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Familial occurrence of adrenocortical insufficiency in two brothers with Allgrove Syndrome.

A Case Report of 4A (Allgrove) Syndrome with epilepsy and a new AAAS gene mutation.

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Abstract

Allgrove syndrome is a rare autosomal recessive disease with achalasia, alacrima, adrenocortical insufficiency, autonomic neuropathy and other neurological disturbances. A case of two brothers with Addison's disease from early childhood is presented. The younger brother with Addison disease died at the age of 5. The older brother was treated for adrenocortical insufficiency from the age 3, and then treated for achalasia and epilepsy from the age of 5. The patient is currently 26 years old and suffers from achalasia and adrenocortical insufficiency. He also suffers from alacrima, autonomic neuropathy, epilepsy and other damages of the central and peripheral nervous system. The clinical picture is typical for Allgrove or 4A syndrome, and the diagnosis was confirmed by means of molecular analysis of a new AAAS gene mutation.

CASE REPORT

Introduction

Allgrove syndrome is a rare autosomal recessive disease first described by Allgrove in 1978. It is characterized by a triad of clinical symptoms: achalasia, alacrima and adrenocortical insufficiency [1]. According to the identified cardinal symptoms, it is named 3A syndrome or AAA syndrome. In 1995, the eponym 4A syndrome was suggested, since among the growing number of case reports another common symptom of the disease was noted – autonomic nerve dysfunction [2]. Several authors at that time suggested that autonomic dysfunction need not necessarily be accepted as the fourth symptom of the disease, but the primary cause of the original triad of symptoms – achalasia, alacrima and adrenocortical insufficiency.

Gradually, with a growing number of reports, there are an increased number of cases with peripheral nerve dysfunction and evident muscle atrophies. This phenomena has resulted in several authors suggesting the term 5A syndrome. Except the damage of the autonomic, peripheral and also central nervous system, there are documented disturbances of other systems, mostly to bones and skin (palmoplantar hyperkeratosis, short

body growth, osteoporosis, microcephalia). These multi-system disturbances may be considered as maldevelopmental and dysplastic disturbance. Recent genetic studies have suggested the disease may be due to various mutations in the so called AAAS gene, on chromosome 12q13, coding the protein called ALADIN (alacrima, achalasia, adrenal insufficiency, neurological disturbances). ALADIN belongs to the group of regulator proteins (WD-repeat) [3, 4, 5]. The ubiquitous occurrence of ALADIN protein in the human body suggests that the damage may be attributed to a multisystemic developmental disturbance. High gene expression was shown in the adrenal gland, gastrointestinal tract and nervous system. This correlates with heightened clinical symptomatology from those sites. The functional diversity of ALADIN protein in protein-protein interaction, in signal transduction, RNA processing, cellular transport, regulation of cell division, cytoskeletal system etc., explains the principal disturbances of cellular functions when it is deficient, and thus it could be the cause of degeneration of cholinergic neurons. Neurological manifestations could also be partially related to glucocorticoid deficiency during the development of the nervous system. It is still not clear if, in pathogenesis of the disease, damage is primarily at suprarenal functions, or alternately, autonomic neuropathy with secondary adrenocortical insufficiency.

Case Report

Presently, the 26-year-old male patient, has parents and grandparents without any noteworthy diseases. He had two siblings. His younger brother died of Addison's disease as a 5-year-old (according to available data). His older sister is healthy. The patient's intrauterine development, delivery and his early childhood period were normal. At the age of 3, psychomotor retardation and mental retardation, together with Addison's disease, were confirmed. At the age of 5, the patient was operated on for achalasia. During this time generalized tonic and clonic epileptic seizures occurred and he was set on carbamazepine treatment. The suspicion of Allgrove's syndrome was first assumed 20 years later, on the basis of adrenocortical insufficiency, achalasia, and deficiency of lacrimation according to a positive Schirmer's test. Bilateral atrophy of the optic nerve was diagnosed, too. Consequently, the patient was subjected to neurological testing. Clinical investigation of cranial nerves revealed a marked slowing of the pupillar reflex in the sense of pupillatonia and the presence of bulbar syndrome (decreased vomiting reflex bilaterally and dysarthria). Motor examination revealed mild muscle weakness, symmetric tendon hyperreflexia on both upper and lower extremities besides Achilles tendon areflexy, higher muscle tone in the sense of spasticity and small hand muscles amyotrophies. Thus the clinical investigation alone has proved the damage to autonomic nervous system (pupillatonia), peripheral nervous system (polyneuropathic syndrome, bulbar syndrome) and central nervous system (mental retardation, epilepsy, central spastic quadruparesis, optic neuropathy). Actually the patient is seizure free with carbamazepine 600 mg/day.

