DOI: 10.4274/jcrpe.galenos.2023.2023-1-23

Case report

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

Short title: Manifested PSIS in Newborns

Ira Winkler[1], Elisabeth Steichen[2], Klaus Kapelari[2], Peter Wöckinger[1], Vera Neubauer[1], Ursula Kiechl-Kohlendorfer[1], Elke Griesmaier[1]
[1]Department of Paediatrics II (Neonatology), Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria
[2]Department of Paediatrics I, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria

What is already known on this topic?
Pituitary stalk interruption syndrome rarely manifests immediately after birth. First clinical signs are elusive. Delayed diagnosis and treatment lead to life-threatening complications.

What this study adds?
Hypoglycaemia, hyponatraemia, jaundice, cholestasis, sucking weakness and micropenis should be regarded as early leading symptoms suggesting neonatal endocrine testing. If findings are suspicious, cerebral magnetic resonance imaging should be performed early during postprandial sleep. We are first to describe a persistent substitution dependent thrombocytopenia and a new variant of *GLI2* mutation.

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 a very early manifestation immediately after birth. First clinical signs are elusive and lead to delayed diagnosis and treatment, often resulting in life-threatening complications. Objective of the current report is to point out early leading symptoms and key issues of neonatal manifested PSIS to increase the awareness, improve the 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 newborns with manifested 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 in delayed PSIS diagnosis. In patient 2, due to recognised above-mentioned 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. *GLI2* gene mutation (NM_005270.5:c.2537del; p.(Pro846Argfs*66)) heterozygous was detected in patient 1. No mutation was found in patient 2. Conclusively, the early diagnosis of neonatal PSIS is indispensable in the treatment and prevention of the possible severe clinical manifestation of this orphan disease. Therefore, increased awareness for early leading symptoms and proper clinical management are crucial.
Keywords: Pituitary stalk interruption syndrome, hypopituitarism, neonatal manifestation, clinical management in newborns, neonatal cerebral magnetic resonance imaging, haematological abnormalities, *GLI2* mutation

Ira Winkler, MD, Department of Paediatrics II (Neonatology) - Medical University of Innsbruck, Anichstraße 35 - Innsbruck, 6020, Austria
+0043 512 504 27309
ira.winkler@tirol-kliniken.at
https://orcid.org/0000-0002-6668-9942
30.01.2023
05.03.2023

Published: 19.04.2023

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 - leads to variable onsets of time 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 clinical appearance (2, 3). Infants suffering from a combined pituitary insufficiency including adrenocorticotropic and thyroid stimulating hormone are usually more severely affected. Since early symptoms during the neonatal period are unspecific and literature to date still remains sparse, life-threatening complications can arise in delayed diagnosis (1, 2). Our following report focuses on the neonatal onset of PSIS, pointing out early leading symptoms and key issues of its clinical manifestation and management, to increase the awareness of this rare disease and to facilitate early diagnosis.
Methods

We report on two full-term male infants with neonatal onset of PSIS, treated at our 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 visualised in **Figure 1**. In both patients, whole exome sequencing was performed. 150 bp paired end sequencing was produced using an Illumina HiSeq4000 platform 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*). Variants in disease-associated genes (OMIM-listed) were taken into consideration. Findings are added in **Table 1**. Written informed consent for publication of the case reports including images was obtained from the caregivers.

Case descriptions

Fetal ventriculomegaly and hexadactyly were conspicuities in patient 1. Birth took place in an emergency caesarean section under general anaesthesia after pathological cardiotocography. The infant presented 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. It furthermore revealed a cleft uvula, glandular hypospadia with presence of micropenis and microorchidism. Fetal ventriculomegaly regressed in time and postnatal cerebral sonography showed normal ventricular sizes. Blood test 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 6th 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 in a dose of 55 mg/m²/day. Empiric antibiotic therapy was started and adapted in accordance to the antibiogram. Blood and coagulation factors, such as 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, being 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, as seen in **Table 1**. In 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 in a dose of 18.75 mg/m²/day was restarted and levothyroxine in 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 *GLI2* mutation (gene: GLI family zinc finger 2; variant: NM_005270.5:c.2537del; p.(Pro846Argfs*66); state: heterozygous) and the cMRI scan at the age of three years identified pituitary hypoplasia as seen in PSIS, presented in **Figure 1A**.

