DIAGNOSIS OF ENDOCRINE DISEASE

Pituitary stalk interruption syndrome: etiology and clinical manifestations

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Abstract

Pituitary stalk interruption syndrome (PSIS) is a congenital pituitary anatomical defect. This syndrome is an antenatal developmental defect belonging to the holoprosencephaly phenotype spectrum. It is heterogeneous regarding clinical, biological and radiological presentation and is characterized by the following triad: thin (<1 mm) or interrupted pituitary stalk connecting the hypothalamus to the pituitary gland, no eutopic posterior lobe, and hypoplasia or aplasia of the anterior lobe. This review reports current knowledge about the composite pathogenesis, for which underlying mechanisms remain unclear. Current data suggest genetic origins involving early developmental gene mutations with complex inheritance patterns and environmental influence, placing PSIS at the crossroads between Mendelian and multifactorial diseases. The phenotype associated with PSIS is highly heterogeneous with a high incidence of various combinations of hormonal deficiencies, sometimes associated with extra-pituitary birth defects. The age at onset is variable, but typical presentation is evolutive combined anterior pituitary hormone deficiencies at pediatric age, which progress even during adulthood to panhypopituitarism. Therefore, patients' follow-up throughout life is essential for adequate management.

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Introduction

Pituitary development is a complex embryonic process involving oral and neural ectoderm to form functionally distinct lobes, anterior and posterior. Many aspects of pituitary embryogenesis have become better understood over the past decades. The initial gland formation and the following differentiation require cascades of signaling pathways with accurate interactions of transcription factors, acting as activators or repressors with a precise spatiotemporal expression (1).

As the differentiated gland contains specialized cell types that produce hormones to regulate basic physiological functions in response to signals from the hypothalamus, failure of physiological embryonic development results in congenital hypopituitarism.

Pituitary stalk interruption syndrome (PSIS, ORPHA 95496 (2)) was first reported in 1987 with the presence of an ectopic posterior pituitary (EPP) being the cardinal feature together with an interrupted stalk (3). The diagnosis

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is confirmed through magnetic resonance imaging (MRI), which is the technique of choice to observe pituitary size, shape and microstructure in patients with pituitary-related endocrine disease (4). Improved MRI performance allowed distinction between thin and interrupted pituitary stalk. PSIS was therefore characterized by: thin or interrupted pituitary stalk connecting the hypothalamus to the pituitary gland, EPP, and hypoplasia or aplasia of the anterior lobe. Over the last decades, the definition of PSIS seems to have widened to include patients with one single feature (such as EPP or interrupted stalk) or interrupted stalk with absent (as opposed to ectopic) posterior pituitary (2). Isolated missing posterior pituitary with normal pituitary stalk could not be considered as PSIS, this feature being described in 10% of healthy population, and since the posterior lobe 'bright spot' becomes recognizable by the second month of life (5). To sum up, PSIS is defined as a lack of visible pituitary stalk or no eutopic posterior lobe hypersignal in the shallow sella turcica. The hyperintense nodule may be in the region of the infundibular recess of the third ventricle (6), at the end of a short pedunculated pituitary stalk or along the pathway of a thin pituitary stalk connecting the hypothalamus to the pituitary gland (5). Both conditions are associated with a significantly increased risk of developing anterior pituitary deficiencies.

Neuroradiological investigations may reveal other abnormalities and PSIS can also be associated with various extra-cerebral midline defects, responsible for extremely diversified clinical manifestations. To date, PSIS is considered as a part of the holoprosencephaly (HPE) wide spectrum.

The present review will examine the current theories for PSIS pathogenesis and the wide phenotype spectrum of this heterogeneous disease.

Etiology and pathogenesis

PSIS pathogenesis has not been fully understood yet, and various hypotheses have been suggested. Birth trauma with perinatal pituitary injury causing mechanical stalk rupture or ischemia has been the initial theory considering the high frequency of perinatal events and breech delivery in patients with PSIS with normal delivery or cesarean section. However, no pathological proof has been found and many observations of PSIS in children with normal delivery were published. Furthermore, the occurrence of familial or consanguineous cases and the frequent association with other congenital abnormalities suggest antenatal origins. Perinatal complications may therefore

be considered as an effect of previous developmental abnormalities rather than a cause (7) and the hypothesis of an abnormal pituitary development caused by genetic defects is widely accepted nowadays (8).

