The monitoring of endocrine functions in children with rare genetic syndromes

P2 – 878

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OBJECTIVES

Children with rare genetic disorders may have different endocrine problems. We present paediatric patients with different genetic syndromes: Pallister-Hall, Holt-Oram, Ellis–van Creveld and Marshall.

METHODS

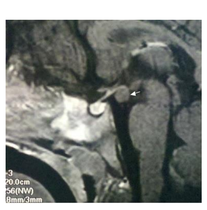
We have described clinical course and laboratory data of 4 patients (3 M, 1 F, all Caucasian) with rare genetic syndromes. As complete genetic analysis was not available, clinical data were pitfalls for the diagnosis.

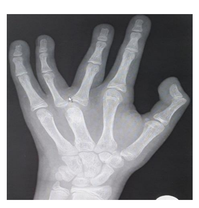
RESULTS

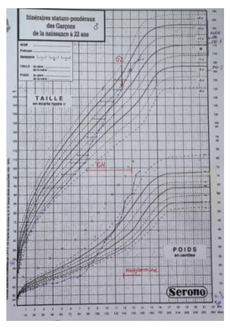
1 Pallister-Hall syndrome (PHS) - AD inheritance with unknown frequency, mutations/ mosaicism in the *GLI3* gene; about 25% are *de novo* - includes hypothalamic hamartoma (often gelastic epilepsy and central precocious puberty), postaxial/central polydactyly, syndactyly, anal atresia, bifid epiglottis, craniofacial dysmorphism, cardiac, pulmonary and renal anomalies, behavioral problems. Different degree of hypopituitarism can be present, in neonatal period, adrenal insufficiency may be life-threatening condition..

The case: the child was born in term to non-consanguineous parents (**BW 4300 gr**, BH 54 cm, Apgar 8/8) with polydactyly on both hands and atrial septal defect. Karyotype 46, XY. At $1^{4}/_{12}$ y. cerebral palsy - motor and mental retardation. First visit to **paediatric endocrinologist at 5 $^{3}/_{12}$** y., the main complain - poor growth and appetite, speech and developmental delay, unexplained mood changes, laughting, aggression. **Height 95 cm (-3,4 SDS),** weight 13 kg (-3 p.c.). MPH 179 cm (+0,75 SDS). **Postaxial polydactyly on both hands.** Tanner st I. **Genetic syndrome was suspected**. Investigation results: BA was $3^{0}/_{12}$. **Brain MRI –** in the floor of the 3[d] ventricle **posterior to the pituitary – an isointense mass**, 25*20 mm, non-enhancing. Abdominal US – right kidney hypoplasia. TFTs and cortisol - normal. **Two deficient GH stimulation tests**. Insulin test GH peak – 1,1 IU/l; clonidine test GH peak – 14,6 IU/l; NR 0-20 IU/l). Neurosurgeon consult – hypohalamic hamartoma with no need for surgery. **Diagnosis**: **Pallister-Hall syndrome (hypothalamic hamartoma, polydactyly, syndactyly, kidney hypoplasia, isolated GH deficiency, developmental and behavioral problems)**. **No signs of precocious puberty. No adrenal insufficiency. GH treatment** was started at **$7^{9}/_{12}$ y.** - 0,025 mg/kg daily. After 5,5 y. of GH treatment his height was161 cm (+1 SDS), weight 61 kg (>97 p.c.), BMI 23,4 kg/m^2 (>90 p.c.). Puberty started spontaneously at the age of 12 y. Due to BA progression GH treatment was stopped when pt. was 13 y.o. Due to **weight gain**, insulin resistance signs (HOMA IR 3,6), antipsychotic' intake and food behavioral problems **metformin** 1000 mg daily was prescribed. At the age of 14 y. BA=$14^{6}/_{12}$, GV 5,5 cm after 1 y. of GH discontinuation with predicted height 176,5 cm (within target height).

