THE CASE OF CONGENITAL HYPOPITUITARISM DUE TO MUTATION POU1F1 IN 3 AZERBAIJANI NEWBORN BOYS.

Yulia Skorodok[1], Anzhelika Arestova[1], Irina Ioffe[1]
Natalia Kazachenko[2], Maria Turkunova[2]
Dmitry Ivanov[3]
Oksana Vorozhko[4], Natalia Filatova[4]

[1]*St.Petersburg State Pediatric Medical University, St. Petersburg, Russia.*
2City multi-field children's clinical centre of high medical technologies for K.A. Rauchfuss, St. Petersburg, Russia
3City Children's Hospital №1, St. Petersburg, Russian Federation.
4St. Nicholas's City Children's Hospital №17, St. Petersburg, Russia.

Background:

Growth hormone deficiency in conjunction with the function loss of other anterior pituitary hormones is called combined pituitary hormone deficiency (CPHD).[1] Up to 30% of congenital CPHD cases are associated with mutations of genetic (transcription) factors [2]

POU1F1 mutations are extremely rare among the Indo-European ethnic type (1% of all cases of congenital hypopituitarism) and more common among the Turkic peoples (7.3%, according to Turkish researchers).[3]

Due to the migration and the influx of Azerbaijanis in particular, we can observe such cases more often in St. Petersburg in recent years.

Methods:

3 Azerbaijani boys (one of them born to consanguineous marriage) were examined using standard clinical and laboratory methods.

The levels of blood glucose, TSH, free T4, GH, IGF-1, ACTH, cortisol, prolactin and liver function tests were evaluated.

PROP1, POU1F1, HESX1, LHX3, LHX4, OTX2, GLI2, SOX3, ARNT2, GH1, GHRH, GHRHR, GHSR, IGSF1, PAX6, SHH gene mutations were investigated by a new generation sequencing (NGS) method.

[1] Diagnosis and treatment of endocrine diseases in children and adolescents: manual/ under the edit of Prof. Shabalov N. P.– 3 ed, 2017
[2] Berseneva O.S., Glotov A.S., Glotov O.S. etc. Congenital hypopituitarism in children. Molecular-genetic characteristics// HERALD of North-Western State Medical University named after I.I.Mechnicov– 2018 – T.10 -№1. – p.49-54
[3] Baş F, Uyguner ZO, Darendeliler F and others/ Molecular analysis of PROP1, POU1F1, LHX3, and HESX1 in Turkish patients with combined pituitary hormone deficiency: a multicenter study/Endocrine. 2015 Jun;49(2):479-91. doi: 10.1007/ s12020-014-0498-1. Epub 2014 Dec 11.

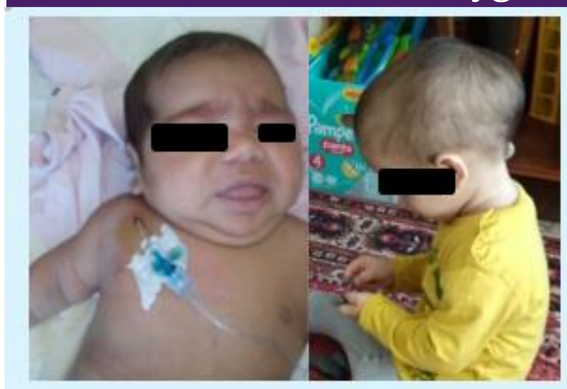
Results

Patient№1 on the second day of life had persistant hypoglycemia, accompanied by convulsions. The patient had a craniofacial anomaly, shortening of the proximal extremities.(Picture 1) By 1 month of life he had no growth increments. Patients №2 and №3 were hospitalized at the age of 1 month due to prolonged jaundice. Patients had general symptoms of hypothyroidism, craniofacial dysmorphisms.(Picture 1) Unconjugated hyperbilirubinemia, hypoglycemia were diagnosed.(Table 2) After 1 month of life they had poor growth.

