków.

Wyniki: Najczystszymi przyczynami PST u dzieci są guzy zarodkowe (GCTs), histiocytoza z komórek Langerhansa (LCH) i limfocy- tarne zapalenie części nerwowej i szypuły przysadki (LINH). Z kolei neurosarkoidoza, gruźlica przysadki, zraniniałowość lub inne specyficzne stany zapalne przysadki w populacji pediatrycznej stanowią jedynie opinie przypadków. PST dotyczy głównie nastolatków i jest często wykrywane za pomocą rezonansu magnetycznego (MRI) mózgu i pacjentów z centralną moczkową prostą (CDI). Nie jest możliwe różnicowanie przyczyn PST na podstawie samego obrazu MRI. Pomimo dostępności markerów biochemicznych, onkologicznych oraz innych badań obrazowych rozpoznanie przyczyn PST pozostaje istotnym wyzwaniem diagnostycznym dla klinykistów. Ostateczną diagnozę stawia się na podstawie badania histopatologicznego. Wskazania do biopsji nie są jednolite. Większość ekspertów, w tym autorzy konsensusu brytyjskiego z 2021 r., zalecają biopsję w przypadku PST o średnicy zmiany w szypule ≥ 6,5–7 mm.

Wnioski: Diagnostyka różnicowa PST jest wyzwaniem. Strategia diagnostyczna i leczenie powinny być dostosowane indywidualnie do pacjenta i należy je przeprowadzać w dużych ośrodkach klinicznych mających doświadczenie w tej dziedzinie.

Słowa kluczowe: dzieci, pogrubienie szypuły przysadki, moczkówka prosta, rozrodczak, histiocytoza.
Introduction

Pituitary stalk thickening (PST) is a relatively rare abnormality in children. The diagnosis may be challenging due to its diverse clinical picture.

PST develops for a variety of reasons, such as neoplastic, inflammatory, infectious diseases, or congenital abnormalities (Figs. 1, 2). PST mainly affects teenagers and is often detected with magnetic resonance imaging (MRI) in patients with central diabetes insipidus (CDI) [1]. Sometimes, pituitary stalk lesions are accidentally detected during brain MRI. In most cases, the diagnosis is based on radiological imaging and laboratory tests. Because of the risks associated with obtaining a pituitary stalk biopsy, only a small subset of patients had their diagnoses histopathologically confirmed [2]. Despite the development of MRI imaging techniques, PST remains a conundrum for clinicians.

Previous studies determined the correct pituitary stalk dimension as 3.25 ±0.56 mm in the transverse diameter at the

Figure 1. T1-weighted images, sagittal plane. A) 10-year-old boy with germinoma involving pituitary stalk. Pituitary stalk thickening (9 × 8 mm). B) 2-year-old girl with multifocal histiocytosis with involvement of hypothalamic-pituitary region. Pituitary stalk thickening (3.5 mm). C) 16-year-old girl with lymphocytic hypophysitis. Pituitary stalk thickening (4 mm), enlargement of the pituitary gland (11 × 14 × 10 mm), in the intermediate lobe hypointense lesion (8 × 4 × 5.5 mm) – pituitary cyst. D) 5-year-old boy with hyperintense congenital lesion in infundibular recess (3 × 2 mm) – ectopic posterior pituitary.
tuberculosis

The clinical presentation and time to diagnosis reflects the location and size of the tumour. Most patients with neurohypophyseal germinoma present endocrinological findings like polydipsia/polyuria, short stature, precocious puberty/delayed puberty, signs of central hypothyroidism, or central adrenal insufficiency. Additionally, the manifestations include ophthalmological ones (eye movement abnormalities, blurred vision, diplopia, visual field defect, ptosis, pupil dysfunction), neurological ones (headdache, nausea/vomiting, dizziness/vertigo, and drowsiness), and motor impairment (dyskinesia/ataxia and focal/general weakness, facial palsy) [18]. According to Chang et al. [14], who described 49 children with intracranial pure germinoma in Taiwan, growth hormone (GH) deficiency or low insulin-like growth factor 1 (IGF-1) was diagnosed in 85.7%, adrenal insufficiency in 77.8%, CDI in 55.1%, central hypothyroidism in 48.4%, and factor 1 (IGF-1) was diagnosed in 85.7%, adrenal insufficiency in 77.8%, CDI in 55.1%, central hypothyroidism in 48.4%, and hypogonadotropin hypogonadism in 44.4% of children.

patient age is within the range of young adolescence, usually 10-14 years. A higher incidence is observed in Asian than in Western countries. CNS GCTs account for approximately 3–4% of primary paediatric brain tumours in the West, and 8–15% in Asia (based on data from Taiwan, Japan, and South Korea) [12]. The incidence rate in the United States is 0.1 per 100,000 person-years, and the incidence is 0.4-0.5 per 100,000 children per year in Taiwan [13, 14]. Three main germinoma locations may be distinguished. The most common site of origin is the pineal region (45%), and the second most common site is the suprasellar region (30%) within the pituitary stalk. A strong association between location and sex was noted in accordance with the literature, with the predominance of men in pineal lesions (75%) and of women in suprasellar lesions (70%) [15]. Approximately 5% to 10% of patients present with synchronous tumours arising in both the suprasellar and pineal locations, with the most frequent histology being a germinoma [16]. A rare phenomenon known as ectopic germinoma means that other areas of the CNS may be involved. They include the basal ganglia, ventricles, thalamus, cerebral hemispheres, and brain stem (5–10%) [17].