Genetic diversity

There have recently been great improvements in genetic knowledge concerning CPHD (9). Mutations have been found in early development genes (10, 11) involved in pathways critical for hypothalamic-pituitary development such as Wnt, Notch and Sonic Hedgehog (SHH) signaling pathways. After candidate gene approach, whole-exome sequencing made it possible to identify new genetic disorders implicated in PSIS (12, 13, 14, 15, 16). Those are autosomal (dominant or recessive) or X-linked, with possible digenic (15) and polygenic inheritance (16).

Single pituitary-specific genes

Molecular disorders of transcription factors involved in the pituitary gland embryogenesis have been considered the most plausible explanation for CPHD and PSIS (17, 18). Familial forms of PSIS are usually explained by single gene mutations causing complete gene function inactivation. According to the time of the transcription factor expression, the phenotype associated with PSIS is more complex.

The *PROP1* gene encodes a late pituitary-specific transcription factor and is the most recurrently mutated gene known to cause CPHD (9). *PROP1* mutations are responsible for variable pituitary morphology (19) but are never associated with PSIS or extra-pituitary malformation in *Ames* mice model. In *PROP1* human mutation, the radiological phenotype does not typically include PSIS and the hormonal phenotype is more severe than in murine models, as it often includes ACTH deficiency. Only one familial case of PSIS has been reported in association with a *PROP1* homozygous mutation in a patient born from a consanguineous union (7), and further consanguinity-related genetic variations are likely to underlie the PSIS phenotype in this case.

The homeobox gene *HESX1* plays a role in the development of multiple anterior structures derived from the placode including the developing forebrain, optic nerves, hypothalamus and Rathke's pouch (20, 21). *HESX1* transcription factor interacts with the Wnt signaling pathway. Both recessive and dominant inheritance of mutations are reported in patients harboring variable phenotypes including a constellation

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of extra-pituitary abnormalities, with or without eyes abnormalities. Evolutive anterior pituitary deficiencies up to panhypopituitarism has been described in a patient with hypoplastic anterior pituitary gland, EPP located at median eminence and interrupted pituitary stalk without septo-optic dysplasia (SOD) (22). However, *HESX1* mutations causing PSIS remain very rare (9, 23). Noteworthy, missense mutations within the homeodomain are first reported with SOD (20), which is a rare clinical condition including at least two features of the classical triad (24): (1) optic nerve hypoplasia, (2) pituitary hormone abnormalities and (3) midline brain defects.

This association of PSIS with ophthalmic malformations has also been reported with other genes such as *OTX2*, *ARNT2*, *CHD7*, *PAX6* and more recently *ROBO1* and *LHX4*.

The transcription factor *OTX2* is required for activation of *HESX1* expression in the developing forebrain (9). *OTX2* mutations are associated with variable pituitary manifestations but without clear genotype–phenotype correlations (25). Heterozygous missense or loss-of-function *OTX2* mutations within its homeodomain are responsible for PSIS along with ocular anomalies.

ARNT2 is a basic helix-loop-helix transcription factor expressed in the developing brain and pituitary gland at 8 weeks of human embryonic development. *ARNT2* mutations are not classically associated with PSIS, but homozygous mutations in a consanguineous family lead to severe syndromic phenotype: the loss of *ARNT2* affects the hypothalamo–pituitary axis, post-retinal visual pathway, cerebral post-natal growth causing microcephaly along with renal anomalies (12). Affected children presented missing posterior pituitary bright spot, thin pituitary stalk, and hypoplastic anterior pituitary gland.

CHD7, chromodomain helicase DNA-binding protein 7, interacts with *SOX2*. Heterozygous loss-of-function gene mutation leading to CHARGE syndrome (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) have been published, associated with PSIS (11).

