Autosomal recessive spastic paraplegia type 51caused by homozygous mutation of the AP4E1 gene in a 17 years old boy

Abstract
Autosomal recessive spastic paraplegia-51 (SPG51) is caused by a homozygous mutation in the AP4E1, adaptor related protein complex 4 subunit epsilon 1 gene, on chromosome 15q21. Spastic paraplegia-51 (SPG51) is an extremely rare autosomal recessive neurodevelopmental disorder characterized by neonatal hypotonia that progresses to hypertonia and spasticity. Mutations in the AP-4E1 gene on chromosome 15q21.2, which is part of the AP-4 complex, can lead to autosomal recessive spastic paraplegia 51 (SPG51). Different mutations in this gene have been identified in affected individuals, leading to disruption of the AP4 complex and vesicular trafficking processes.The specific characteristics of SPG51 are, due to only few cases, not well understood due to limited reports of affected families. Affected individuals also have global developmental delay with impaired intellectual development and poor or absent speech. Studies linked to an additive symptom of persistent stuttering. Affected individuals typically present with hypotonia in the neonatal period, which progresses to muscular hypertonia, especially in the lower limbs. They may also exhibit contractures, talipes equinovarus, decreased muscle mass, short stature, and microcephaly. Severe mental retardation, absent speech, and dysmorphic facial features are common. Some patients may experience seizures. Neurological examination often reveals spastic paraplegia of the lower limbs, and brain imaging may show atrophy of the cerebellar vermis and cortical atrophy. We present an extremely rare case of a 17 years-old boy with autosomal recessive spastic paraplegia type 51.

Introduction

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative diseases with genetic and clinical heterogeneity characterized by spasticity and weakness of the lower limbs. It includes four genetic inheritance forms: autosomal dominant inheritance (AD), autosomal recessive inheritance (AR), X-linked inheritance, and mitochondrial inheritance.HSP patients may have either pure or complicated HSP, differing based on symptoms. Patients with pure HSP simply develop spasticity and weakness of the lower limbs, while patients with complicated HSP are often accompanied by other symptoms, such as early cognitive impairment, ataxia, visual disturbance, macular degeneration, dysarthria, and callosal agenesis [18].

Case Report

We present a case of a 17-years-old German boy with an autosomal recessive spastic paraplegia type 51 (SPG51). A compound heterozygous mutation in the AP4E1 gene was found in genetic analysis. An unclassifiable epilepsy most likely with complex focal seizures is mostly present in SPG51. An anticonvulsant medication with Perampanel was initiated after past therapy with Sultiam, Lacosamide, Lamotrigine, Oxcarbazepine, Levetiracetam and Zonisamide. SPG51 is a combined developmental disorder and a severe expressive language development disorder. Past medical history showed an epileptological situation quite stable. No major seizure events were observed anymore, occasionally episodes of smacking occur, which were interpreted differently. These episodes were hardly noticeable and very brief with a duration of less than a minute. The current medication consisted of Baclofen 10-0-20 mg and Perampanel 3.5 mg.The main problem affecting both school and especially the home environment were extreme episodes of restlessness and aggression, provoked by unfamiliar people and environments. They also occur in the home environment. Examination findings included the patient in a fairly good general condition, quite communicative, but mostly with non-verbal communication. Muscle tone increasingly spastic distally and leg-dominant, there were no side differences, no clearly recognizable cranial nerve abnormalities.The EEG showed a polymorphic mixed wave rhythm, emphasized in the upper theta frequency spectrum. The amplitudes barely exceeded 70 volts. An on/off effect was hardly discernible. Plenty of muscle activity overlayed, but no specific pathological patterns, especially no seizure predisposition, was found. The assessment and recommendations included the epileptological situation was not the main focus, rather the behavioral disorder was hardly bearable.

Discussion

Most of all hereditary spastic paraplegias (HSP) are classified due to the genetic loci that are classified by numbers according to their discovery (1-17). Four types are described in HSP and have been related to disturbances of different adaptor protein complex subunits (4). The functional loss of the AP-4 protein complex is the molecular mechanism in all AP-4 HSP disorders (4,10). AP-4-associated hereditary spastic paraplegia (HSP) is a group of progressive neurodegenerative disorders that typically present in infancy or early childhood.Spastic paraplegia type 51is a genetic disorder characterized by the degeneration and dysfunction of certain nerve tracts (1-17). The AP-4 complex subunit ϵ-1 (AP-4E1) plays a role in recognizing and binding sorting signals in cells. It is involved in sorting proteins to specific cell membranes and establishing protein localization in neurons (4,8).The AP4E1 gene encodes a member of the adaptor complexes large subunit protein family, which are essential components of adaptor protein complexes involved in vesicle formation and sorting of integral membrane proteins in the secretory and endocytic pathways. The encoded protein is a large subunit of adaptor protein complex-4, associated with both clathrin- and nonclathrin-coated vesicles. Mutations in this gene may be linked to cerebral palsy. Multiple isoforms of this gene have been identified due to alternative splicing. This gene is expressed ubiquitously, including in lymph nodes.AP4 complex-mediated trafficking is essential for brain development, with the AP4E1 gene encoding the AP-4 adaptor protein complex subunit $\epsilon - 1$. Knock-out mice with mutations in this gene exhibit abnormal white blood counts, enlarged lateral ventricles, a smaller corpus callosum, and hypoferremia. The clinical phenotype observed in this study aligns with previous reports of SPG51. Further mutational

analysis and evaluation of AP4E1 in individuals with spastic paraplegia and their families are warranted to assess the disorder's frequency.
This condition is often mistaken for cerebral palsy, but differs in its association with parental age and birth order (5,9,14). Symptoms include hypotonia progressing to spasticity, leading to difficulty walking or standing. Upper extremities may also be affected, resulting in spastic tetraplegia. Other complications include bladder and bowel dysfunction, dysphagia, foot deformities, and contractures (3,9,12,14). Seizures occur in about half of patients, and the condition is associated with microcephaly and developmental delays. Speech development is delayed or absent, stuttering could be rarely found (6).One case report describes the genetic defect with a mycobacterial disease (15).

conclusion

In conclusion, spastic paraplegia type 51 in childhood is rarely found and diagnosed and often found with clinical inconsistencies, leading to overlook or misdiagnosis.

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