Hypothalamic hamartoma on MRI, central metacarpal syndactily on the wrist X-ray and growth chart in suspected Pallister-Hall syndrome



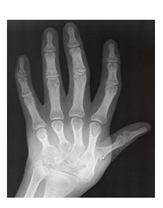


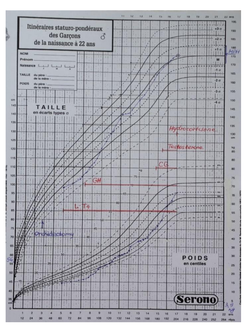


2 Holt-Oram syndrome (HOS) - AD inheritance, the frequency is 1 in 100,000 individuals, mutations in the *TBX5* gene, 85 % of cases are *de novo* - is characterized by skeletal abnormalities of the hands and arms (a hypoplastic thumb, malformations or fusions of the carpal bones, partial or complete absence of bones in the forearm) and heart problems (atrial/ ventricular septal defects, cardial conductive disease). No endocrine problems described..

The case: the baby was born to the family with no consanguinity known, to G2P2 mother at 41 week of gestation (BW 3900 gr, BH 56 cm), with **chriptorchidism** on the right. Growth retardation became evident after 12 mo. of life. Neurological status was normal. First visit to **paediatric endocrinologist at 3 $^{0}/_{12}$ y**. with the complains to poor growth and small hands. ECG - I degree **atrio-ventricular block.** Cardiac US – **atrial septal defect. Levothyroxine** 25 mcg daily was prescribed due to slight **TSH elevation.** Karyotype 46, XY. The right abdominal gonad (atrophic) was surgically removed. **Genetic Holt-Oram syndrome was suspected clinically**. At the age of **6 y.: Height 102cm (-3,2 SDS),** weight 13 kg (< -3 p.c.). MPH 176 cm (m). **Hypoplasia of the wrists, thumbs** and hypomobility of the elbows was evident. Tanner st I with prepubertal scrotal testis on the left. **BA was $4^{0}/_{12}$** . Brain **MRI – pituitary hypoplasia** described. TFTs (normal FT4 and low TSH **under L-T4 replacement**), cortisol - normal. **IGF-1 – 41,5 ng/ml** (NR 98-156). **Insulin stimulation test** - GH peak – 0,65 IU/l, test was interrupted due to **severe hypoglycemia developed. GH treatment** was started at **$7^{3}/_{12}$ y**. - 0,025 mg/kg daily. No spontaneous puberty, at 14 y. of age, with BA=12 y.the **chorionic gonadotropin** 1500 IU twice per week was added followed by **testosterone** replacement. At 16 y. low morning cortisol was confirmed, **hydrocortisone** (8 mg/m^{2}day) was introduced. At the age of 17 y., after 10 y. of GH treatment, H=176 cm (his target height), BMI is 22 kg/m^2 Complete epiphysis fusion, transition to metabolic doses of GH. **Diagnosis: Combined pituitary hormone deficiency (GHD, hypothyroidism, hypogonadism, adrenal insufficiency) due to pituitary hypoplasia associated with Holt-Oram syndrome.**

Upper limbs, wrist X-ray and growth chart in suspected Holt-Oram syndrome

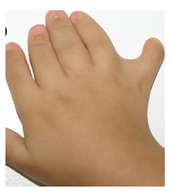


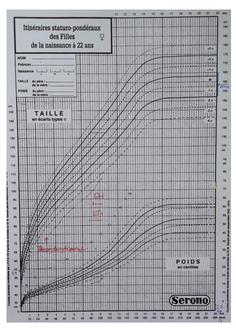


3 Ellis-van Creveld syndrome (EvCS) - AR disease, is frequency varies from 1 in 60,000 to 1 in 150,000 live birth, mutations in either *EVC1* or *EVC2* genes in about 60% of cases - short-limbed disproportionate dwarfism, postaxial polydactyly, ectodermal dysplasia and in 50-60% of cases congenital heart defects. In unique cases renal, pulmonary, ocular, hemopoietic malformations, hypospadias and cryptorchidism were present. Some EvCS patients may benefit from GH treatment.