Signs and symptoms

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CDI is the most common initial manifestation of neurohypophyseal germ cell tumour. Occasionally, CDI precedes the emergence of radiological abnormalities that indicate neurohypophyseal germinoma by several months or years. Such a germinoma-causing CDI was termed occult germinoma, which may result in a critical delay in the accurate diagnosis and, therefore, treatment of the disease [19]. Germinomas have an almost exclusive predominance as the occult cause of CDI in teenagers. Similarly to CDI, spontaneous and on stimulation, GH secretion deficiency often preceded the obvious tumour mass formation. Therefore, the association of CDI with evolving anterior pituitary endocrinopathy point to the presence of an occult neurohypophyseal germinoma. Czernichow et al. [20] conducted a study among 17 children with PST and CDI and diagnosed germinoma in 4 of them (15% of the patients). In another series of 9 children with PST and CDI, the transsphenoidal biopsy of PST showed germinoma in 7 of 9 patients (77.7%) [21].

Neurohypophyseal germinomas may be pure or contain syncytiotrophoblastic giant cells that secrete human choric gonadotropin (hCG). Any tumours affecting the neurohypophyseal region and producing hCG may cause pseudoprecocious puberty in boys [22]. Because hCG is structurally similar to luteinizing hormone (LH), its excessive increases may stimulate the Leydig cells of the testes to produce testosterone. Reduced follicle stimulating hormone (FSH) levels may explain the lack of correlation between testicular growth and other sexual characteristics, because testicular maturation depends upon this hormone. Precocious puberty in girls is extremely rare. Kita-naka et al. [23] described a 6-year-old girl who presented precocious puberty due to an hCG-secreting suprasellar immature teratoma. Starzyk et al. [24] presented a 5-year-old girl manifest- ing gonadotropin-releasing hormone-independent precocious puberty. The β-subunit human choric gonadotropin (β-hCG) and α-fetoprotein (α-FP) tumour markers were markedly elevated, and suprasellar germinoma cell tumour was visualized with MRI [24]. It was believed that hCG did not trigger precocious puberty in girls in the absence of FSH, and it was used as an explanation for the rarity of precocious puberty in girls with hCG-secreting tumours. However, it was also reported that hCG was not only characterized by LH activity but also intrinsic, although weak, FSH-like activity [23]. It was also hypothesized that precocity was due to high aromatase activity in germ cell tumours [24].

Children with pineal lesions are at a high risk of presenting with acute hydrocephalus. In up to two-thirds of patients, lesions in the pineal region are associated with increased intracranial pressure and symptoms such as headache and vomiting, while Parinaud syndrome or upward gaze palsy are classic common manifestations seen in almost one-third of patients [18].

Germinoma arising from the basal ganglia, also known as ectopic germinoma, is a rare entity representing 5-10% of all intracranial germinomas. Basal ganglia are responsible for the control of movements, cognitive processes, emotions, and learning. Hemiparesis, cognitive decline, and behavioural disorders are common signs of basal ganglia germ cell tumour [25]. The ventricles, internal capsule, thalamus, putamen, cerebral hemispheres, and brain stem are other sporadic ectopic locations of GCTs.

The time from symptom onset to the diagnosis varies depending on the location of the tumour. The most prolonged interval was observed in case of suprasellar tumour (from one month to 9 years), the shortest in case of pineal tumour, and intermediate for a location in the basal ganglia (one month to 4.5 years) [26].

**Diagnoses**

GCTs may secrete measurable oncoproteins such as β-hCG and α-FP into the serum or cerebrospinal fluid (CSF). Although hCG is a glycoprotein with a molecular weight of about 45kD and has α- and β-subunits, germinoma may also independently secrete the β-subunits in the free form. β-hCG is produced by the normal trophoblast in the placenta. Serum levels are normally elevated in pregnant and postnatal women, and abnormally increased in patients with chorionicarcinoma and germ cell, bladder, pancreatic, gastric, and lung tumours [27]. Tumour markers may be useful surrogate biomarkers and may spare some patients the need for biopsy. Typically, chorionicarcinoma produces β-hCG, and yolk sac tumour produces α-FP. Germinoma with syncytiotrophoblastic giant cells also produces β-hCG, but its serum titre in germinoma with syncytiotrophoblastic giant cells is usually lower than in chorionicarcinoma. 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. Mixed germ cell tumours produce various amounts of tumour markers according to the histological elements they contain. The markers may then be detected in both the serum and CSF. The assay of lumbar CSF is imperative for an accurate diagnosis and staging because oncoprotein levels are often much higher than in the serum [28].

The evaluation of the clinical diagnostic value of β-hCG and α-FP for GCTs is an interesting and confusing topic for endocrinologists, neurologists, and neurosurgeons.

The National Academy of Clinical Biochemistry emphasized that the detection of β-hCG should include the whole hCG and free β subunit at the same time. The recommendations of the International Society of Paediatric Oncology (SIOP) CNS GCT 96 protocol indicated that β-hCG concentration ≥50 IU/l and α-FP ≥25 ng/ml represented a strong indicator of the presence of germinoma. However, according to other authors, CSF concentrations that were much lower, but still greater than expected under normal conditions, were indicative of cerebral germinoma [29].

