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Case Report

A case of motor neuron involvement in Gaucher disease

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ABSTRACT

Gaucher disease (GD) is a genetic disorder characterized by an accumulation of glucosylceramide in cells in the monocyte-macrophage system. We describe a case of a 33-year-old man with a previous diagnosis of type 3 GD who displayed a progressive weakening of the limbs followed by upper motor neuron involvement. A diagnosis of definite Amyotrophic Lateral Sclerosis was made. This is the first reported case of concurrent Gaucher disease and the ALS phenotype in the same patient.

1. Introduction

Gaucher disease (GD), the most common inherited lysosomal storage disorder, is due to the acid- b-glucosidase (GBA) gene mutation located on chromosome 1q21, which leads to a defect in glucocerebrosidase enzyme activity. This defect causes an accumulation of glycolipids in organs such as the spleen, liver and bones, with or without central nervous system involvement [1]. GD is inherited in an autosomal recessive manner and has a prevalence of 1/50,000 in the general population. There are three main forms of GD: type 1, which is non-neuropathic and is the most widespread in the Western world; type 2, which is characterized by acute neurological involvement and usually results in death within 2 years of age; type 3, which is characterized by mild neuropathic involvement and a wide range of phenotypes [2]. Neurological features in type 2 GD include presentation in the early stages of life associated with degeneration of the brainstem and the pyramidal and the extrapyramidal tracts, which in turn leads to sucking problems, dysphagia and hypertonia. The neurological manifestations in type 3 GD instead occur several years later and include neuro-ophthalmic, epileptic and cognitive disorders [3].

Amyotrophic lateral sclerosis (ALS) is a sporadic or familial (10% of cases) fatal neurodegenerative condition that affects the motor system. Its prevalence is 3–5/100,000 while the average age of diagnosis in the sporadic form is 55–60 years [4]. Patients can present either with a spinal onset of the disease, characterized by limb wasting, fasciculations and brisk tendon reflexes, or with a bulbar onset, which is accompanied by difficulty in swallowing, dysarthria and dyspnea. Diagnosis can be based on a clinical examination and electrophysiological studies that reveal an impairment in both the upper and the lower motor neurons [5]. Electrophysiology can indicate upper motor neuron involvement, explicitly the corticobulbar one, through positivity of the heteronymous temporalis H reflex as a result of the stimulation of the masseteric nerve [6]. Whereas lower motor neuron involvement can be revealed by the presence of denervation, defined by fibrillation potentials or positive sharp waves at electromyography (EMG) testing [7]. Death generally occurs 3–5 years within the onset of symptoms and is due to weakness that progressively involves all the voluntary musculature and leads to respiratory insufficiency [8].

2. Case report

The patient in question was a 33-year-old Caucasian man who had been diagnosed with type 3 Gaucher disease at the age of 12 years after an enzyme assay showing low glucocerebrosidase activity (< 5% of normal activity) and a molecular analysis demonstrating homozygous D409H mutations (D409H/D409H). Thrombocytopenia, splenomegaly, bone involvement (Erlenmeyer flask deformity at the distal femur) and oculomotor apraxia were found. The patient was immediately placed on enzyme replacement therapy (ERT) at a dosage of 60 IU/kg/month. Clinical, laboratory and instrumental evaluations were performed at planned intervals. When the patient was 14 years old, he underwent an echocardiography examination that revealed valvular calcifications. His condition remained stable, with no neurological involvement, until the age of 31, when a clinical evaluation disclosed a weakening of the facial muscles, mentalis muscle fasciculations, hypotrophy of the first dorsal interosseous muscle and a residual strength of 4/5 on the medical research council (MRC) scale in both the upper and lower limbs. The tendon reflexes were brisk and symmetric. No sensory deficits were

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present. Brain MRI and somatosensory evoked potentials were normal. EMG and ENG testing showed signs of neurogenic damage in various non-contiguous regions. ERT therapy dosage was increased to 120 IU/kg/month. No other treatment for Gaucher disease was started. Three months later, the patient displayed additional fasciculations involving the orbicularis oris and corrugator supercilia muscles. The patient's tongue became weak and a mandibular reflex appeared. A spirometry examination showed a restrictive pattern. A Babinski sign appeared bilaterally. A diagnosis of definite ALS, made on the basis of the El Escorial Criteria, was made. He therefore started ALS treatment with Riluzole 100 mg/day. He subsequently developed dysarthria and dysphagia. The latter was detected by means of fiber-optic laryngoscopy, which revealed penetration into the larynx following the intake of a semisolid bolus and hypopharyngeal stagnation following the intake of liquids. The patient had no family history for ALS or dementia. Genetic testing for familial ALS was nevertheless carried out[1] but no mutation was found.

In summary, we present the case of a 33-year-old male with Gaucher disease who developed progressive weakness associated with upper and lower motor neuron signs, features of pseudobulbar palsy and electrophysiological evidence that are consistent with a diagnosis of ALS.

