Somatotropic pituitary insufficiency in Kearns-Sayre syndrome – the clinical picture, genetic diagnosis and efficacy of rhGH therapy.

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OBJECTIVES

Kearns-Sayre syndrome (KSS, OMIM #530000) is a rare disease belonging to a heterogeneous group of mitochondrial cytopathies.

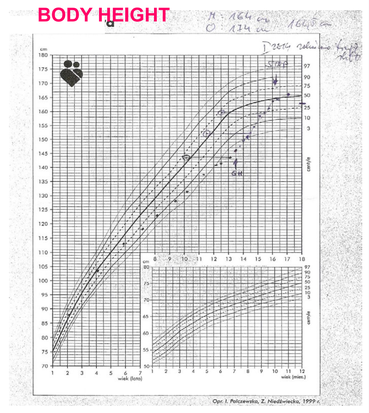
KSS is manifested by many systemic abnormalities:
(1) a progressive external ophthalmoplegy,
(2) pigmented degeneration of the retina
(3) cardiac block,
(4) neurological problems
(5) several endocrine disorders.

KSS is caused by Mitochondrial DNA (mtDNA) rearrangements (deletions and/or duplications), which lead to the dysfunction of the respiratory chain and to disorders in tissues with a high energy demands (muscle, nervous system).

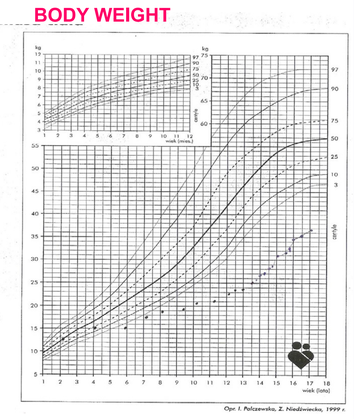
CASE PRESENTATION

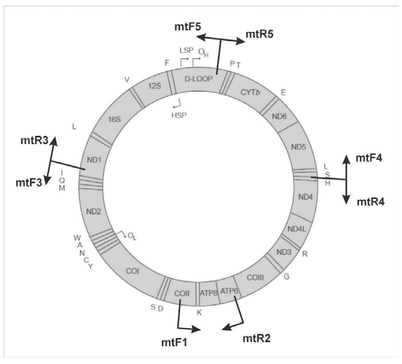
- The girl (now aged 17 5/12) was admitted to the hospital at the age of 13 yrs with the suspision of KSS (ophtalmological symptoms and GH deficiency)
- The girl from the first pregnancy (41/42 w.), Apgar 10/10, body weight 3890g, body length 56 cm,
- Progressive body mass deficiency has been noticeable since the age of 4-5 yrs (celiac disease excluded)
- Beginning of the eye movements disorders were difficult to ascertain
- Retinal pigmentary retinopathy, ptosis, external ophthalmoplegia characteristic for KSS were observed
- Neurological examination revealed limitation in both eyes abduction, significantly reduced upward movement, bilateral ptosis, without cerebellar symptoms, and features of myopathy or neuropathy
- Cardiological examination (Holter ECG) was normal
- MRI of the head and serum lactate levels were normal
- EMG revealed discrete myogenic features
- Current pubertal stage is A2, P4, Th4/5 (spontaneous puberty at the age of 14, menarche at the age of 16 4/12)
- Somatotropic pituitary insufficiency was diagnosed
- At the age of 14 yrs rhGH treatment was started (Omnitrope; Sandoz) (height 149.3 cm; **<3rd percentile**, weight 26.5 kg, bone age 10 yrs, the rate of growth 3.4 cm/year) which ended at the age of 16 yrs 4/12 (height 164.2 cm, ~ 50 percentile)
- The current height at the age of 17 yrs and 2/12 is 165.9 cm (> 50 percentile)
- Plastic correction of eyelids with very good results

BODY HEIGHT



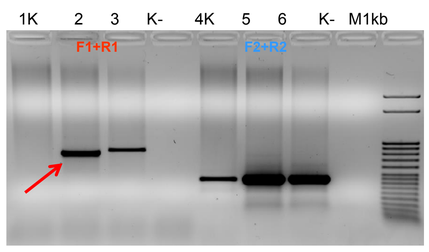
BODY WEIGHT

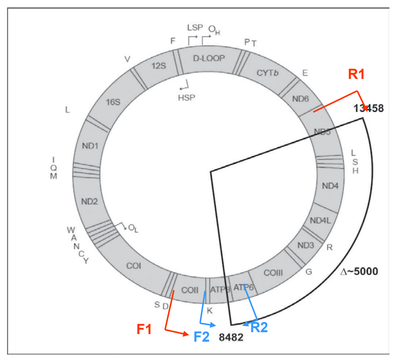




Molecular analysis of mitochondrial DNA was done with total DNA isolated from patient's whole blood using QIAamp® DNA Mini Kit (QIAGEN). To detect and localize the approximate position of the deletion 200 ng of DNA was used for PCR amplification with various sets of primers (HotStarTaq DNA Polymerase from QIAGEN was used). Primers' positions were designed so that the PCR reactions could cover the whole mtDNA molecule sequence, allowing to detect every possible deletion in mtDNA. PCR products were separated by electrophoresis in 1 % agarose gel and visualized by ethidium bromide staining.

Reaction	Primers combination	Product length
1	mtF3 + mtR4	8276 bp
2	mtF4 + mtR3	8340 bp
3	mtF1 + mtR5	8234 bp
4	mtF5 + mtR2	9255 bp
5	mtF3 + mtR2	4859 bp
6	mtF2 + mtR4	3835 bp
7	mtF4 + mtR5	3935 bp
8	mtF5 + mtR3	4409 bp





A deletion of 4977 bp in positions 8482-13458 was detected. It is so-called "a common deletion" and is frequently found in patients with KSS. This deletion encompasses genes encoding subunits of complex I, IV (1 gene) and V (2 genes) of the oxidative phosphorylation chain as well as 5 tRNA genes (12 genes in total).

HORMONAL STUDIES

- **Growth hormone after sleep test (GH levels in serum)**

	0'	30'	60'	90'	120'	Units
GH	1,9	0,6	0,5	0,9	4,3	ng/ml

- **Growth hormone stimulating tests:**

Clonidine (150 ug/m2 p.o.)

	0'	15'	30'	45'	60'	90'	120'	180'	Units
GH	0,2		0,3		1,1	1,3	0,6		ng/ml

Glucagon (0,030 mg/kg i.m.)

	0'	15'	30'	45'	60'	90'	120'	180'	Units
GH	0,2				0,3	0,3	5,5	1,8	ng/ml

LHRH (2,5 ug/kg i.v.)

	0'	30'	60'	90'	120'	Units
FSH	3,0	8,44	8,93	9,25		mIU/ml
LH	<0,5	3,03	2,2	1,51		mIU/ml

LH and FSH in normal range

CONCLUSIONS

(1) KSS is usually detected after the diagnosis of a variety of endocrine disorders,
(2) clinical course of the disease is variable, but the growth deficiency is dominant in childhood,
(3) Muscle biopsy plus mtDNA analysis diagnosed the true molecular background of the disease as mitochondrial abnormalities,
(4) PCR can be used as a quick, easy and reliable method for the analysis of mtDNA rearrangements
(5) In some children, KSS may be the reason for the weak results of the therapy with the standard dose of rhGH
(6) In our patient the significant improvement of growth velocity was observed.

References

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