PAX6 is a regulator of eye development and is a dorsal marker of early anterior pituitary gland. Its expression controls the established sharp boundaries of somatotrope, lactotrope, and thyrotrope cell types, based on the inhibition of SHH ventral signals. There is a wide phenotypic spectrum in *PAX6* heterozygous mutation carriers, from severely impaired eye and pituitary development with PSIS to apparently normal phenotype (26).

Haploinsufficiency of the axon guidance receptor *ROBO1* gene has been identified as a new cause of PSIS. Heterozygous nonsense or missense mutations were found to cause PSIS with various hormone deficiencies and ocular anomalies such as strabismus or ptosis (14), but no functional study has been performed.

Genetic alteration of *LHX4*, involved in pituitary primordium ontogenesis (Rathke's pouch), is responsible for phenotypical variability: *LHX4* mutations were found to be associated with variable expressivity, and most of them with incomplete penetrance and variable pituitary hormone deficiencies and MRI abnormalities (17, 27, 28). Heterozygous mutations causing *LHX4* haploinsufficiency are responsible for PSIS with poorly developed sella turcica, inconstant pituitary hypoplasia and brain malformations (27).

PROKR2 is a G-protein-coupled receptor involved in endocrine angiogenesis and neuronal migration, and it is a key receptor in both development of the olfactory bulb and gonadotropin-releasing hormone secretion. *PROKR2* alteration induces Kallmann syndrome and hypogonadotropic hypogonadism, and heterozygous mutations have recently been identified in PSIS patients (29).

Single HPE-related genes

Mutations in HPE-related genes have been reported in previous studies (30) such as genes involved in SHH pathway.

GLI2 is a zinc-finger transcription factor downstream SHH signaling which acts in the Wnt pathway, early in the pituitary development (16). Some *GLI2* variants have been reported in PSIS at a relatively high frequency with incomplete penetrance and a wide phenotypic spectrum of hormone deficiencies (31).

TGIF encodes a homeodomain protein that represses transforming growth factor (TGFB) and retinoid response. It is a component of the Wnt signaling pathway and is expressed in the developing midline structures. Heterozygous mutations have been described linked to HPE and PSIS (30).

Other genetic defects have been reported only once and keep on being confirmed according to new recommendation as strong pathogenic variant (32).

CDON is a cell-surface SHH-binding protein that promotes SHH signaling activity; a heterozygous nonsense mutation of its gene is associated with PSIS (13), but a milder form of the phenotype is also described.

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GPR 161 downregulates SHH pathway, as it leads to proteolytic conversion of GLI2 and GLI3 into repressor forms. It also regulates WNT and retinoic acid signaling. One homozygous missense mutation has been reported by Karaca *et al.*, associated with PSIS and diabetes insipidus (33). For the last two genes, no functional studies have been performed.

Digenic inheritance

The association between a *PROKR2* mutation and a rare *HESX1* polymorphism in a PSIS patient suggests an oligogenic mechanism (29).

WDR11 is a member of the WD repeat protein family which contains a homeodomain transcription factor necessary for olfactory bulb morphogenesis. Digenic inheritance with both *WDR11* (c.1306A.G;p.I436V) and *PROKR2* (c.253C.T;p.R85C) mutations has been established, even though those two proteins are not in the same pathway (15).

Micro rearrangements

In addition to monogenic mutations, PSIS was diagnosed in patients having microdeletion or duplications (34, 35) identified with array comparative genomic hybridization. SOX3 is a member of the HMG transcription factors related to SRY. Its dosage seems critical for normal hypothalamo-pituitary development: both SOX3 over- and under-dosage caused by X-linked genetic alterations are associated with similar phenotypes with infundibular hypoplasia and hypopituitarism (36). Varying lengths duplications or deletion at Xq26-q27 involving SOX3 have been described in families with X-linked hypopituitarism (37).

Toward a more complex etiology

Very few PSIS patients have been detected with one single molecular defect and Mendelian inheritance (38): PSIS etiology thus remains non-documented for most patients.