Endocrinological tests confirmed adrenocortical insufficiency with adequate substitution therapy (hydrocortisone 20 mg/day and fludrocortisone 0,1 mg/day).

The electroencephalogram (EEG) showed both diffuse and focal abnormalities with two probably independent foci of specific epileptic activity in both fronto-temporal regions. The electromyographic (EMG) investigation confirmed a mixed axonal and demyelinating type of sensory-motor neuropathy with collateral reinervation and maximum of pathologic changes in the region of the ulnar nerve bilaterally. Brain-stem auditory evoked potentials (BAEP) were normal, visual evoked potentials (VEP) found a mild demyelinating lesion of the right optic pathway and somatosensory evoked potentials (SSEP) with stimulation of the median nerve showed slightly prolonged cortical latencies with absent peripheral and cervical potentials. Thus peripheral nerve system damage was confirmed, with the possible simultaneous involvement of the central nervous system. Similar findings were revealed by the investigation of SSEP with stimulation of the tibial nerve.

For testing of the autonomic nervous system we used Ewing's tests, evaluating variations of heartbeat frequency during deep breathing, Valsalva's manoeuvre, and variation of heartbeat frequency and blood pressure during orthostasis. The results of all these tests presented evidence for disturbed vegetative functions.

The brain magnetic resonance imaging (MRI) showed three small non-specific cortico-subcortical foci of gliosis (in the right frontal and left parietal and insular regions), with mild brain atrophy.

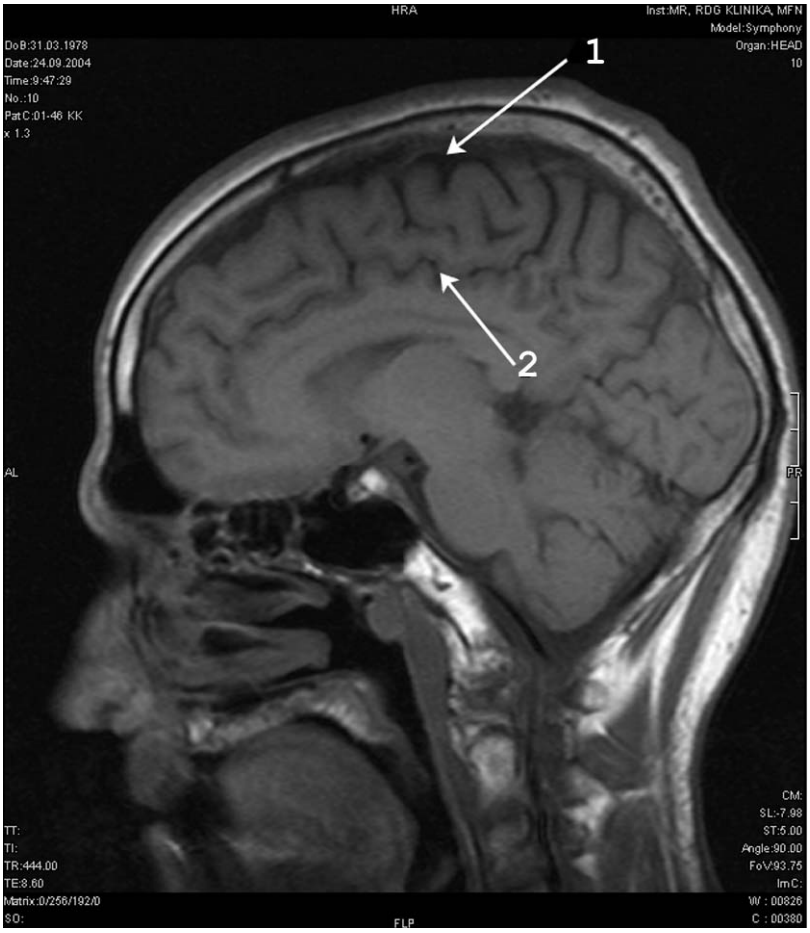
Psychological investigation confirmed intellectual abilities on the level of mild mental retardation. The distribution of intellectual faculties suggested impaired memory, attention, and creativity as well as decreased psychomotor abilities.

