CASE REPORT

Septo-optic dysplasia: fitting the pieces together

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SUMMARY

A 7-year-old boy was admitted for a general tonic-clonic seizure with severe hypoglycaemia (1.39 mmol/l). His medical history was remarkable for a congenital left eye strabismus, unilateral cryptorchidism and three previous episodes of hypoglycaemic seizures with inconclusive metabolic and neurological investigations. Physical examination revealed a hoarse tone voice, dry skin, cold extremities and height in the third percentile (target height between 50th and 85th percentile). Left wrist radiography revealed a bone age of 4.5 years $\pm$ 6 months. Laboratory studies confirmed growth hormone deficiency and central hypothyroidism. The brain MRI showed an ectopic neurohypophysis. Neuroophthalmology investigation revealed left optic nerve hypoplasia and septo-optic dysplasia was then diagnosed. Thyroid and recombinant growth hormone replacement were started showing clinical improvement. A detailed clinical history and a careful physical examination in children presenting with multiple clinical signs of hypopituitarism may lead to a timely diagnosis, avoiding clinical morbidity associated to untreated hormonal abnormalities.

BACKGROUND

Septo-optic dysplasia (SOD), also known as de Morsier syndrome, is a rare congenital condition with a highly heterogeneous phenotype.^{1–3} The diagnosis is clinical, based on the presence of two or more features of the classical triad of optic nerve hypoplasia, pituitary hormone abnormalities and midline brain defects.^{1–8}

We report a case of SOD with unilateral optic nerve hypoplasia and hypopituitarism due to ectopic neurohypophysis. Although the patient had a congenital left eye strabismus and presented with a short stature, several episodes of hypoglycaemic seizures and other clinical signs of hypopituitarism, the correct diagnosis and proper treatment were established only at the age of 7 years.

This case report highlights the importance of a detailed clinical history and a careful physical examination as the cornerstones of an accurate diagnosis.

CASE PRESENTATION

We report the case of a 7-year-old Romanian boy with an unremarkable family history.

He was the first child of non-consanguineous young parents; he had an uneventful full-term gestation and spontaneous vaginal delivery. His birth was complicated with a grade I asphyxia with an Apgar score of 6 in the first minute and 10 in the fifth minute of life. His birth weight was in the 50th percentile and his height in the 75th percentile.

Physical examination at birth revealed a congenital convergent strabismus of the left eye and unilateral

cryptorchidism of the right testicle. He had no further complications in the neonatal period.

He had speech and language delay, noticed by the age of 3 years, with no delay in the other developmental milestones.

He was referred to an ophthalmology consultation in Romania and he underwent medical treatment for the strabismus, with corrective lenses. Orchiopexy was performed when he was 4 years old.

His medical history was also particularly remarkable for three episodes of general tonic-clonic seizures, all with hypoglycaemia.

The first episode occurred at the age of 5 years in Romania, and was associated with a glycaemia of 2.39 mmol/l and hypothermia. No further investigation was performed at that time.

The second episode occurred by the age of 6 years, in Portugal, preceded by several vomits and associated with a glycaemia of 1.72 mmol/l. An EEG was performed without identification of paroxysmal activity. Endocrinological and metabolic investigations were also conducted with evaluation of blood levels for insulin, C-peptide, cortisol and lactate as well as urinary reducing substances, all with normal results. The abdominal ultrasound was also normal. He was referred to metabolic diseases consultation for further investigation.

The third episode occurred by the age of 7 years, in Romania, with non-quantifiable glycaemia. At this time he underwent cranial CT scan that revealed an arachnoid cyst on the left temporal lobe, with no other abnormalities. He was prescribed carbamazepine (10 mg/kg/day) and pyritinol.

Three months later he was admitted, for the first time, to our hospital with another general tonic-clonic seizure associated with severe hypoglycaemia of 1.39 mmol/l. After hypertonic dextrose infusion (2 ml/kg of 30% dextrose solution), blood glucose levels returned to normal values, the seizure stopped and he recovered consciousness.

Physical examination revealed a Glasgow coma scale score of 15, tympanic temperature of 36°C, normal heart rate and arterial blood pressure. He had a hoarse tone voice, dry skin, brittle hair, cold extremities and left eye convergent strabismus.

His thyroid gland was palpable, especially the right lobe. There were no abdominal masses or organomegalies. The neurological examination was normal.

His weight was in the 10th percentile and his height was in the 3rd percentile, for a target height between 50th and 85th percentile.

INVESTIGATIONS

Investigation was conducted in order to find the cause of the recurrent hypoglycaemic seizures and the findings in the physical examination.

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The EEG had a normal baseline electrogenesis without paroxysmal activity.

Laboratory work-up revealed hypercholesterolaemia with total cholesterol of 6.32 mmol/l and low-density lipoprotein (LDL) cholesterol of 4.35 mmol/l.