Genotype-phenotype discordances are very common with major variations (11, 13, 14, 15, 26, 27, 30, 31): clinical presentation, endocrine profiles and MRI findings vary within the same families (8), frequently with mildly affected or unaffected mutation-carrying relatives.

These complex inheritance patterns highlight the fact that penetrance of a genetic defect may be modified by other factors (9).

Polygenic hypothesis

As PSIS patients present heterogeneous endocrine and extra-endocrine features, it is possible that this wide spectrum of phenotypes may be caused by a multigenic background with synergy of compound mutations of functionally related genes.

Zwaveling-Soonawala *et al.* (16) performed a whole exome sequencing (WES) in 20 unrelated PSIS patients to support the hypothesis of a polygenic etiology. Most patients had a combination of various potentially pathogenic variants inherited from unaffected parents, from genes related to pituitary formation or associated with other midline brain malformations. Candidate genes were identified for isolated PSIS (*DCHS1*, *ROBO2*, *CCDC88C*, and *KIF14*) and syndromic PSIS (*KAT6A*) when associated with other variants in developmental genes. *DCHS1* is implicated in neuronal migration and is expressed in the developing pituitary gland in mice. *ROBO2* plays a role in axon guidance across the midline of the mammalian central nervous system. *CCDC88C* is a negative regulator of the Wnt signaling pathway. *KIF14* causes ciliopathies and mutant mice have olfactory bulb disorganization. *KAT6A* mutations are responsible for neurodevelopmental disorder.

Similarly, Guo *et al.* (39) performed a WES on 24 sporadic PSIS Chinese patients to search for synergistic genetic interactions. They identified 41 heterozygous variants in genes that are either members of or associated with the Notch, SHH and Wnt signaling pathways. Most patients had multiple (up to five) mutations, mostly localized in conserved functional domains of genes involved in those critical pathways. The most frequently mutated were *NCOR2* (of Notch pathway), *NKD2* (of Wnt pathway) and *ZIC2* (of SHH pathway), suggesting that they play more important roles in the normal pituitary development. *NKD2* is a negative regulator of Wnt/b-catenin signaling. *NCOR2* is involved in developmental and homeostatic processes, it is associated with tumor and hematopoiesis. *ZIC2* is essential for patterning and morphogenesis, influences the transcriptional outcome of SHH signaling and inhibits Wnt/b-catenin protein signaling.

Suspected environmental influences

Since gene mutations are reported in less than 5% of PSIS patients, non-genetic risk factors must obviously also be considered. Gene-environment interaction is likely to be significant in the multifactorial etiology of HPE (40).

As PSIS may be considered as a mild form of HPE, it could be a multigenic disease interacting with multiple contingent factors (41), such as low cholesterol, maternal alcoholism or diabetes as suggested by the 'multiple hit hypothesis' (42) involving epigenetic mechanisms (16). Moreover, vasoactive drugs such as cocaine have been associated with various HPE presentation and pituitary abnormalities such as septo-optic dysplasia (43).

Clinical manifestations: wide spectrum of phenotypes

Epidemiology

Exact prevalence of PSIS is unknown but it remains a rare disease. Incidence is increasing because of routine use of MRI as a primary radiological modality in patients with hypopituitarism (44): the post-marketing data base analyses by C. Deal (44) and M. Maghnie (45) in more than 8000 and 13,000 patients studied, respectively, showed PSIS in 4–8% of the cohorts. Most PSIS cases are sporadic and only occasionally familial (22). There is a male predominance (39, 46, 47) and an ethnic clinical characteristics variability between cohorts in terms of sex repartition and age at diagnosis (48).

Clinical consequences of PSIS: a complex phenotype

PSIS phenotype is highly heterogeneous and diagnosis may be suspected on clinical findings: the initial presentation can be either a congenital association with various extra-pituitary midline malformations or an isolated pituitary defect later revealed through a failure to thrive. Although PSIS diagnosis is confirmed by MRI, clinical features are described first in this review.

The common clinical presentation includes symptoms associated with anterior pituitary hormone deficiencies, depending on hormone profile, age at onset, and linked defects.

