CASE REPORT

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Pituitary Stalk Interruption Syndrome – clinical Presentation and Management of a Potentially Life-threatening Disease in Newborns

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What is already known on this topic?

Pituitary stalk interruption syndrome (PSIS) rarely manifests immediately after birth. The first clinical signs are elusive but delayed diagnosis and treatment may lead to life-threatening complications.

What this study adds?

Hypoglycaemia, hyponatraemia, jaundice, cholestasis, sucking weakness and micropenis should be regarded as early leading symptoms of neonatal PSIS suggesting endocrine testing. If findings are suspicious, cerebral magnetic resonance imaging should be performed early during postprandial sleep. This is the first report to describe a persistent substitution-dependent thrombocytopenia together with a new variant in *GLI2* in PSIS.

Abstract

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disease resulting in hypopituitarism of variable degree. Serious courses, due to severe combined pituitary insufficiency, are even rarer and associated with very early manifestation immediately after birth. The first clinical signs are elusive and lead to delayed diagnosis and treatment, often resulting in life-threatening complications. The objective was to highlight early leading symptoms and key issues of PSIS in neonates to increase awareness, improve clinical management and thereby enable an early diagnosis and treatment to prevent further complications. This report presents and compares the clinical course and management of two male neonates with PSIS. Early leading symptoms were the same in both patients, including recurrent hypoglycaemia, hyponatraemia, jaundice, cholestasis, sucking weakness and genital abnormalities. Patient 1 developed an infection-induced adrenal crisis, persistent substitution-dependent thrombocytopenia and convulsions due to severe hypoglycaemia because of delayed PSIS diagnosis. In patient 2, with recognition of the leading symptoms, endocrine testing and a subsequent cerebral magnetic resonance imaging were performed early and he was diagnosed and treated before major complications occurred. Genetic testing was performed in both patients. A heterozygous variant in *GLI2* [NM_005270.5:c.2537del; p.(Pro846Argfs*66)] was detected in patient 1. No potential PSIS-associated variant has been found in patient 2. In conclusion, the early diagnosis of neonatal PSIS is key to prompt treatment and prevention of potential severe clinical manifestation of this orphan disease. Therefore, increased awareness of early leading symptoms among clinicians caring for neonates will lead to improved care.

Keywords: Pituitary stalk interruption syndrome, hypopituitarism, neonatal manifestation, clinical management in newborns, neonatal cerebral magnetic resonance imaging, haematological abnormalities, *GLI2* mutation

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Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disease characterised by a thin or absent pituitary stalk, associated with anterior pituitary hypoplasia/aplasia and an ectopic posterior pituitary. Hypoplasia of the pituitary is diagnosed by cerebral magnetic resonance imaging (cMRI) and, depending on the extent, is associated with variable timing of onset and degree of hypopituitarism (1). In most cases, PSIS results in a growth hormone insufficiency. Thus, persistent short stature in the course of child and adolescent development is the main presentation (2,3). Infants suffering from a combined pituitary insufficiency including compromised adrenocorticotropic and thyroid stimulating hormone secretion are usually more severely affected. Since early symptoms during the neonatal period are non-specific and current literature remains sparse, life-threatening complications may arise in delayed diagnosis (1,2). The following report focuses on the neonatal onset of PSIS in two cases, highlighting early leading symptoms and key issues in the clinical manifestation and management of neonatal onset PSIS. The objective is to increase awareness of this rare syndrome and to facilitate early diagnosis.

This report describes two, full-term, male infants with neonatal onset PSIS, treated at the Department of Paediatrics II, Neonatology, Medical University of Innsbruck. Clinical characteristics, biochemical analyses including endocrine hormone levels, and cMRI findings were obtained and are listed in Table 1. Selected cMRI scans are shown in Figure 1. In both patients, whole exome sequencing was performed. 150 bp paired end sequencing was performed using an Illumina HiSeq4000 platform (Illumina, Inc., San Diego, CA) after exon enrichment with the Agilent Sureselect V6 Exome kit (Agilent Technologies, Santa Clara, CA). Identified variants were filtered for autosomal recessive mode of inheritance and minor allele frequency of $<0.5\%$, X-chromosomal and autosomal dominant mode of inheritance with minor allele frequency of $<0.1\%$, and analysed in public databases (Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation, Exome Sequencing Project, and Exome Aggregation Consortium). OMIM-listed variants in disease-associated genes were taken into consideration. Findings are also shown in Table 1. Written informed consent for publication of the case reports including images was obtained from the caregivers.