A cut-off value of β-hCG for the diagnosis of intracranial germinomas has not been established, thus limiting its diagnostic value. Institutions usually define their own normal range of serum β-hCG for intracranial germinomas. Commonly reported cut-off values range from 0.1 to 8 mIU/ml [30]. Zhang et al. [30] in their study including 93 intracranial germinoma and 289 intracranial non-germ cell tumour patients, recommended that the cut-off value of serum β-hCG of 0.5 mIU/ml could be used in assisting the diagnosis of germinoma, because it had the highest specificity (96.16%). Allen et al. [28] suggested the cut-off CSF β-hCG of 7.2 IU/l for germinoma and revealed that among 58 patients with histopathologically confirmed germinoma, approximately 34.5% of patients had elevated lumbar CSF β-hCG values with normal serum values, and in 87% of patients with hCG elevations abnor-
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ormal CSF values were higher than the serum value. Hu et al. [31] proposed new biomarker diagnostic cut-off points: CSF β-hCG ≥ 8.2 IU/l and serum β-hCG ≥ 2.5 IU/l, while empirically adjusted criteria for α-FP are ≥ 3.8 ng/ml in the CSF and ≥ 25 ng/ml in the serum. According to the results published by Gonzales-Sanchez et al. [29] CSF β-hCG concentrations that exceeded the established reference interval (undetectable values to 0.7 IU/l) in the presence of suprasellar lesions and hypophyseal stalk thickening should be considered pathological, establishing the need to exclude the presence of germinoma. Katagami et al. [32] also claimed that a CSF/serum hCG ratio ≥ 2 represented a strong indicator of the presence of germinoma. However, it should be remembered that Hu et al. [31] reported a slightly increased level of β-hCG in the CSF in patients with LCH and with craniopharyngioma, with the respective values being 6 and 8 IU/l.

The determination of β-hCG in the serum or CSF is a sensitive indicator not only in the diagnosis of neurohypophyseal germinoma but also in monitoring treatment response and recurrence.

Other biomarkers associated with germinomas include lactate dehydrogenase and placental alkaline phosphatase. S-kit, a soluble product of the c-kit oncogene, appeared to be a more sensitive screening tool than hCG for germinoma in several series from Japan [33]. New markers were investigated, including CSF micro-RNA 371-373 and 302 levels, which were significantly increased in GCTs, but decreased significantly after treatment. This marker might be used for the future diagnosis of germinoma [34].

Despite the new diagnostic criteria proposed by the authors mentioned above, the surgical confirmation of tumour histology is still the standard of care in the absence of significant oncoprotein elevations (β-hCG ≥ 50 IU/l, α-FP ≥ 25 ng/ml). A single exception should be mentioned, i.e. the presence of normal CSF and serum β-hCG and normal levels of α-FP supports the clinical impression of a germinoma in patients with bifocal germinoma, so histologic confirmation is not usually obtained.

Based on MRI findings, suprasellar lesions were classified into 5 types: a 3rd ventricle floor tumour extending dorsally with or without an identifiable pituitary stalk (Type Ia, Ib), ventrally (Type III), in both directions (Type II), a small lesion at the 3rd ventricle floor extending to the stalk (Type IV), and a tumour located in the stalk (Type V) [26]. The thickening of the hypophyseal stalk is the most common MRI finding, together with the loss of neurohypophyseal hyperintensity in T1-weighted sequences, in which the lesion appears isointense or slightly hyperintense with respect to the normal hypophysis. The uptake is less pronounced than in the normal hypophysis after gadolinium contrast injection [29]. The imaging findings are not specific, and differential diagnosis must encompass lymphocytic hypophysis, which is an infrequent disorder in children. Particular difficulty in the differential diagnosis is the fact that histological findings compatible with a lymphocytic inflammatory process may represent the first sign of a host reaction to occult germinoma [35]. This would justify the determination of hCG in the CSF in all prepubertal patients with a presumed or histological diagnosis of lymphocytic hypophysis, as well as the immunohistochemical study of the histological specimen with the determination of placental lactogen, c-Kit, and CD30 [36].

Secondary hypophysitis is believed to be triggered also by other focal pituitary processes, such as craniopharyngiomas, adenomas, and Rathke cleft cysts.

Treatment
The treatment includes chemotherapy (carboplatin, etoposide) and radiation therapy (18 Gy WV with a 12 Gy boost to the primary site). High-dose chemotherapy followed by autologous stem cell transplantation may be effective in patients with relapsed or progressive disease [37]. Because a number of patients are resistant or relapse after curative treatment, there is a pressing need for new therapeutic options. Genetic abnormalities that are present in such cases indicate that targeted therapies such as tyrosine kinase inhibitors may have promising activity. Results from a study evaluating dasatinib are awaited. CNS germinoma tumours may also express programmed death ligand-1 (PD-L1), which indicates the potential antitumour activity of immunotherapy. Additionally, the inhibition of the RAS/MAPK pathway may be a potential therapeutic option, but it requires further research [38]. Endocrine dysfunction manifested in germinoma cases might not be ameliorated even after undergoing successful therapy.

Surveillance and prognosis
Various authors emphasized that repeated brain MRI and the investigation of the tumour marker β-hCG in the serum and CSF should be performed every 3-6 months during the first 3 years after the onset of CDI and PST, in order to rapidly establish a diagnosis before the developing large tumour contributes to visual and neurological symptoms. Subsequently, MRI should be performed every year during the following 2 years and every 2–5 years thereafter, depending on the size and evolution of the lesion [20].

The prognosis of the tumour is dependent upon the histology, but also upon the size of the tumour and the extent of the disease at diagnosis. An early diagnosis is a key to treat such tumours before hypothalamic-hypophyseal damage proves irreversible or adjacent structures suffer compression or metastatic disease becomes apparent.

Cerebral histiocytosis
LCH is a rare disease of the monocyte-macrophage system characterized by the clonal proliferation of epidermal dendritic cells. In recent years, increasing evidence has been presented to support the idea that LCH is a “neoplasm”, which means that LCH tumours contain cells with gene mutations that cause them to make abnormal copies of themselves. A specific gene called the BRAF is mutated in about half of LCH tumours [39].