Hormonal presentation

The mature pituitary gland produces several hormones that regulate physiological functions, including growth, reproduction, and homeostasis. The pituitary stalk enables hormone transportation from hypothalamus to pituitary cells; its interruption has been established as an important marker of pituitary function (49).

Two typical PSIS clinical manifestation includes permanent anterior pituitary hormone deficiencies: (1) at birth with a severe hormonal phenotype including hypoglycemia and jaundice; (2) during the pediatric age, which appear gradually and generally progress in adulthood to panhypopituitarism. After diagnosis of one deficiency, the endocrine outcome seems to be a progressive partial or total deficiency in other pituitary axes leading to CPHD (50).

GHD is the most frequently existing deficiency and reaches 100% of all patients (51). It is mostly permanent and severe (as defined by The Pediatric Endocrine Society by very low peak GH levels on provocative testing) (52, 53), but not always since non-persistent cases of GHD have been described after transition (54, 55). Interestingly, considerable variation in height has been pointed out for patients who did not receive any GH supplementation treatment (51), and some children maintain normal linear growth despite abnormal GH secretion (56). Among nearly 600 GHD patients with short stature caused by pituitary lesions, 7.8% cases of PSIS were identified in a recent study (57). In terms of treatment, growth response to GH substitution was better in the context of a pituitary defect than for isolated idiopathic GHD without any MRI abnormality (58); the most significant catch-up growth occurred before 3 years of treatment, especially during the first year of GH initiation (50).

Gonadotrophin deficiency (LH, FSH) is frequently associated with other deficiencies but can also be isolated with highly variable severity, ranging from complete gonadotrophin deficiency to normogonadotrophic amenorrhea (59).

ACTH deficiency can cause neonatal cholestasis (60) and recurrent hyponatremia (61). ACTH measurement and cortisol level after stimulation test are significantly lower in patients with PSIS as compared to CPHD patients with visible pituitary stalk (51).

TSH deficiency may also be found. Serum TSH level is not associated with pituitary stalk status or with the height of the anterior pituitary gland, and measurement may be within the normal limits in most patients with central hypothyroidism (62). Isolated sparing of TSH secretion with deficiency of the remaining anterior pituitary hormones has also been described (63).

Prolactin (PRL) varies depending on the degree of dopaminergic pathway disconnection. It can be deficient (22), or on the opposite hyperprolactinemia can be observed, from 17% (22) to one-third of patients (48).

Very few patients have central diabetes insipidus (41, 47) compared to other hormonal deficiencies, as

Figure 1

Early diagnosis with isolated PSIS. PSIS was diagnosed in the post-neonatal period in a context of severe fetal growth retardation in a context of premature birth (birth weight 670 g, length 32 cm at 25 weeks). Neonatal MRI revealed anterior pituitary hypoplasia (*), ectopic posterior lobe (**), absence of pituitary stalk (***), with no other brain abnormality. Hormonal tests showed both somatotropin and thyrotropin deficiencies. Here PSIS was isolated, notably there were no intellectual delay or dysmorphic features associated with the endocrine profile. Sagittal T1-weighted image obtained at 5 years and 7 months of age shows anterior pituitary hypoplasia (anterior lobe height 1.8 mm), absence of the pituitary stalk and ectopic posterior lobe of high signal at the level of the third ventricle floor.

anterior and posterior lobes have different embryonic origins. Patients harboring congenital hypopituitarism and EPP seem to have normal posterior pituitary function since isolated EPP is not responsible for diabetes insipidus. However, defective osmoregulated AVP can be observed in case of EPP with more complex midline brain abnormalities: the hypothesis of hypothalamic dysfunction causing osmoreceptor disturbances has been previously proposed (64).

Every series report a high but variable frequency of CPHD. The clinical factors that best discriminate CPHD patients from those with isolated GHD are breech presentation, hypoglycemia, and micropenis (65).

Therefore, patients' long-term follow-up with regular biological endocrine monitoring remains essential as soon as the first signs appear, regardless of initial endocrine features.