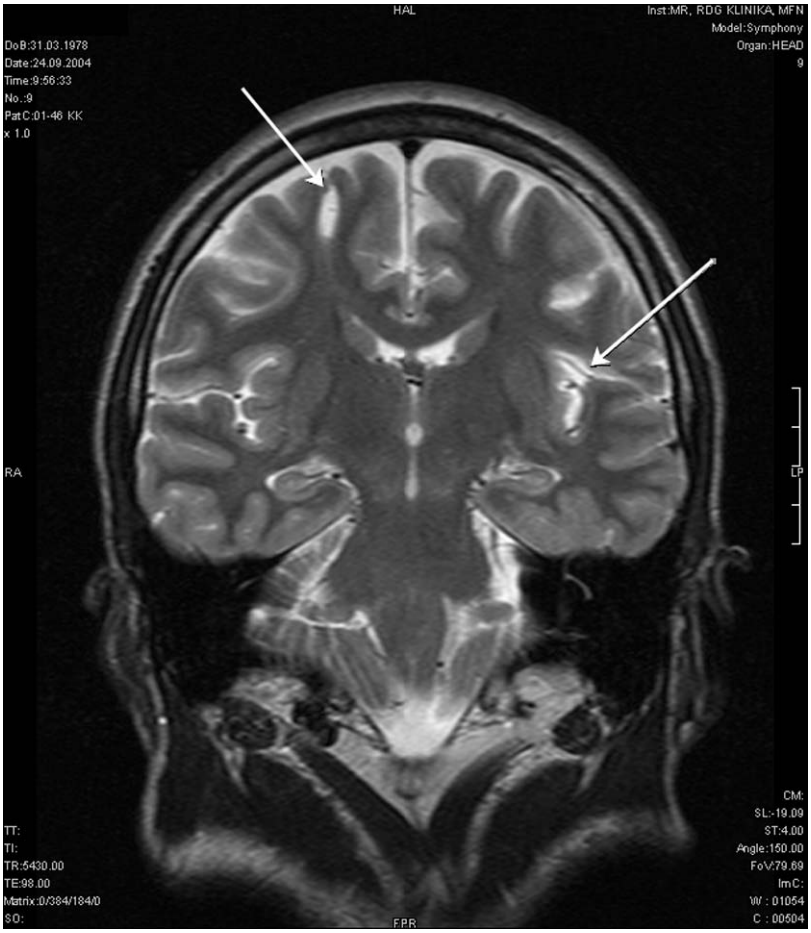
In ophthalmologic examination alacrima (coniunctivitis sicca) was confirmed by Schirmer's test and during ophthalmoscopy, maculopathy, pale papillae and atrophy of the optic nerve in both sides were discovered.

Genetic examinations performed by means of molecular analysis of the AAAS gene, (on chromosome12q13), confirmed the newly discovered heterozygotic mutation in exon 9 (missense change W272S TGG-TCG) in the patient's mother, and the already described heterozygotic mutation in exon 11 (1066-1067 deletion CT) in the patient's father. The patient himself had both mutations of the AAAS gene as a compound heterozygote.