Epidemiology
LCH is a rare disorder, which mainly affects the paediatric population with peaks between 1 and 3 years of age. The estimated annual incidence of LCH is approximately 6:100,000 to
of the posterior pituitary [41]. It is still difficult to differentiate HPR-involved LCH from other diseases, such as germinoma or lymphocytic hypophysitis with MRI. An isolated HPR lesion is a clinical challenge, because neither the clinical manifestations nor MRI may be sufficient to make a definitive diagnosis, and the risk associated with obtaining a diagnostic biopsy remains high. Nagasaki et al. [44] described a 13-year-old girl with CDI and PST and biopsy-confirmed LCH. The diagnostic work-up performed in this patient also revealed slightly elevated β-hCG in the cerebrospinal fluid, which indicated a difficulty not only with imaging but with biochemical differential diagnosis between neurosarcoidosis and germinoma.

Skeletal survey can be performed by multiple X-ray images and CT scans, but 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) offers greater accuracy and allows a precise localization of lesions that are more easily accessible for biopsy than the pituitary stalk. 18F-FDG PET/CT is also a highly sensitive method for the staging and follow-up of paediatric patients with LCH.

The diagnosis of LCH should be based on the histological and immunophenotypic examination of the lesional biopsy. The presence of Birbeck granules under electron microscopy and positive immunohistochemical staining for S100 and CD1 and/or CD 207 (Langerin) protein markers is characteristic [46].

**Treatment**

Very low incidence of localized HPR LCH is the main reason why there is no consensus as to optimal treatment. The treatment of isolated HPR LCH is controversial and individualized. Simple observation, surgery, low-dose radiation, and chemotherapy (glucocorticoids, methotrexate, vinblastine) are considered in treatment planning. Limited literature data show that low-dose irradiation (≤ 22 Gy) is usually the first-line therapy adequate for most cases of isolated HPR LCH with a sporadic recurrence of the illness [47].

The natural history of LCH is poorly understood. In fact, spontaneous regression is well reported in numerous body systems including the skin, bone, lung, and CNS [44].

**Lymphocytic hypophysitis**

LYH is a neuroendocrine disorder characterized by autoimmune inflammation of the pituitary gland with various degrees of pituitary dysfunction. It was initially considered to be restricted to women in relation to pregnancy, but it is now clear that LYH may occur in children and adults, men and women [48].

The following types of LYH may be distinguished: lymphocytic adenohypophysitis (LAH – an inflammation limited to the anterior hypophysis), lymphocytic infundibuloneurohypophysitis (LINH – autoimmune infiltration involving the infundibular stem and posterior lobe), and lymphocytic panhypophysitis (LPH – both the adenohypophysis and the infundibuloneurohypophysitis are affected), depending on which part of the HPR is involved in the immune process. LAH was first described in 1962 by Goudie and Pinkerton [49]. They reported a case of a 22-year-old woman, who died 14 months after her second delivery, probab-
ly because of adrenal insufficiency. LINH was first described in 1970 by Saito et al. [50], who observed a 66-year-old asthmatic woman with a one-month history of polydipsia and polyuria. LINH was reported especially in children and adolescents. LPH was first described in 1991 in a 40-year-old man with a 3-month history of headache, polydipsia, polyuria, and impotence [51].

**Epidemiology**

The annual incidence of LYH may be estimated at one case per 9 million. Data from 4 large patient analyses (905–2500 people) indicate that LYH is seen in less than 1% (0.88-0.24%) of all surgical pituitary specimens [52–54]. In 2012, Kalra et al. [55] indicated that the number of children under 18 years old with LYH was greater than 96 in the literature. The incidence in children was much lower compared to approximately 460 adults with autoimmune hypophysitis [56]. In contrast to adults (more female patients were identified with a female-to-male ratio of 8:1) no significant sex predilection was seen among children.

Concurrent autoimmune conditions were reported in 20–50% of cases of LYH in adults [57]. The most common association was observed with autoimmune thyroid disease, reported in 15–25% of LYH cases, i.e. 70-80% of cases with an associated autoimmune disease. Chronic autoimmune thyroiditis constituted about 75%, while Graves’ disease and subacute thyroiditis were reported less frequently. Autoimmune adrenalitis was reported in 5–7% of cases (15–25% of patients with an associated autoimmune condition), while pernicious anaemia and type 1 diabetes were seen in 2% of cases [57]. Associated autoimmune disorders occurred in 7 out of 96 children, with an incidence of 7% as compared to 20–50% in adults [55].

**Signs and symptoms**

The clinical presentation of LYH is variable and comprises 4 categories of symptoms: sellar compression, hypopituitarism, CDI, and hyperprolactinaemia. In adults with LYH, 96% have PST and 72% have CDI.

The symptoms of sellar compression, represented by headache and visual disturbances, are the most common and usually the initial complaints in LAH. Headache is the result of the distortion of the dura mater and diaphragma sellae by the expanding pituitary mass. However, a recent study showed that pituitary volume did not correlate with its severity [58]. Headache is observed more often in patients with LAH (53%) than in those with LINH (13%). Visual abnormalities include visual field defects, decreased acuity, and diplopia, which are secondary to the compression of the optic chiasm by a pituitary mass expanding upward or laterally to the cavernous sinus. Visual disturbances are described in 43% of LAH and seldom in LINH, i.e. only in 3%. The other most common symptoms are due to a partial or complete deficit of the anterior pituitary hormones. CDI is another of the most common problems, which may be attributed either to direct immune destruction or to the compression of the posterior lobe and infundibular stem. CDI is the cardinal feature of LINH (98%) and may be very rare in LAH (1%). CDI may be masked in the presence of a coexisting glucocorticoid deficit because it opposes the action of antidiuretic hormone (ADH) at several levels. Glucocorticoids inhibit the secretion of ADH from the neurons of the paraventricular nucleus and suppress the synthesis of aquaporin 2, an ADH-dependent water channel expressed in the renal collecting tubules.