The case: The girl is a product of the 1[st] uncomplicated pregnancy, normal delivery (BW 3200 gr, BH 54 cm) into non-consanguineous family. Multiple dysplastic features at birth (**facial dysmorfism**, **polydactily**, hip dislocation). **Growth was always poor.** At 3 y. she manifested with **thrombocytopenic purpura.** Fanconi anemia was excluded. Karyotype 46, XX **The Ellis-van Creveld syndrome was suspected. At 8 y.: height 99,5 cm (<-4 SDS),** weight 14 kg (< 3 p.c.). MPH 158,5 cm (-0,25 SDS).- a **disproportionate dwarf child with polydactily, hypoplastic nails, oral anomalies** (enamel hypoplasia, microdontia, conical teeth**),** minor neurodevelopmental delay. Tanner st 1. Abdominal US - **dysplastic dystopic right kidney,** heart US **– minor cardiac anomalies. BA was $4^{0}/_{12}$. Brain MRI** demonstrated a **remarkable pituitary hypopasia.** An **elevated TSH** level and **thyroid hypoplasia** at US, L-T4 was prescribed for **hypothyroidism**. IGF-1 level – 66,2 (NR 76-499 ng/ml). **GH stimulation test both deficient**: insulin GH peak – 4,5 IU/l; clonidine – GH peak – 4,9 IU/l; NR 0-20 IU/l). **GH deficiency** was **confimed**. **GH treatment was started at $8^{3}/_{12}$ y.** - 0,025 mg/kg daily.
Due to thrombocytes decrease less than 50*10^9/l
GH was stopped and restarted again.
After 10 mo. of treatment she achieved 7 cm in height.
She is under careful control of endocrinologist and hematologist .

Postaxial polydactily (6[th] finger on the right hand) and growth chart in suspected Ellis-van Creveld syndrome

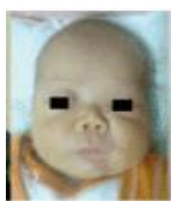


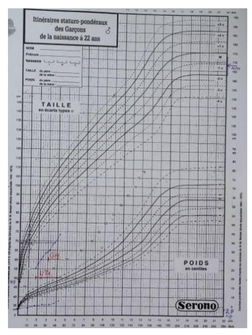


4 Marshall syndrome – AD chondrodisplasia (mutation of *COL11A1* gene) - characterized by mid-facial hypoplasia, short stature, hearing damage and ocular defects (cataract, high myopia), bone maturation can be advanced.

The case: The boy was born to G2P2A0 mother (hydramnion, anemia, smoking) at 39 weeks of gestation by C-section (BW 2900 gr, BH 49 cm); Apgar score 4. He was diagnosed with congenital pneumonia and had **hypospadia**. **After 5 mo. of age he stopped putting on his weight and growing;** appetite was good. The child had slight motor development, teeth eruption delay and anemia with. At the **age of $1^{9}/_{12}$ y. L-T4** was prescribed (TSH-6,7 with NR 0,17-4,05 mIU/l; FT4-5,6 with NR 11,5-23 pmol/l). His linear growth was improved but weight remained almost unchanged. **Genetic consult - Marshall syndrome (clinically) - a flattened nasal bridge, tilted upward nostrils, hypertelorism, epicantus, microgenia, short stature**. After **3 y. of age** he developed several **hypoglycemia episodes**. The serum cortisol level was normal. **IGF-1 - 45,0** (NR 76-499 ng/ml). BA corresponded to neonate. After hypothyroidism compensation, **GH stimulation clonidine test** was **deficient** – GH peak after stimulation – 0, 52; NR 0-20 IU/l**). Pituitary hypolasia and fronto-parietal scull' calcifications** was seen on brain **MRI**. **Diagnosis: Combined pituitary hormone deficiency (GHD, hypothyroidism) due to pituitary hypoplasia associated, presumably, with Marshall syndrome. GH treatment was initiated at $3^{3}/_{12}$ y. -** 0,025 mg/kg daily. **Before treatment: height 63 cm (<-4 SDS), weight 5,2 kg (< 3 p.c.) No more hypoglycemia**. In one year he put on 2,5 kg, **growth velocity was 10 cm/year**.
He needed L-T4 dose adjustment after GH initiation.
BA is not accelerated, no visual or hearing damage up to now.

Face appearance and growth chart in suspected Marshall syndrome





CONCLUSIONS

Children with rare genetic syndromes may have different endocrine problems, as a part of the condition or associated with it. Such children require a multispecialistic approach and can benefit from endocrine treatment. As the syndromes are rare and genetic investigation is not always available even if very desirable, a thorough clinical monitoring remains crucial for diagnosis.

The authors have nothing to disclose

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Syndromes : Mechanisms and Management

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