Discussion

The disease manifests typically in childhood when the earliest symptoms would be most commonly dysphagia, due to achalasia, and symptoms of adrenocortical insufficiency, commonly in a form of hypoglycaemic episode, which, on occasion, are fatal. Less frequently, the disease manifests itself in a form of hypotensive





attack, skin hyperpigmentation and with general symptoms of fatigue and lethargy. Adrenocortical insufficiency symptoms can manifest even later – in adolescence or even in adulthood. Alacrima is usually described as an early manifestation of the syndrome, however, it can be easily overlooked. Autonomic symptoms have variable manifestations and they can occur both in childhood as well as in adulthood.

In adulthood the disease manifests first of all by neurological symptoms. Less severe forms of achalasia and alacrima can be easily overlooked. In some cases clinical manifestations of adrenocortical dysfunction were described as late as in the fifth decade, which provides evidence for its later development. The disease may also present without any of these mentioned clinical manifestations. In such cases the only symptoms of the disease are the neurological disturbances, which may be due to damage of autonomic, peripheral and central nervous system. In the literature, manifestations of autonomic nervous system damage are described as achalasia, alacrima, disturbance of pupillary function – most frequently pupillatonia, Horner's syndrome, postural hypotension, regional hyperhydrosis, and impotence. The most frequent signs of peripheral nervous system damage are acrodistal motor or sensory-motor polyneuropathy with marked small hand muscles amyotrophies. Myopathy with Allgrove syndrome was described, too. Central nervous system damage manifests also with heterogenous symptomatology (cognitive impairment, motor pyramidal and extrapyramidal disturbancies and less frequently epilepsy) [6, 8, 9, 10, 11, 12].

In cases when Allgrove's syndrome is suspected, in order to establish the diagnosis, it is necessary to perform endocrinologic tests to prove clinical or subclinical adrenocortical insufficiency characterized by the resistance to both exogenous and endogenous adrenocorticotropic hormone (ACTH). Additional tests include an ophthalmologic examination with Schirmer's test for detection of tear production deficiency, gastroenterologic tests for achalasia and neurological tests for determining damage to autonomic, peripheral and central nervous systems. However, definitive diagnosis can only be made by means of molecular analysis of the AAAS gene.

The diagnostic algorithm of Allgrove's syndrome is very complicated, because this syndrome has a multisystemic character, and the disturbance in function of some systems may have a subclinical character, which may not be apparent or visible. If the disease becomes manifest in adulthood with initial neurological symptoms, a definite diagnosis is, in some cases, problematic and obscure. Among the imaging methods, we prefer MRI of the brain (usually a normal finding) to exclude leukodystrophy and mitochondrial diseases. However, also described were the findings of non-specific sites of gliosis and periventricular heteropy as signs of disturbed neuronal migration in prenatal or early postnatal period [7]. The cause of lesions of the nervous system is not clear. The genetically encoded metabolic pathway disturbances, induced by adrenocortical insufficiency (hypoglycaemia or oxygen deprivation), may play a role in the development of nervous system damage. The intracellular disturbance to some cellular organelles is not known.

Conclusions

1. Allgrove's (so called 4A) syndrome is a genetic disturbance encoded on chromosome 12 at the AAAS gene. The symptoms include adrenocortical insufficiency, achalasia, alacrima and autonomic and peripheral nerve disturbance. In some cases various central nervous system damage is also seen.

2. The typical course in childhood frequently manifests with adrenocortical insufficiency, achalasia and alacrima, and lesions of the autonomic and peripheral nervous systems are less apparent. In adulthood usually the first symptom seen is a lesion of the nervous system. Other multisystemic involvement may be less apparent hence the diagnostic procedure seems to be more complicated.

3. The authors report a case of familial occurrence of this rare autosomal recessive syndrome with the early manifestation in childhood in two brothers. From the age of 3 years, the older brother had adrenocortical insufficiency and 2 years later presented with achalasia and epilepsy. Genetic examination confirmed a new mutation of the AAAS gene.

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