The manifestations of hyperprolactinaemia, mainly represented by amenorrhoea and galactorrhoea, are the least common. Hyperprolactinaemia results from stalk compression, with the resulting decrease in dopamine delivery to the anterior pituitary. The inflammatory process may directly destroy the lactotrophs, inducing the release of prolactin (PRL) into the general circulation [59]. Headache, visual disturbances, hypothyroidism, and hypothyroidism are more common in LAH than in LINH or LPH. In contrast, CDI suggests LINH, a condition in which other presenting symptoms, such as visual disturbances, hypopituitarism, hypogonadism, and hyperprolactinaemia are rare.

**Diagnosis**

A presumptive diagnosis of LYH may be made based on clinical, laboratory, and imaging studies, but the definitive confirmation requires a pituitary biopsy.

Antibodies against pituitary protein and vasopressin-secreting hypothalamic cells may be found in patients with LYH. They may be measured with indirect immunofluorescence, immunoblotting, or enzyme-linked immunosorbent assay (ELISA). However, the specificity and sensitivity of pituitary antibodies is poor, as they were found in various pituitary diseases such as Cushing’s disease, pituitary adenoma, empty sella syndrome, as well as in other autoimmune diseases, such as type 1 diabetes mellitus, Hashimoto’s thyroiditis, and Graves’ disease. A retrospective analysis of 379 patients with LYH conducted by Catereggi et al. [51] revealed that antibodies against pituitary protein were detected in 10–80% of patients depending on the form of LYH and the method used (they were more often confirmed in immunoblotting).

The authors of a case series presenting LAH reported that MRI studies showed an enlarging pituitary mass in 75-90% of patients [48]. Even in cases with CDI, in which the initial scan was normal, repeated imaging evaluations performed months later might reveal a mass-like image [60]. Heinze and Bercu [61] published a review of 63 patients in which they reported a post-contrast enhancement of the lesion in 70%. Honigeler et al. [54] reported a tongue-like extension toward the hypothalamus as a characteristic finding of LAH. A diffuse thickening of the pituitary stalk is a very characteristic MRI feature in patients with LINH. Its greater diameter was found to exceed 3.5 mm at the level of the median eminence of the hypothalamus [62]. The normal smooth tapering of the infundibular stalk is lost, and a varying degree of asymmetry may exist. Marked gadolinium enhancement of the stalk is quite common, extending even into the lower hypothalamus. The loss of the usual neurohypophyseal “bright spot” was also commonly reported. However, it should be kept in mind that this MRI sign may be absent in 10% of normal subjects [63]. Extensive pituitary inflammatory changes were reported in LINH, extending upwards to the suprasellar area and affecting the optic pathway, or laterally to the cavernous sinuses, with thickening of the pituitary stalk, enlargement
of the neurohypophysis, or lack of the neurohypophyseal bright spot on the normal neurohypophysis on MRI [64]. Histopathology remains the gold standard for the diagnosis of LYH. The infiltration of the pituitary gland with lymphocytes, with the predominance of T cells and particular CD4 cells is the defining pathological feature of LYH. Plasma cells, eosinophils, macrophages, histiocytes, and neutrophils are also present. Fibrosis and rare necrosis may be reported in pathological specimens [63].

LINH should be suspected as a cause of PST when we observe: an acute onset of CDI with headache and mass-effect symptoms; isolated, early or disproportionate disruption of ACTH or TSH secretion, disproportionate disruption of anterior pituitary function for the magnitude of the changes on MRI; the presence of other autoimmune conditions and/or positive autoantibodies, including thyroid peroxidase antibodies, antinuclear antibodies, antiparietal cells, adrenal antibodies, and anti-smooth muscle antibodies; the presence of antipituitary antibodies in the serum; lymphocytic pleocytosis in the CSF; and characteristic MRI findings (diffuse thickening of the pituitary stalk with or without enhancement after gadolinium, loss of the normal posterior “bright spot” on T1-weighted images) [51].

**Treatment**

Currently, the treatment of LYH is only symptomatic. It includes reducing the size of the pituitary/stalk mass and/or replacing the defective endocrine function. Mass reduction may be achieved via pituitary surgery, immunosuppressive drugs, or radiotherapy. Glucocorticoids should be used as the first line of treatment, rather than surgery. Glucocorticoids may be effective for treating LYH, both as anti-inflammatory agents to reduce the size of the pituitary mass or the thickened stalk, and as the replacement of defective adrenal function. Prednisone, hydrocortisone, and methylprednisolone were the most commonly used glucocorticoids [65]. In the case of patients with poor response to glucocorticoids, other immunosuppressive drugs, such as azathioprine, methotrexate, or cyclosporine A, may be used [53]. Surgery should be performed only in the presence of serious and progressive deficits of visual field, visual acuity, ocular movements, or increased intracranial pressure, not responsive to pharmacological treatment. Radiotherapy (conventional fractionated external-beam radiotherapy, Gamma Knife radiosurgery) should be limited to cases with severe mass-effect symptoms, those who show poor response, or those who are poor candidates for high doses of glucocorticosteroids and/or surgery. However, it is important to mention the findings of some authors, e.g. Catureglici et al. [51], who reported that LYH resolved spontaneously without any treatment in 11 patients (3%).

**Neurosarcoidosis**

Sarcoidosis is an auto-inflammatory, granulomatous disorder of unknown aetiology, with multi-organ involvement, hilar lymphadenopathy, and pulmonary interstitial infiltrations being the most common manifestations. Furthermore, it affects the eyes, skin, liver, and spleen. Sarcoidosis may also involve any area of the CNS: the meninges, ventricles, cerebellar hemisphere, white matter of the frontal lobe, adjacent brain or spinal cord parenchyma, pituitary stalk, pituitary, hypothalamus, thalamus, optic nerve and chiasm, cranial nerves such as the facial, auditory, and vestibulocochlear nerve.