Case Reports

Fetal ventriculomegaly and hexadactyly were conspicuous in patient 1. Birth took place with an emergency caesarean section under general anaesthesia after pathological cardiotocography. The infant presented as floppy, bradycardic and apnoeic. Despite initial sustained inflations, the apnoea persisted and the patient was ventilated for approximately 4 minutes, resulting in respiratory stability without breathing support. Initial blood glucose level was decreased (33 mg/dL) and returned to normal after a total glucose administration of 4.5 mg/kg/min on day 1. Partial parenteral nutrition was continued due to sucking weakness and vomiting after feeding. Physical examination confirmed hexadactyly with bilateral hypoplastic sixth finger and a postaxial polydactyly with a sixth toe on both sides. Furthermore, there was a cleft uvula, glandular hypospadias with presence of micropenis and microorchidism. Fetal ventriculomegaly regressed in time and postnatal cerebral sonography showed normal ventricular sizes. Blood testing revealed progressive leukocytopenia/neutropenia and thrombocytopenia. Recurrent electrolyte analysis showed persistency of mild hyponatraemia. On day 4, he developed jaundice requiring phototherapy for 24 hours. On the sixth day of life, he developed a *Klebsiella oxytoca* infection resulting in a systemic inflammatory response syndrome with fluid- and catecholamine-resistant septic shock, severe hypoglycaemia (21 mg/dL) and transient multiple organ failure. Cardiovascular function improved and blood pressure normalized after administration of hydrocortisone at a dose of 55 mg/m²/day. Empiric antibiotic therapy was started and adapted in accordance to the antibiogram. Blood and coagulation factors, including fresh frozen plasma, antithrombin III, platelet and erythrocyte concentrates, immunoglobulins and granulocyte colony stimulating factor were administered during the critical phase of sepsis. Whereas leukocytopenia/neutropenia recovered, a low thrombocyte count persisted and platelets had to be substituted regularly until the 25th day of life, as illustrated in Figure 2. Possible further underlying pathologies, including neonatal alloimmune thrombocytopenia, coagulation disorders and Wiskott-Aldrich syndrome, were excluded. As soon as the patient remained clinically stable, hydrocortisone was tapered and discontinued at day 11. Substitution of thyroid hormones was started due to decreased levels of free triiodothyronine, thyroxine and inadequately low thyroid stimulating hormone level (Table 1). At week five, the patient presented with convulsions due to severe hypoglycaemia of 18 mg/dL. Endocrine hormone testing revealed a combined pituitary insufficiency with secondary adrenal insufficiency. Hydrocortisone at a dose of 18.75 mg/m²/day was restarted and levothyroxine at a dose of 6 µg/kg/day was continued, whereupon the patient rapidly improved and was discharged a few days later. Genetic analysis revealed a heterozygous *GLI2* variant [GLI family zinc finger 2; variant: NM_005270.5:c.2537del;

Table 1. Clinical characteristics, biochemical analyses, cerebral magnetic resonance imaging findings and genetic data of both cases