Metabolic investigation showed normal lactate and ammonia levels. Chromatography analysis of free amino-acids, organic acids and sugars was normal. Inherited metabolic diseases screening was negative.

Endocrinological work-up revealed normal levels of fasting insulin (4.86 pmol/l), cortisol (275.9 nmol/l) and adrenocorticotrophic hormone (4.85 pmol/l). Antithyroid antibodies were negative, thyroid-stimulating hormone was normal (2.47 mIU/l) but free thyroxine T4 was below normal levels (7.98 pmol/l). Insulin-like growth factor-1 (IGF 1) had also abnormal low levels (<3.3 nmol/l) with a normal insulin-like growth factor-binding protein 3 (IGF BP3) (1.1 mg/l).

Thyroid ultrasound was normal. Bone age (Greulich and Pyle) was 4 years for a chronological age of 7.5 years.

Based on the endocrinological results, the diagnosis of hypopituitarism with deficient secretion of growth and thyroid hormones was established. He was referred to the pediatric endocrinology for further evaluation.

Brain MRI revealed a normal pituitary fossa with a small round mass adjacent to the optic chiasm, with hyperintense signal on T1-weighted images, representing an ectopic neurohypophysis. The pituitary stalk was not seen. It also showed an arachnoid cyst in the left temporal lobe (figure 1).

Neuro-ophthalmology consultation was performed to evaluate a possible connection between congenital left strabismus and the midline anomalies in the brain MRI. The neuro-ophthalmological investigation led to the diagnosis of left optical nerve hypoplasia with severe amblyopia of the left eye.

These findings allowed for the diagnosis of SOD. Genetic investigation was been performed with no identified mutation so far.

TREATMENT

Carbamazepine was stopped when hypoglycaemia was identified as the cause of the seizures. When hypopituitarism with deficient secretion of growth and thyroid hormones was diagnosed, thyroid hormone replacement therapy was started as well as recombinant human growth replacement therapy.

An adjustment in the corrective ophthalmological lenses and occlusion therapy of the right eye was proposed by neuro-ophthalmology.

OUTCOME AND FOLLOW-UP

Since the beginning of hormone replacement therapies there was no recurrence of the hypoglycaemia episodes and the associated seizures.

Normalisation of thyroid hormones occurred soon after the beginning of hormone replacement with levothyroxine, and the

patient has been euthyroid since then. Clinically, there was a regression of hypothermia, hoarse tone voice, cold extremities, dry skin and brittle hair.

Recombinant human growth replacement therapy led to a marked increase in the growth rate. Two years after the start of therapy, the patient's height is now in the 75th percentile, with a medium height velocity of 11 cm/year (figure 2). No adverse side effects of recombinant human growth replacement therapy have occurred.

School performance improved after the adjustment in corrective ophthalmological lenses and the neuro-ophthalmological treatment; however, there is still a language delay, requiring special educational support.

The patient maintains close follow-up in endocrinology and ophthalmology consultations.

DISCUSSION

Seizures are a common childhood disorder occurring in 4–10% of children.⁹ A seizure represents a clinical symptom of an underlying pathological process with many possible causes: infectious, neurological, metabolic, traumatic, toxicological and idiopathic.¹⁰ It is extremely important to differentiate seizures from epileptic and non-epileptic conditions and to try to find a possible corrigible aetiology for the seizure.

In this case, the patient presented with three previous general seizures, all with low blood glucose levels. Hypoglycaemia was not taken into account as a possible cause for the recurrent seizure episodes, and not only the patient was inadequately treated with carbamazepine, but the cause for the recurrent hypoglycaemia has not been properly investigated.

Hypoglycaemia in infants and children can have multiple causes.¹¹ In this case, normal chromatography of free amino-acids, organic acids and sugars as well as normal levels of lactate and fasting insulin ruled out disorders of carbohydrate, fatty-acid and amino-acid metabolism as well as hyperinsulinism.

The concomitant presence of a short stature, cryptorchidism, hypothermia, hoarse tone voice, dry skin, brittle hair and cold extremities pointed to pituitary hormone deficiencies as the most probable cause for the recurrent hypoglycaemia. Evaluation of the different pituitary axes confirmed a deficiency in growth hormone and a central hypothyroidism, leading to the diagnosis of hypopituitarism. Pituitary–gonadal axis was not evaluated due to the prepubertal age of the patient.

Ectopic neurohypophysis is a form of defective neural migration during embryogenesis with an incomplete downward growth and fusion of the neurohypophysis with the adenohypophysis in the sella. It may be a part of other midline cranial anomalies including agenesis of the corpus callosum and the

Figure 1 Brain MRI showing an ectopic neurohypophysis.

Figure 2 Growth rate after the recombinant human growth replacement. 307×162 mm.

septum pellucidum, cerebellar atrophy, vermicular dysplasia or optic pathway abnormalities.^{12–15}

In this case, ectopic neurohypophysis was associated with left optic nerve hypoplasia allowing for the diagnosis of SOD.