Treatment is based on substituting hormones with life-long polyhormonal replacement therapy. Since pituitary deficiency leads to excess of long-term morbidities and life-threatening events (66), early detection of missing hormones and treatment initiation influence both the prognosis and the quality of life of patients with hypopituitarism (67, 68).

PSIS neuro-radiological presentation: the MRI contribution

MRI is key for pituitary investigations, and it helps in the diagnosis and endocrine prognosis of patients with hormone deficiency (69). PSIS triad has a heterogeneous radiological presentation due to the multiple etiological mechanisms. Imaging reveals numerous anatomical variations in case of PSIS, concerning the anterior lobe (absence, hypoplasia, normal), the posterior pituitary lobe (absence, ectopic along the stalk, ectopic at the hypothalamus base, normal in the sella turcica) and/or the stalk (interrupted, thin, normal) (65). Correlations have been reported between endocrine pituitary function and MRI characteristics: non-visible anterior lobe (38), non-visible pituitary stalk (70), and EPP in the infundibular recess of the third ventricle (71).

MRI with gadopentetate dimeglumine (Gd-DTPA) is more sensitive than the unenhanced MRI technique in identifying the vascular component of pituitary stalk and improves information about hypothalamo-hypophyseal portal vessels preservation (72).

A relationship between anatomical and functional status is therefore possible: if the pituitary stalk is not visualized by Gd-DTPA, the risk of developing CPHD is 27 times greater than for GHD patients with identified pituitary stalk.

Extra-pituitary malformations associated with PSIS

Recent findings suggest that PSIS belongs to the spectrum of midline abnormalities and constitutes mild form of HPE (73). The occurrence of extra-pituitary malformations and its association with endocrine function varies between series (6, 8), but birth defects seem to be more frequent in case of CPHD (almost 60%) than facing isolated GHD (6, 65). The high rate of related malformations highlights the need for systematic screening.

Figure 2

(A and B) Late diagnosis with isolated PSIS. Diagnosis of PSIS was made at the age of 8 years because of isolated progressive growth retardation, from +1 SDS to -2 SDS (A). Dynamic function tests revealed very low peak GH levels compatible with severe growth hormone deficiency (GHD). MRI showed anterior pituitary hypoplasia (*), interruption of pituitary stalk (**), ectopic posterior lobe (***) with no other brain abnormality on the sagittal T1 weighted image (B). Later, further tests revealed onset of thyroid and gonadotropic deficiencies in addition to GHD.

Midline defects involve the central nervous system with mainly brain and eyes defects (74), such as microcephaly, hydrocephalus, periventricular nodular heterotopia, bilateral perisylvian polymicrogyria, cerebellar vermis atrophy, cerebellar dysgenesis, septo-optic dysplasia, partial agenesis of the corpus callosum, Arnold–Chiari malformations, septal agenesis, aqueductal stenosis, optic nerve hypoplasia, coloboma of the retina, craniopharyngeal canal, central respiratory failure. Craniofacial structures may also be altered with cleft lip or palate (8), and dental anomalies such as single central incisor (30).

Distinct but inconstant facial features were reported, such as sparse fine hair, broad forehead with frontal bossing, hypotelorism, anteverted helix, high nasal bridge, bulbous nasal tip, deep philtrum with a thin upper lip, short chin (33, 34). Many of these features are those of GHD patients.

Extra-cerebral abnormalities are also described, affecting skin, heart, extremities, axial skeleton, gastrointestinal tract, urinary tract such as unilateral renal agenesis or hypoplasia included or not in CHARGE syndrome (8). Moreover, Fanconi anemia, Pallister–Hall, Currarino, and Stilling–Duane syndrome can be associated (8).

The presence of extra-pituitary malformations was first associated with more severe hormonal impairment (22), but this association has not been recently confirmed (38).

Variable age at onset

There is a variable timing in the onset of manifestations. PSIS is primarily encountered in infancy and childhood since clinical signs often appear in the first decade of life, but diagnosis is often delayed (42). Deficits might evolve over time, with the onset of new affected pituitary hormone secretion or the occurrence of reversible hormone deficiencies. Clinical, hormonal and MRI characteristics at baseline and during follow-up according to the initial presentation has previously been described (38).