Pregnancy of 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/d, 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 9th 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 scan (**Figure 1B**) identified a PSIS with combined pituitary insufficiency, secondary adrenal insufficiency and an incipient secondary thyroid dysfunction. Administration of hydrocortisone in a dosage of 14.5 mg/m²/day on day 13 resulted in good feeding and adequate weight gain. Serum sodium returned to normal and cholestasis parameters decreased, so that the patient could be discharged on day 23. Blood analysis shortly before discharge showed a progressing thyroid dysfunction, following by the administration of levothyroxine in 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 rare clinical course of two patients with neonatal onset of 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. Male gender predominance of this disorder might be present (1) as our two patients also were male, yet not to be forgotten is the more notable phenotype of hypogonadism in males. 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 substituted on day 13, thus very early and before major complications arose. cMRI is inevitable for the diagnosis and anatomical dimension of PSIS (1), this can be performed safely in neonates during postprandial sleep without the risk and burden of anaesthesia (4).

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

Mendelian inheritance is present in less than 5% of PSIS cases, additionally digenic and polygenic inheritance is likely (1, 7). *GLI2* variants coding for zinc-finger proteins are associated (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, we are first to add the above-mentioned mutation to the *GLI2* variants responsible for a hypopituitarism phenotype.

In literature research on PSIS and *GLI2* mutations, thrombocytopenia remains unmentioned, still, the association of abnormal Gli2-signalling and megakaryocytic differentiation is possible (11). In patients with Sheehan´s syndrome, it was shown that anterior pituitary hormones affect bone marrow function and that cytopenia in various combinations are frequent (12). Leukocytopenia/neutropenia was observed in 20-50% of patients with Addison disease (13). *Elmelhat et al* described the presence of congenital hypothyroidism with leukocytopenia/neutropenia and thrombocytopenia during the neonatal period, which improved after thyroxine administration (14). Regarding the incidence of congenital hypothyroidism (15), this isolated case is perhaps negligible, yet has to be mentioned due to the similarity to patient 1. He suffered from the same bicytopenia and recovered a few days after beginning with thyroxine treatment as can be seen in **Figure 2**.

To conclude, the presentation of our two cases with 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 timely to identify PSIS and reassure diagnosis. During the neonatal period, it can be performed safely during postprandial sleep without the risk and burden of anaesthesia.

Declaration of interest

The authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Data sharing statement

All data underlying the results are available as part of the article and its supplementary material files. No additional source data are required.

Authorship Contribution

Medical Practices: IW, ES, KK, PW, VN, EG
Concept: IW, ES, EG
Design: IW
Data Collection or Processing: IW, ES, PW, VN
Analysis or interpretation: IW, ES, KK, UK, K, EG
Literature Research: IW, ES
Writing: IW, EG

List of abbreviations

cMRI	cerebral magnetic resonance imaging
PSIS	pituitary stalk interruption syndrome

Acknowledgements

The authors would like to thank the patient´s parents for agreeing to the publication of this report. The authors would also like to thank Tanja Janjic, MD PhD, for cMRI interpretation (professional relationship), and Andrea Katharina Lindner, MD, for her writing assistance and critical input (professional relationship).

References

1. Vergier J, Castinetti F, Saveanu A, Girard N, Brue T, Reynaud R. DIAGNOSIS OF ENDOCRINE DISEASE: Pituitary stalk interruption syndrome: etiology and clinical manifestations. European Journal of Endocrinology 2019;181:R199-R209.
2. Bar C, Zadro C, Diene G, Oliver I, Pienkowski C, Jouret B, Cartault A, Ajaltouni Z, Salles JP, Sevely A, Tauber M, Edouard T. Pituitary Stalk Interruption Syndrome from Infancy to Adulthood: Clinical, Hormonal, and Radiological Assessment According to the Initial Presentation. PLoS One 2015;10:e0142354.
3. Diwaker C, Thadani P, Memon SS, Sarathi V, Lila AR, Arya S, Krishnappa B, Karlekar M, Patil VA, Shah N, Bandgar T. Pituitary stalk interruption syndrome: phenotype, predictors, and pathophysiology of perinatal events. Pituitary 2022;25:645-652.
4. Neubauer V, Griesmaier E, Baumgartner K, Mallouhi A, Keller M, Kiechl-Kohlendorfer U. Feasibility of cerebral MRI in non-sedated preterm-born infants at term-equivalent age: report of a single centre. Acta Paediatrica 2011;100:1544-1547.
5. Wang Q, Meng X, Sun Y, Liu F, Xu C, Qiao Y, Yang J, Li G, Wang Y. Hypoglycemia and jaundice in newborns with pituitary stalk interruption syndrome. Medicine (Baltimore) 2021;100:e25843.
6. Rathbun KM, Nguyen M, Singhal M. Addisonian Crisis. StatPearls. Treasure Island (FL) 2022.
7. Zwaveling-Soonawala N, Alders M, Jongejan A, Kovacic L, Duijkers FA, Maas SM, Fliers E, van Trotsenburg ASP, Hennekam RC. Clues for Polygenic Inheritance of Pituitary Stalk Interruption Syndrome From Exome Sequencing in 20 Patients. The Journal of Clinical Endocrinology and Metabolism 2018;103:415-428.