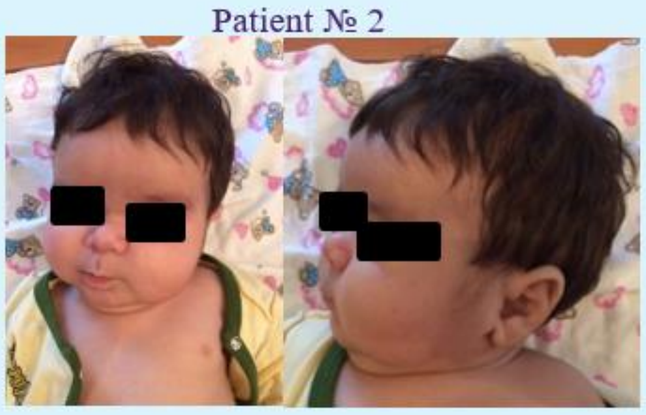
The diagnosis of congenital hypopituitarism was completed with confirmation of FT4, GH, PRL deficiencies. Patients 2 and 3 had severe hypothyroidism while the patient №1 had moderate hypothyroxinemia. (Table 1)

Homozygous mutations in POU1F1 were found in all infants.(Picture 1) In the latter two cases mutations were not previously considered to be pathogenic. Replacement therapy with levothyroxine and then growth hormone led to the elimination of hyperbilirubinemia, hypoglycemia.

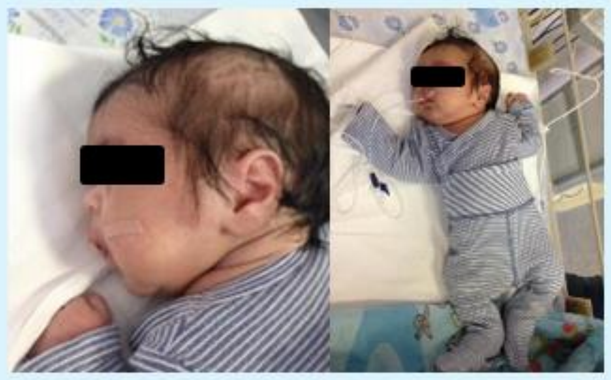
Picture 1. Patients. Homozygous mutations in POU1F1.



Patient № 2



Patient № 1



Patient № 3

patient №1 - missense mutation s.793S> T: p.R265W is pathogenic and early described.

patient №2 - frameshift mutation s.638_642delGGAAAp.R212KfsX12

patsient№3 - frameshift mutation c.634_638delGAAAGp.R213KfsX12.

Table 1. **The levels of blood hormones.**

Patient № Age	Insulin IU/L (2,3-26)	TSH mIU/mL (0,62-8,0)	FT4 pmol/l (10-26)	Cortisol nmol/l (138-635)	GH ng/ml (1,3-9,1)	IGF-1 ng/ml (28 – 156)	PRL mIU/ml (137-627)
№ 1 2 day of life	0,3	0,012	6,81	533,7	0,002	6,775	4,73
№ 2 1,5 month	0,2	0,008	2,27	355,3	0,005	21,32	5,9
№ 3 17 day of life	0,2	<0,005	1,88	999,0	<0,05	<15	9,15

Table 2. The levels of blood glucose, **biochemical liver function parameters**

Patient №	Glucose mmol/l (3,9-6,1)	BiT µmol/L (<20,5)	BiD µmol/L (<10% BiT)
1	0,6	37	-
2	0,93 - 1,82	358,5	24,9
3	2,5	355	18

Conclusion

Infant jaundice and /or persistent hypoglycemia require CPHD exclusion, moreover male gender and Turkic ethnic type increase the risk of the POU1F1mutation.

Thyrotroph dysfunction degree determines the severity of clinical and laboratory manifestations of the hypothyroidism syndrome and can be associated with the type of genetic defect.