**Epidemiology**

The incidence of clinically recognized sarcoidosis in children is 0.22–0.29/100,000 children per year, and gradually increases with age to a small peak in teenagers at 13–15 years of age [66]. However, adults aged 45–55 years are most often affected, with half of them being older than 55 years of age at the time of diagnosis. Neurosarcoidosis was reported in 5–10% of adults with systemic sarcoidosis and was seldom recognized in children [67]. Isolated neurosarcoidosis is very rarely diagnosed. According to the English sources, a total of 54 children and adolescents were diagnosed with neurosarcoidosis, and only 9 children with isolated neurosarcoidosis. The average age of onset was 12 years (3 months – 18 years) [68].

**Signs and symptoms**

General symptoms of sarcoidosis are fatigue, weight loss, fever, persistent cough, skin changes (subcutaneous infiltrates, erythema nodosum, lupus pernio), eye lesions (uveitis, retinal changes, conjunctival nodules), and peripheral lymphadenopathy.

The manifestations of neurosarcoidosis include seizures, headache, vomiting, somnolence, cranial neuropathies (common: VII, II, infrequent: III, IV, VI, V, VIII), pituitary and hypothalamic dysfunction, cerebellar signs, neuropsychological deficits, myelopathy, and peripheral neuropathy. Granulomatous masses that involve the hypothalamus and pituitary gland cause the following: diabetes insipidus, growth and sexual maturation failure, and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hypothalamic-pituitary involvement accounts for 6–9% of all neurosarcoidosis cases. Endocrine investigations mostly identify GH, gonadotropin and thyrotropin deficiency, CDI in over half of cases, and – the least frequently – corticoadrenal insufficiency [69]. Convulsions are the most common symptom of neurosarcoidosis in children, while cranial neuropathies, especially in nerve VII, are the most common after puberty and in adults [68].

**Diagnosis**

Neurosarcoidosis is a diagnosis of exclusion. There is no single diagnostic test for sarcoidosis. Diagnosis is achieved by the combination of history, examination, CNS MRI, CSF analysis, gallium-67 scintigraphy, 18F-FDG PET/CT, and biopsy. The MRI features of neurosarcoidosis include diffuse leptomeningeal thickening and enhancement, focal dural or brain parenchymal enhancement with or without mass effect, periventricular radial vascular enhancement, and enhancement, enlargement, or atrophy of the cranial nerves or enlargement of the pituitary stalk. Criteria for the paediatric diagnosis of neurosarcoidosis have not been established, although most clinicians use the classification scheme (definitive-probable-possible) by Zajicek et al. [70]. Anaemia, leukopaenia, and eosinophilia are commonly seen on blood counts [71]. Hypercalcaemia and/or hypercalciuria occur in up to 10% and 40% of children, respectively, because
a sarcoid macrophage is able to synthesize 1,25-dihydroxyvitamin D [72]. Angiotensin-converting enzyme (ACE) is a biomarker of sarcoidosis. ACE levels are elevated in sarcoidosis because of the activation of monocytes, which are the precursors to the epithelioid cells that form granulomas. ACE is not specific for sarcoidosis. However, it is elevated in the serum of 68-88% of patients with systemic disease and in the CSF of 24-55% of patients with neurosarcoidosis [73]. It should be noted that other disease processes that have also shown elevated serum ACE levels include tuberculosis, lung cancer, Hodgkin lymphoma, and cirrhosis of the liver. Normal serum/CSF ACE level cannot exclude the diagnosis of sarcoidosis. However, an elevated CSF ACE level should prompt further neurosarcoidosis evaluation.

The analysis of the CSF may show pleocytosis (> 5 white blood cells) with slight lymphocytosis (10–100 cells per μl), slightly elevated protein (> 50 mg/dl) in 76% of samples, slightly decreased glucose (< 50 mg/dl) in 51% of samples and increased immunoglobulins with oligoclonal banding [73]. However, CSF abnormalities are not specific to neurosarcoidosis, and normal CSF results were obtained in more than a third of cases [70]. A retrospective review of the Mayo Clinic record system revealed that oligoclonal banding was present in the spinal fluid of 18% of patients [74].

Kidd et al. [72] presented 6 patients with hypothalamic involvement of neurosarcoidosis in MR imaging. Stalk enlargement was reported in 2 of those patients.

In a case of HPR involvement, a whole-body gallium or FDG-PET scan can show other lesions that are more accessible for biopsy.

Biopsy still provides the strongest evidence for this disease. The diagnosis of sarcoidosis is confirmed by demonstrating a typical noncaseating granuloma on a biopsy specimen.

Treatment

No established treatment guidelines exist for neurosarcoidosis. High-dose corticosteroids, particularly oral prednisone, are widely used and are often effective in the treatment of sarcoidosis. If corticosteroid therapy is unsuccessful, a second-line immunosuppressants are administered, e.g. methotrexate, azathioprine, mycophenolate mofetil, and leflunomide [75]. More recently, third-line agents, including tumour necrosis factor inhibitors, i.e. infliximab or adalimumab, have been indicated in the treatment [75]. Infliximab was identified as an effective treatment option for patients, including those who had previously been refractory to other immunosuppressants [71].

Pituitary tuberculosis

Epidemiology

Pituitary tuberculosis should also be considered in the differential diagnosis of PST. The incidence of tubercular hypophysitis is 0.5–4% of all intracranial lesions. 25–30% of tubercular hypophysitis cases reported in the literature had previous or active tuberculosis. Primary pituitary tuberculosis caused by Mycobacterium tuberculosis is a sporadic condition, and only 106 cases were reported from 1924 to 2019 [76]. It mainly affects young adults with the median age being 35 years (from 5 to 60). Several cases of children with pituitary tuberculosis were also reported, especially in endemic countries.