8. Lichiardopol C, Albulescu DM. Pituitary Stalk Interruption Syndrome: Report of Two Cases and Literature Review. Acta Endocrinologica (Bucharest) 2017;13:96-105.
9. Bear KA, Solomon BD, Antonini S, Arnhold IJ, Franca MM, Gerkes EH, Grange DK, Hadley DW, Jaaskelainen J, Paulo SS, Rump P, Stratakis CA, Thompson EM, Willis M, Winder TL, Jorge AA, Roessler E, Muenke M. Pathogenic mutations in GLI2 cause a specific phenotype that is distinct from holoprosencephaly. Journal of Medical Genetics 2014;51:413-418.
10. Arnhold IJ, Franca MM, Carvalho LR, Mendonca BB, Jorge AA. Role of GLI2 in hypopituitarism phenotype. J Mol Endocrinol 2015;54:R141-150.
11. Ghezali L, Liagre B, Limami Y, Beneytout JL, Leger DY. Sonic Hedgehog activation is implicated in diosgenin-induced megakaryocytic differentiation of human erythroleukemia cells. PLoS One 2014;9:e95016.
12. Laway BA, Mir SA, Bashir MI, Bhat JR, Samoon J, Zargar AH. Prevalence of hematological abnormalities in patients with Sheehan's syndrome: response to replacement of glucocorticoids and thyroxine. Pituitary 2011;14:39-43.
13. Baez-Villasenor J, Rath CE, Finch CA. The blood picture in Addison's disease. Blood 1948;3:769-773.
14. Elmelhat AM, Khadora MM. A Neonate with Bicytopenia: Unusual Underlying Etiology. Dubai Medical Journal 2019;2:54-58.
15. Klett M. Epidemiology of congenital hypothyroidism. Exp Clin Endocrinol Diabetes 1997;105 Suppl 4:19-23.

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

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, hypospadia, 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

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; * during hypoglycaemia

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 (***)

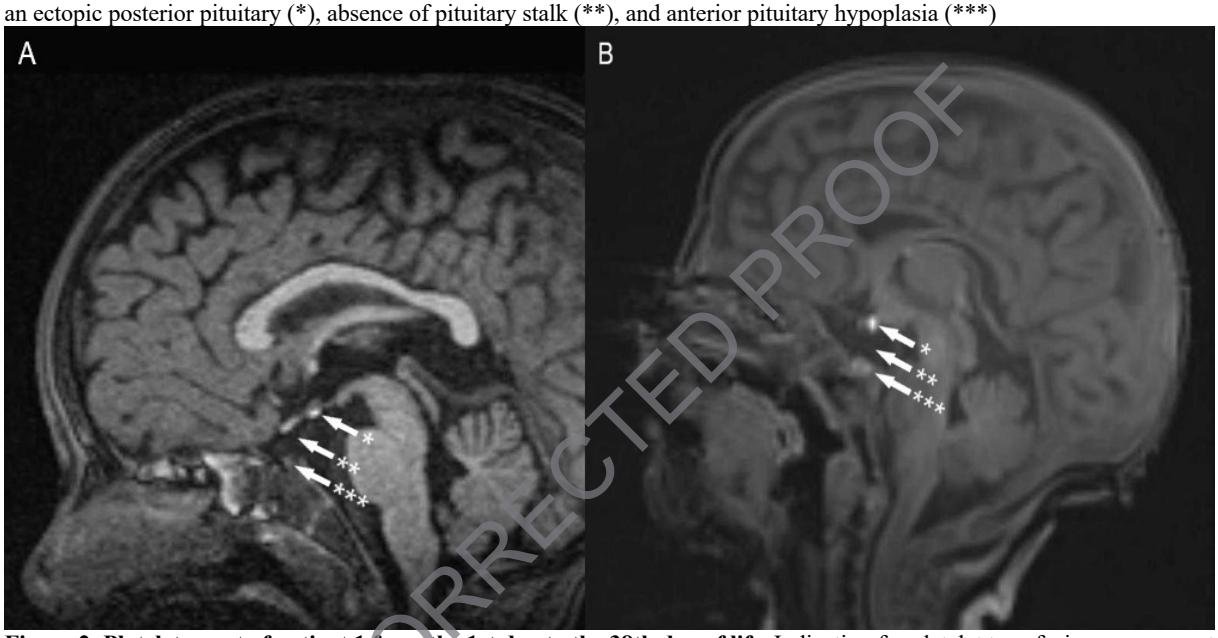

Figure 2: **Platelet count of patient 1 from the 1st day to the 38th day of life.** Indication for platelet transfusion was a count of < 50 G/l. This occurred nine times, accumulated during severe infection (6th day of life onwards). Thyroxine substitution started at day 21. Four days later, platelet transfusion was required for the last time, afterwards, platelet count increased to normal