

Clinical and genetic diagnosis of Allgrove syndrome

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Background: Allgrove syndrome (Triple A, 4 A syndrome) a rare autosomal recessive disorder, characterized by the triad of **ACTH resistant adrenal insufficiency, alacrima** and **achalasia**, was described for the first time in 1978. Several years later **progressive neurologic impairment** such as progressive peripheral polyneuropathy, hyperreflexia, nasal speech and disautonomia was observed in many patients. From 1996 it is known that mutations of the ADRACALIN (AAAS) gene on the 12q13, that encodes the Nuclear pore complex protein ALADIN, are responsible for the clinical presentation.

Methods and objectives: To present the case of an 18 years old girl, from second normal pregnancy of no consanguineous parents, who came at our hospital for first time at the **age of 10**, with complain of lower limb weakness. On examination limited dorsal flexion of the feet, thin calves, high plantar arches, but normal tendon reflexes were observed.

EMG – showed low velocity of conduction of both sensory and motor peripheral neurons.

Conclusion – **Peripheral polyneuropathy**

Next 2 years – **progression of neurologic impairment** – appearance of saccadic speech, central motor neuron damage manifested with hyperreflexia and a **new symptom** – episodes of severe **vomiting** imposing hospital admission

Twelve years old - episode of **severe hypoglycemia** that lead to coma

Next year - **hyperpigmentation, hypotension, alacrima** and mild optical atrophy were observed

Differential Diagnosis

1. ACTH resistant syndromes:

- Alacrima – Achalasia - Addison disease s-me + Autonomic abnormalities (Allgrove s-me)
- Familial Glucocorticoid deficiency s-me type I, II

2. Metabolic disorders:

- Adrenoleucodystrophy
- Other peroxisome disorders – Zellweger s-me, NALD

3. Autoimmune disorders with adrenal insufficiency

- APS type 1
- APS type 2

4. Congenital adrenal hypoplasia - X linked or with AD inheritance

Laboratory investigation:

- Electrolytes: Na⁺ 137 mmol/l, Cl⁻ 97 mmol/l, K⁺ 4,9 mmol/l
- Fasting blood glucose 3,5 mmol/l
- Free 24 –hour urine cortisol 35 nmol/24 h (100 – 379)
- ACTH – 600 ng/l (7,20-63,30)
- Barium esophagography – excluded achalasia of cardia
- Normal values of Very long chain fatty acids in serum excluded Adrenoleucodystrophy
- Molecular genetic analysis showed two heterozygous mutations of the AAAS gene
 1. c1024C>T;p.(Arg342) exon 11 (inherited from father)
 2. c1331+2dupT intron 14 (from mother)

Results: This proved the clinical diagnosis of **Allgrove syndrome** three years after initial presentation
This is the first genetically proven case of Tripple A syndrome in Bulgaria

Treatment: Follow up by endocrinologist, neurologist, gastroenterologist and ophthalmologist

Hydrocortisone, tabl. 15+ 15 mg p.os

Cortineff 0,1 mg, 2 x ½ tabl.

Topical eye lubricants

Rehabilitation for neurologic symptoms

At the age of 18 : Height 162 cm (50 p), Weight 53 kg, BMI 20, 2 kg/m² (36 p), normal development and still mild neurologic symptoms

Conclusion: There is great variability in the time and order of presentation of symptoms. It is crucial for the patient's quality of life and lifespan to receive an early diagnosis and efficient treatment in order to avoid life threatening complications as in presented case.

References:

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