SOD is a rare congenital anomaly, with a reported incidence of 1 in 10 000 live births.³ The majority of SOD cases are sporadic and several aetiologies have been postulated, such as viral infections, environmental teratogens, vascular or degenerative injury and genetic mutations.

Some antenatal risk factors such as younger maternal and paternal age, primigravida birth, drug and alcohol abuse, maternal diabetes and first trimester bleeding have been associated with SOD.^{16–17} The association of SOD and increased first trimester bleeding may indicate that SOD is a vascular disruption sequence.¹⁷

In this particular case report, only young maternal and paternal age and primigravida birth were present, with no other identified antenatal risk factors.

The identification of transcription factors important in the development of the pituitary gland and forebrain has led to the discovery of three genetic mutations in SOD.^{18–20} HESX1, a paired-like homeobox gene, is one of the earliest markers of murine pituitary development. Five homozygous (autosomal recessive inheritance) and eight heterozygous (autosomal dominant inheritance) pathogenic mutations have been identified in HESX1.¹ The homozygous mutations are fully penetrant, whereas heterozygous mutations are variably penetrant and usually associated with a milder phenotype.¹ Mutations in SOX2 and SOX3 have also been identified, some of them being associated with severe bilateral eye abnormalities (anophthalmia, microphthalmia) and defects of the corpus callosum with anterior pituitary hypoplasia.^{1–20}

The fact that these mutations account for less than 1% of cases, suggests that the precise aetiology of SOD is most likely multifactorial involving contributions from environmental factors in addition to an important role for crucial developmental genes.^{19–20}

SOD diagnosis is clinical and can be made when two or more features of the classical triad are present: optic nerve hypoplasia, midline brain defects and pituitary hormone abnormalities. Only about 30% of the cases have the complete triad.^{1–8} The phenotype of this syndrome is heterogeneous with a wide variation in the severity of the clinical features.

The optic nerve hypoplasia can be unilateral or bilateral, the latter being more common (>70% of cases).^{16–21} Clinically, the child may present with microphthalmia, coloboma, strabismus or nystagmus and a variable degree of visual impairment.^{16–22}

Neurological involvement is very frequent and may be direct, as a result of involvement of cerebral structures, or secondary to hormonal disorders or visual problems.¹⁸ Neurological findings may include mild to moderate developmental delay (more common in children with bilateral (57%) as opposed to unilateral optic nerve hypoplasia (32%)), neurological focal deficits, mental retardation, cerebral palsy and seizures.²³

In this case, the patient presented with speech and language delay. A recent study with 17 patients found developmental/cognitive delay in nearly half the patients, particularly in motor skills and language. Relational and communication difficulties and stereotyped behaviours (motor stereotypes and echolalia) were also reported.^{22–24–26} A correlation between the development/cognition and the degree of visual impairment was found, supporting the important role of vision in child development.²²

Neuroradiological anomalies are present in up to 75–80% of the patients with optic nerve hypoplasia, rising to 90% in those with associated neurological deficits. Apart from the typical

midline abnormalities, intracranial arachnoid cysts also appear to be associated with SOD, as they are present in 12.5% of the patients, as we can see in this case. They can represent the cause of the injury to the optic tract or can be derived from a common aetiopathogenic process.^{21–27–29}

Hypopituitarism is usually found in 62–80% of SOD cases.²⁵ With growth hormone deficiency being the commonest endocrine abnormality.^{1–6} Hypopituitarism, even with clinical signs that can be noticed after birth, is usually diagnosed much later, as it happened in this case, leading to an increased risk of death and brain injury.³⁰

Hypoglycaemia, neonatal jaundice and the presence of micropenis and/or cryptorchidism are clinical neonatal signs that may alert to the existence of hypopituitarism, allowing for an early diagnosis.³⁰

In conclusion, although rare, SOD is an important cause of congenital hypopituitarism and should be considered in all children with optic nerve hypoplasia signs or midline defects. A careful clinical history and physical examination may lead to timely diagnosis of SOD, which improves the endocrine and neurological outcomes of these patients by decreasing the morbidity associated with untreated hormonal abnormalities.

Learning points

- ▶ When evaluating childhood seizures, an accurate clinical investigation must be made and multiple causes must be considered.
- ▶ Hypoglycaemia, cryptorchidism, short stature, hoarse voice, and cold extremities are clinical signs of hypopituitarism that need to be valued.
- ▶ Septo-optic dysplasia is a rare congenital condition with a highly heterogeneous phenotype that should be considered as a cause of congenital hypopituitarism in all children presenting with optic nerve hypoplasia or midline defects.
- ▶ Timely diagnosis of septo-optic dysplasia improves the endocrine and neurological outcome by decreasing the morbidity associated with untreated hormonal abnormalities.
- ▶ A careful clinical history and physical examination are the cornerstones for accurate diagnosis.

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