3. Discussion

Type 3 GD is generally associated with a subacute neurological involvement, which may include slowed horizontal saccadic movements, myoclonic seizures and supranuclear palsy [9]. The specific mutation that our patient presented, i.e. D409H/D409H, is linked to a typical phenotype that has been described in several case reports and whose main manifestations are cardiovascular calcifications, corneal opacities, oculomotor apraxia [10], ophthalmoplegia and abnormal saccadic eye movements [11].

Our patient presented the typical D409H genotype-phenotype, with cardiac and oculomotor involvement along with signs of motor neuron degeneration, which does not occur in GD but is characteristic of ALS.

He presented a standard ALSFRS (ALS Functional Rating Scale) score slope, as revealed by studies in which the ALSFRS score is used as a predictor of outcome [12], and was defined as a slowly progressing patient with a prognosis of 2.4 years from the initial visit [13].

The GBA gene is located on chromosome 1 [14] while genes associated with ALS are located on other chromosomes such as 6, 9 and 21. [15]. Interestingly, a large meta-analysis [16] of studies on the susceptibility of ALS identified a single nucleotide polymorphism on chromosome 1, thereby demonstrating that the onset of symptoms in patients with at least one copy occurs at an earlier age. Our patient's age at diagnosis was well below that of the average ALS patient [17], which means he may present the polymorphism. However, the two loci are found on different parts of chromosome 1, with the ALS one being located on the short arm (1p34.1) and the GBA one being located on the long arm (1q21) [18]. Rather than being due to an association between genes, evidence suggests that accumulation of ceramides and cholesterol esters may induce motor neuron death through oxidative stress [19] or calcium release via the ryanodine receptor [20]. Abnormalities in sphingolipid metabolism and the accumulation of glucosylceramide have been found in the spinal cord of ALS patients and SOD1 mutated mice (a familial model of ALS) [21]. The accumulation of sphingolipids in SOD1 mice preceded the clinical phenotype [19]. Hence, we hypothesize that GBA activity, and consequently glycolipid accumulation, may be directly correlated with the ALS phenotype.

[1] ALS2, ANG, ANXA11, C9ORF72, C21ORF2, CCNF, CHCHD10, CHMP2B, DAO, DCTN1, ERBB4, EWSR1, FIG4, FUS, GLE1, HNRNPA1, HNRNPA2B1, KIF5A, MATR3, NEFH, NEK1, OPTN, PFN1, PRPH, SETX, SIGMAR1, SOD1, SPG11, SQSTM1, TAF15, TARDBP, TBK1, TREM2, TUBA4A, UBQLN2, VAPB, VCP.

The strongest link to date between the GBA gene mutation and neurodegenerative disorders is found in idiopathic Parkinson's disease. Hypotheses include both a gain and a loss of function, which are believed to affect alpha synuclein clearance through reciprocal feedback [22]. A growing body of evidence also points to an association between glycosphingolipid accumulation and hereditary spastic paraplegia, spinocerebellar ataxia and ALS [23,24].

An association between lipid storage disorder and ALS has previously been reported only once, i.e. in a 38-year-old patient who was diagnosed with both Fabry disease (FD) and ALS. The authors of that case report postulated that the autophagy impairment that is typical of FD may be a predisposing factor to ALS on the basis of the similarities observed in autophagy-associated marker staining between the mouse model of FD and that of ALS [25]. Anomalies in autophagy have also been observed in multiple models of Gaucher disease, including mouse and Drosophila, with findings including dysfunctional mitochondria, mTOR downregulation, and an autophagic flux block, all leading to neurodegeneration [26,27]. Autophagy plays a central role also in the pathogenesis of ALS, with defects involving different stages of the process, including substrate recognition and autophagosome formation, fusion of the autophagosome with a lysosome and lysosomal clearance of autophagic substrates [28]. Autophagy enhancement is considered a potential therapeutic strategy, a hypothesis supported by the fact that rapamycin, a potent mTOR inhibitor, has been found to improve locomotor performance and lifespan in a Drosophila model of ALS [29]. Interestingly, when rapamycin was used in a Drosophila model of Gaucher disease, it led to improvements in motor activity, lifespan and oxidative stress [30]. We therefore postulate that common autophagic pathways may underlie the two disorders.

To our knowledge, this is the first case report of type 3 GD and ALS phenotype in the same patient. The patient could have been very unlucky to develop both diseases, but considering their very low prevalence, this would be unlikely. So motor neuron degeneration may be due to oxidative stress induced by an accumulation of glucosylceramides caused by low GBA activity. Type 3 GD and ALS also may share the same autophagic pathways. This case report sheds light on the potential link between GD and ALS and it may be helpful for future patients in making early diagnosis and treatment.

Disclosures

The authors declare no conflicts of interest.

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