Signs and symptoms

Headache (85.2%), somnolence, visual disturbances (48.1%), low-grade fever (14.8%), and vomiting are common clinical symptoms. Anterior pituitary insufficiency (51.9%), hyperprolactinaemia (27.6%), and CDI are common endocrine dysfunctions in pituitary tuberculosis [77]. The presence of CDI is one of the key features in distinguishing pituitary tuberculosis from pituitary adenoma.

Diagnostics

It is difficult to differentiate inflammatory lesions from those of pituitary adenoma clinically and radiologically. In MRI, pituitary tuberculosis usually presents the features suggestive of a sellar and suprasellar mass, and it may be very difficult to differentiate between pituitary tuberculosis and adenoma [78]. The thickening and nodularity of the pituitary stalk are also considered to be signs of pituitary tuberculosis. However, this finding is non-specific; it is also seen in other inflammatory conditions like sarcoidosis or lymphocytic hypophysitis.

The following tests should be performed in patients with a suspected tuberculous aetiology of PST: tuberculin skin test, QuantiFERON-TB test (sensitivity 92.6%), and chest X-ray/computed tomography (CT). CSF examination may reveal moderate pleocytosis (100–300 mm²), increased protein level (100–400 mg/dl), and decreased glucose level (< 40 mg/dl). The samples do not always stain for acid-fast bacilli and Mycobacterium spp. when tested with polymerase chain reaction (PCR) method [76]. The definitive confirmation of the diagnosis requires a histopathological examination, which reveals necrotizing granulomatous inflammation, staining for acid-fast bacilli (not usually demonstrable from pathological tissue), and the PCR of Mycobacterium spp. in DNA extracted from the tissue.

Treatment

Surgery is not indicated in tuberculous hypophysitis except for obtaining biopsies to confirm the diagnosis. Antitubercular drugs that cross the blood-brain barrier are administered to patients for 9–24 months depending on the clinical and imaging outcome [77]. A significant reduction in size was reported as early as 2 months after treatment, usually with a complete resolution of sellar mass at the end of the regimen. The improvement of endocrinological status and even eliminated panhypopituitarism were reported in some patients [79]. In cases such as tuberculous hypophysitis, early diagnosis is very important given that panhypopituitarism may be eliminated in clinical terms following an effective anti-tuberculosis treatment. A delayed diagnosis may lead to permanent endocrine dysfunction.

Diagnostic evaluation of patients with PST

Considering the causes of PST described above, Table 1 presents tests used in the diagnostic process of PST in children.
After PST imaging in MRI, diagnostic tests should be planned, taking into account the history and physical examination data. First- and second-line tests may be distinguished. The first-line tests used in the diagnosis of patients with PST include: complete blood count, ESR, ALAT, ASPAT, GGTP, LDH, INR, APTT, Bilirubin level, ALAT, ASPAT, GGTP, LDH, INR, APTT, Ca, 1,25-OHD.

Basic blood tests
- Complete blood count and blood smear
- Erythrocyte sedimentation rate
- Creatinine blood test
- Bilirubin level
- ALAT, ASPAT, GGTP, LDH
- INR, APTT
- Ca, 1,25-OHD

Endocrine tests
- TSH, FT4
- ACTH, morning cortisol
- Synacthen test (1μg)
- LH, FSH, E2, T, LH-RH test
- PRL
- IGF-1, IGF-BP3, GH stimulation tests
- Dehydration-vasopressin test

PST – pituitary stalk thickening; TSH – thyroid-stimulating hormone; FT4 – free thyroxine; MRI – magnetic resonance imaging; hCG – human chorionic gonadotropin; α-FP – α-fetoprotein; LCH – Langerhans cell histiocytosis; ACTH – adrenocorticotropic hormone; PLAP – placental alkaline phosphatase; CSF – cerebrospinal fluid; aTPO – thyroid peroxidase antibodies; LH – luteinizing hormone; FSH – follicle-stimulating hormone; E2 – oestradiol; T – testosterone; LH-RH test – luteinizing hormone–releasing stimulation test; ANCA – anti-neutrophil cytoplasmic antibodies; ALAT – alanine transaminase; ASPAT – aspartate transaminase; GGTP – gamma–glutamyl transpeptidase; LDH – lactate dehydrogenase; PRL – prolactin; INR – international normalized ratio; APTT – activated partial thromboplastin time; IGF-1 – insulin-like growth factor 1; 18F–FDG PET/CT – fluorodeoxyglucose positron emission tomography/computed tomography; ACE – angiotensin-converting enzyme.

Table I. Diagnostic test of pituitary stalk thickening in children

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<tr>
<th>PST diagnostic tests in children</th>
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<table>
<thead>
<tr>
<th>Basic blood tests</th>
<th>Complete blood count and blood smear</th>
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<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Creatinine blood test</td>
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<td>Bilirubin level</td>
<td>ALAT, ASPAT, GGTP, LDH</td>
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<td>INR, APTT</td>
<td>Ca, 1,25-OHD</td>
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<tr>
<th>Endocrine tests</th>
<th>TSH, FT4</th>
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<tbody>
<tr>
<td>ACTH, morning cortisol</td>
<td>Synacthen test (1μg)</td>
</tr>
<tr>
<td>LH, FSH, E2, T, LH-RH test</td>
<td>PRL</td>
</tr>
<tr>
<td>IGF-1, IGF-BP3, GH stimulation tests</td>
<td>Dehydration-vasopressin test</td>
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</table>