		Patient 1	Patient 2
Clinical characteristics			
Gender		Male	Male
Birth weight, grams (percentile)		3,545 (29)	2,730 (24)
Gestational age, weeks		41.1	37.4
Mode of delivery		Caesarean section	Caesarean section
Indication for caesarean section		Pathological cardiotocography	Breech position
Apgar 1/5/10 minutes		5/8/10	5/7/8
Umbilical cord pH		7.26	7.28
Umbilical cord base excess, mmol/L		-0.6	-1.4
Respiratory distress		No	Yes
Hypoglycaemia/with convulsions		Yes/yes	Yes/no
Hyponatraemia		Yes	Yes
Jaundice/cholestasis		Yes/yes	Yes/yes
Hematologic risk factors for jaundice		No	No
Cytopenia		Thrombocytopenia, leukocytopenia/neutropenia	No
Sucking weakness		Yes	Yes
Addisonian crisis		Yes	No
Micropenis/microorchidism		Yes/yes	Yes/no
Associated malformations		Polydactyly, hypospadias, cleft uvula	No
Biochemical index	Normal		
Glucose, mg/dL (day of life)	45-180	33 (1)	19 (1)
Total bilirubin, mg/dL (day of life)	0-1	15 (5)	13.19 (5)
Direct bilirubin, mg/dL (day of life)	0-2.1	-	2.85 (5)
Gamma-glutamyltransferase, U/L (day of life)	8-178	256 (5)	770 (5)
Serum-sodium, mmol/L (day of life)	134-144	130 (2-7)	131 (9-12)
Cortisol, µg/L (day of life)	48.2-195.0	< 1.1 (41)*	5.6 (12)
ACTH, ng/L (day of life)	10-48	< 7 (41)*	< 5 (16)
GH, µg/L (day of life)	0.09-6.29	0.11 (41)*	1.78 (3)
IGF1, µg/L (day of life)	18-179	26 (41)*	-
IGFBP3, mg/L (day of life)	1.4-4.2	0.6 (41)*	-
FSH, U/L (day of life)	0.1-1.4	< 0.1 (214)	< 0.1 (12)
LH, U/L (day of life)	0.8-4.2	< 0.1 (214)	< 0.1 (12)
TSH µU/mL (day of life)	0.7-18.1	3.7 (19)	2.58 (3)
FT3, pmol/L (day of life)	4.6-10.1	3.0 (19)	3.77 (3)
FT4, pmol/L (day of life)	8.5-30.5	6.7 (19)	13.1 (3)
Cerebral magnetic resonance imaging			
Pituitary stalk		Not visible	Not visible
Anterior pituitary		Hypoplastic (severe)	Hypoplastic (mild)
Posterior pituitary		Ectopic	Ectopic
Genetic data		GLI2 mutation	No suspicious mutation

*During hypoglycaemia.
ACTH: adrenocorticotropic hormone, FSH: follicle stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, GH: growth hormone, IGF1: insulin-like growth factor 1, IGFBP3: insulin-like growth factor binding protein 3, LH: luteinizing hormone, TSH: thyroid stimulating hormone

p.(Pro846Argfs*66)] and the cMRI scan at the age of three years identified pituitary hypoplasia as seen in PSIS, presented in Figure 1A.

Patient 2 was conceived by *in vitro* fertilisation. Incipient preeclampsia and breech position at the end of pregnancy resulted in an induced birth by caesarean section. Due to respiratory distress, the patient received continuous positive airway pressure support for two hours. The first blood test one hour after birth showed hypoglycaemia of 19 mg/dL, serum glucose levels stabilised after a glucose administration of 4.5 mg/kg/min on day 1. Despite frequent feeding a gradual withdrawal of continuous parenteral substitution was not successful until the 4th day of life. Physical examination revealed isolated presence of a micropenis, without further clinical abnormalities. On day 3, he presented with jaundice and received phototherapy for 24 hours. Laboratory analysis after treatment detected elevated parameters of cholestasis, seen in Table 1, yet abdominal sonography showed no abnormalities of the biliary tract. From the ninth day onward, laboratory results showed mild hyponatremia. Hypoglycaemia did not reoccur after day 4. Nevertheless, presentation of the patient revealed continuous muscular hypotonia and sucking weakness. Endocrine hormone testing and the cMRI (Figure 1B) identified a PSIS with combined pituitary insufficiency, secondary adrenal insufficiency and an incipient secondary thyroid dysfunction. Administration of hydrocortisone at a dose of 14.5 mg/m²/day on day 13 resulted in good feeding and adequate weight gain. Serum sodium returned to normal and parameters of cholestasis decreased, so that the patient could be discharged on day 23. Blood analysis shortly before discharge showed a progressing thyroid dysfunction, which was treated by the administration of levothyroxine at a dose of 6.5 µg/kg/day. Genetic testing was performed, yet no mutation was found in clinical exomes.