In the neonatal period, combined features suggestive of hypopituitarism are found in about one-third of PSIS patients (38, 48): hypotonia, secondary adrenal deficiency with hypotension and prolonged cholestatic icterus, repeated episodes of hypoglycemia linked to particularly severe form of PSIS (38), genitalia abnormalities such as cryptorchidism or micropenis, and sometimes intra-uterine growth retardation suggesting that hormonal deficiency is precocious and severe (47) (Fig. 1). The incidence of breech delivery, cesarean section, and neonatal distress are high in the PSIS population, with

Figure 3

'Accidental' diagnosis. A two-and-a-half-year-old child was referred to a neuropsychiatrist because of intellectual delay with learning disorders and an MRI was performed. Axial T2 and postcontrast sagittal T1-weighted images obtained at 2 years and 5 months of age shows a small anterior lobe (height 2.7 mm), the absence of the pituitary stalk and a posterior ectopic lobe at the floor of the third ventricle on the postcontrast T1-weighted image. It is associated with the persistence of the craniopharyngeal canal (*) without ectopia in the pharynx. It is also associated to an ependymal heterotopia seen on the T2 image at the right atrial level. Hormonal measurements revealed thyrotropin and somatotropin deficiencies.

a birth length usually in the lower normal range (38). Besides, PSIS patients with CPHD seem more frequently admitted to neonatal intensive care than those with isolated GHD (75).

PSIS patients diagnosed in the neonatal period often have a critical form with greater hormonal impairment and severe radiological phenotype, related to more severely altered pituitary development (38). Accordingly, the absence of neonatal history has been correlated to children having less severe anterior pituitary hypoplasia (>2 mm) compared with those with more severe hypoplasia (<2 mm) (47). CPHD is found in all patients with PSIS revealed in the neonatal period, often complete, but interpretation of hormonal assays is particularly challenging at birth.

In childhood, PSIS critically affects growth, development and quality of life. Most patients are brought to medical attention because of growth retardation with delayed bone age (Fig. 2), or because of pubertal delay and missing grow spurt (48). The median age at diagnosis is about 4 years (38). Exploring intellectual disability may sometimes reveal PSIS (Fig. 3).

In the adult population, CPHD seems more common than reported in children probably due to the longer follow-up: a long-term clinical and biological monitoring throughout life is thus crucial (51). Permanent deficiencies seemed to be more frequent, about 60% in case of EPP (54), but reversible somatotropin and gonadotropin deficiencies have previously been described in adult patients with thin

pituitary stalk (55, 76). Therefore, additional investigation of GH secretion must be considered when final height is achieved in order to validate continuation of GH therapy in adulthood (54).

Conclusions and perspectives

Pituitary stalk interruption syndrome is a heterogeneous multigenic condition with high phenotypic variability. This syndrome is an antenatal developmental defect belonging to the spectrum of the HPE phenotype, which can be diagnosed with MRI.

Clinical features depend on multifactorial interactions including unconventional genetic mechanisms and environmental factors, leading to variable but high rates of hormonal deficiencies and extra-pituitary birth defects, mostly affecting brain, eyes and craniofacial structures. Neonatal and childhood manifestations must alert clinicians to substitute the missing hormones as soon as possible. Patients' follow-up through life is essential for diagnosis and prognosis since there is a progressive development of endocrine deficiencies.

Regarding PSIS etiology, work still needs to be done to find new developmental genes and pituitary transcription factors. High speed gene sequencing will help to detect additional variants, especially located in non-coding regions. This will be necessary for genetic counseling, even though genotype-phenotype discordances often occur.

High throughput whole-genome sequencing analyses might also help identifying novel genetic causes.

To elucidate PSIS wide phenotypic expressivity and incomplete penetrance, the combination of complex patterns of polygenic inheritance and gene–environment interactions is a plausible explanation. Indeed, the influence of environmental factors on genetically predisposed individuals may be responsible for the pathological phenotype, placing PSIS at the crossroads between Mendelian and multifactorial diseases.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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