PST diagnostic tests in children

<table>
<thead>
<tr>
<th>Imaging tests</th>
<th>Pituitary MRI</th>
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<td>Skeletal radiograph</td>
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<tr>
<td>Bone scintigraphy</td>
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<td>Thyroid ultrasound</td>
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<td>Abdominal ultrasound</td>
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<td>Whole body MRI</td>
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<td>18F–FDG PET/CT</td>
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<td>Gallium 67-scintigraphy</td>
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<tr>
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<tbody>
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<tr>
<td>21-hydroxylase antibodies</td>
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<td>ANCA</td>
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<tr>
<td>Antipituitary antibodies</td>
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<tr>
<td>Anti-vasopressin antibodies</td>
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<tr>
<td>ACE in serum and CSF</td>
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<tr>
<td>Tuberculin test</td>
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<td>QuantiFERON</td>
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<td>CSF analysis</td>
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<tr>
<td>Acid-fast bacilli/Mycobacterium sp. (PCR) in CSF</td>
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</tbody>
</table>

After PST imaging in MRI, diagnostic tests should be planned, taking into account the history and physical examination data. First- and second-line tests may be distinguished. The first-line tests used in the diagnosis of patients with PST include: complete blood count, ESR, ALAT, ASPAT, GGTP, urea level, creatinine, INR, APTT, blood electrolytes, 1,25-dihydroxyvitamin D; serum ACE, QuantiFERON, tuberculin test; antipituitary antibodies, anti-vasopressin antibodies, systemic autoantibodies; endocrine tests assessing the function of the anterior and posterior pituitary gland, serum tumour markers (β-hCG, α-FP); imaging tests (chest X-ray, skeletal radiograph, abdominal ultrasound), and neurological and ophthalmic examination.

If first-line tests are inconclusive, it is possible to use the so-called second-line tests in selected cases, depending on the clinical presentation. These tests include the following: tumour markers in CSF, ACE in CSF, the detection of Mycobacterium spp. by PCR in CSF, and immunoglobulin G4 (IgG4) in the serum. Imaging tests of the second line are whole-body imaging with MRI, gallium 67-scintigraphy, 18F–FDG PET/MRI, or PET/CT. It is crucial when LCH or sarcoidosis is suspected because it might detect extracranial lesions not otherwise identified, which may be biopsied.

In 2021, the British national recommendations for diagnosing children and adolescents with PST, CDI, or both, developed by specialists under the auspices of paediatric endocrinology and oncology societies, were published [80]. According to the recommendation mentioned above, a routine CSF examination for acid-fast bacilli is not recommended due to the sporadic occurrence of pituitary tuberculosis in children. Nonetheless, it should be considered in exposed patients or those at a high risk. Likewise, due to the sporadic diagnosis of neurosarcoïdosis as the cause of PST in children and adolescents, the authors do not recommend routine ACE in the CSF, unless neurosarcoïdosis is strongly suspected. Because IgG4-related hypophysitis seldom affects a child or young person, routine measurement of IgG4 concentrations is not currently advisable. The indications for and timing of endoscopic pituitary biopsy in children and young people are controversial. Biopsy should be performed in a specialist pituitary neurosurgical unit with perioperative endocrine support on-site to reduce the risk.
of complications. According to the British recommendations of 2021, pituitary biopsy should be considered only in markedly thickened (≥ 6.5–7 mm) or enlarging stalk with additional visual or endocrine deficits, which continue to pose a worrying diagnostic dilemma after repeated tests [80]. Histopathological examination is conclusive in most cases. However, it is important to remember that histological findings compatible with a lymphocytic inflammatory process may represent the first sign of a host reaction to occult germinoma, which requires a repeated biopsy [35]. In the case of CDI, a repeated brain MRI and investigation of β-hCG tumour marker in the serum and CSF should be performed every 3–6 months during the first 3 years after the onset of CDI (the frequency depending on the presence of a progressively enlarging pituitary stalk), to rapidly establish a diagnosis before the developed large tumour triggers visual and neurological symptoms. Subsequently, MRI should be performed every year for the following 2 years and every 2–5 years thereafter, depending on the size and evolution of the lesion [20]. Therefore, the follow-up strategy should be individually adapted.

**Conclusions**

The spectrum of pathology involving the pituitary infundibulum is broad. The pituitary infundibulum presents a diagnostic imaging challenge because of its small size and the protean spectrum of disease processes.

CNS tumours, especially germinoma, are the most common causes of PST in children. Germinoma should be suspected in all children with PST specially with CDI or pituitary deficiency, even when neurological and ophthalmological symptoms are absent. Young age, male gender, a very large thickening of the stalk, a higher number of anterior pituitary deficits, as well as a serum level of prolactin above 1.3 times the upper limit of normal are all non-invasive parameters increasing the likelihood of a neoplastic origin [81]. Histiocytosis or LYH are rarely diagnosed. Neurosarcoaidosis, granulomatosis, or specific inflammations are only described in the paediatric population as case studies. Despite the progress in biochemical and radiological diagnostic testing, the final diagnosis of a stalk lesion or sellar tumour is still based on a histopathological examination. In the case of sarcoidosis or histiocytosis, the histopathological examination may concern peripheral tissues (if it is not an isolated form).

Patients should be diagnosed and managed in specialist paediatric endocrine centres with experience in pituitary diseases. The cooperation of many specialists, i.e. endocrinologist, radiologist, oncologist, and neurosurgeon, is necessary.

**References**


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47. Horn EM, Coons SW, Spetzler RF, Rekate HL. Isolated Langerhans cell histiocytosis of the infundibulum presenting with fulminant dia-
Pituitary stalk thickening in children

Pogrubienie szypuły przysadki u dzieci