Discussion

This report illustrates the clinical course of two patients with rare neonatal onset PSIS. Leading symptoms were similar with early hypoglycaemia, persistent mild hyponatraemia, unconjugated hyperbilirubinemia in absence of haematological risk factors, cholestasis and sucking weakness. Clinically evident genital abnormalities were indicative for potential gonadotroph pituitary insufficiency. There may be a male gender predominance of neonatal PSIS, as previously suggested (1), as our two patients also were male, yet it should be noted that the phenotype of neonatal male hypogonadism is more easily recognised. In patient 1, diagnosis was delayed and he developed an infection-triggered, life-threatening adrenal crisis, persistent substitution-dependent thrombocytopenia and convulsions due to recurring hypoglycaemia. With hormonal substitution, he recovered. Conversely, patient 2 was diagnosed and received hormone substitution on day 13, thus very early and before major complications arose. cMRI is vital for the diagnosis and anatomical dimension of PSIS (1), and this can be performed safely in neonates during postprandial sleep without the risk and burden of anaesthesia (4).

PSIS remains a rare disorder with an unknown prevalence (1). Manifestation during infancy is even rarer with only 15% of PSIS patients becoming symptomatic during

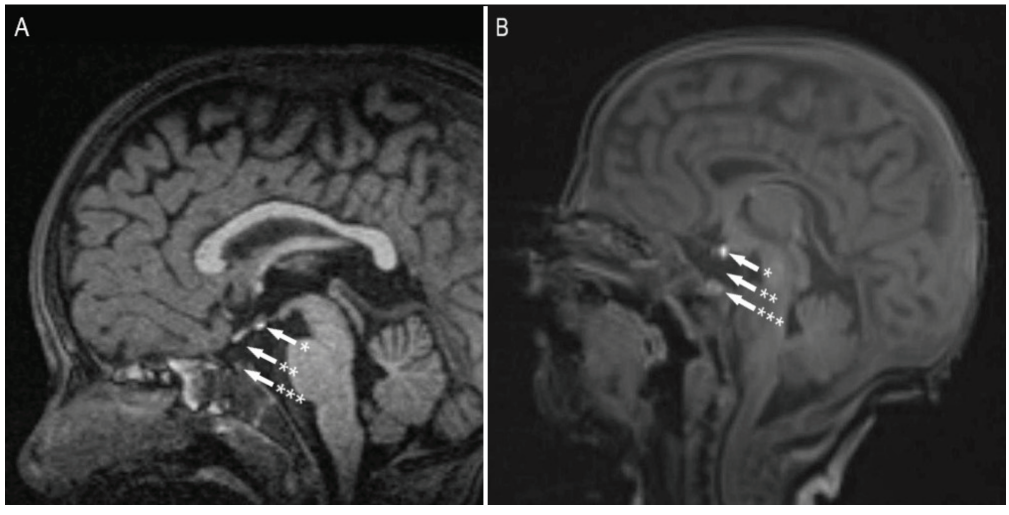

Figure 1. Cerebral magnetic resonance imaging (cMRI) of patient 1 (A) and patient 2 (B). Patient 1 was imaged at the age of 3 years and 3 months, in patient 2 MRI was performed in the 15th day of life. The sagittal T1-weighted image revealed an ectopic posterior pituitary (*), absence of pituitary stalk (**), and anterior pituitary hypoplasia (***)

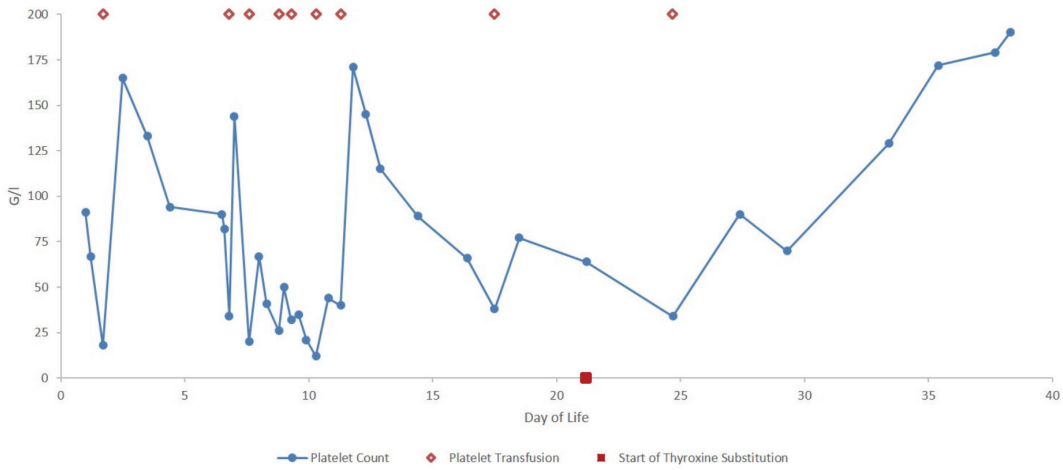

Figure 2. Platelet count of patient 1 from the first day to the 38th day of life. Indication for platelet transfusion was a count of < 50 G/L. This occurred nine times, particularly during severe infection from the sixth day of life. Thyroxine substitution started at day 21. Four days later, platelet transfusion was required for the last time, and subsequently platelet count increased to normal

the neonatal period (2). Case studies regarding neonatal manifestation are still lacking, yet case reports describe a correlation between onset of symptoms and the degree of anatomical disorder. Distinct anatomical phenotypes cause severe combined pituitary insufficiency and result in an earlier clinical manifestation (2,5). Our cases confirm these findings as the cMRI revealed an absent pituitary stalk, a hypoplastic anterior pituitary and an ectopic posterior pituitary. Based on this hypoplasia, both patients manifested with a combined pituitary insufficiency with hypoadrenocorticism, hypothyroidism and hypogonadism, further leading to hypoglycaemia, hyponatraemia, jaundice, cholestasis, sucking weakness and genital abnormalities (5). Of importance, secondary adrenal insufficiency led to an infection-triggered adrenal crisis in patient 1, starting with nonspecific symptoms of recurrent vomiting progressing to hypotension and shock (6). After unsuccessful therapy attempts with catecholamines, administration of stress-dose hydrocortisone led to stabilisation of the patient.

Mendelian inheritance is present in less than 5% of PSIS cases, and so digenic and/or polygenic inheritance is likely (1,7). Variants in *GLI2*, coding for zinc-finger proteins, are associated with PSIS (7,8) and, as seen in patient 1, mutations are often correlated with other malformations, such as polydactyly and midline defects (9). To the best of our knowledge, the variant of *GLI2* mutation found in patient 1 has not been described in public databases or other reports (10). Thus, this is the first report of this specific variant of *GLI2* being associated with a hypopituitarism phenotype.

In literature research on PSIS and *GLI2* mutations, thrombocytopenia was not reported, but an association between abnormal Gli2-signalling and megakaryocytic differentiation is possible (11). In patients with Sheehan syndrome, it was shown that anterior pituitary hormones affect bone marrow function and that cytopenia in various combinations are frequent (12). Leukocytopenia/neutropenia has been observed in 20-50% of patients with Addison disease (13). Elmelhat and Khadora (14) described the presence of congenital hypothyroidism with leukocytopenia/neutropenia and thrombocytopenia during the neonatal period, which improved after thyroxine administration. Regarding the incidence of congenital hypothyroidism (15), this isolated case is perhaps negligible, yet should be noted due to the similarity to patient 1. He suffered from the same bicytopenia and recovered a few days after beginning with thyroxine treatment (Figure 2).

Conclusion

To conclude, the presentation of these two cases of neonatal PSIS emphasises the importance of early diagnosis to avoid life-threatening complications. It is important to implement hormone analysis as soon as a newborn presents with recurrent hypoglycaemia, hyponatraemia, jaundice, cholestasis, sucking weakness and micropenis in males. In the case of conspicuous endocrine findings, cMRI should be performed promptly to identify PSIS and to confirm diagnosis. During the neonatal period, it can be performed safely during postprandial sleep without the risk and burden of anaesthesia.

Ethics

Informed Consent: Written informed consent was obtained from all patients.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Ira Winkler, Elisabeth Steichen, Klaus Kapelari, Peter Wöckinger, Ursula Kiechl-Kohlendorfer, Elke Griesmaier, Concept: Ira Winkler, Elisabeth Steichen, Peter Wöckinger, Design: Ira Winkler, Data Collection or Processing: Ira Winkler, Elisabeth Steichen, Ursula Kiechl-Kohlendorfer, Elke Griesmaier, Analysis or Interpretation: Ira Winkler, Elisabeth Steichen, Klaus Kapelari, Peter Wöckinger, Vera Neubauer, Literature Search: Ira Winkler, Elisabeth Steichen, Writing: Ira Winkler, Peter Wöckinger.

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