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Dyskinesias as a limiting factor in the treatment of Segawa disease

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Abstract

Patients with autosomal dominant Segawa disease (dopa-responsive dystonia) show an excellent and sustained response to small doses of levodopa. In contrast, the development of levodopa limiting treatment dyskinesias is thought to support the diagnosis of other early onset dystonia/parkinsonism syndromes. We describe an atypical phenotype, that of persistent treatment limiting dyskinesias, in a family with prominent brachial dystonia and a novel *GCH1* mutation. The pedigree comprised two affected members, the proband aged 13 years and her mildly affected mother aged 48 years. Phenylalanine loading test, cerebrospinal fluid for biogenic amines and pterins, guanosine triphosphate cyclohydrolase I enzyme activity, and direct exonic sequencing of *GCH1*were performed revealing a novel mutation (c.235_240delCTGAGC[p.L79_S80del]) in the *GCH1* gene. Despite continuous l-dopa therapy from age 7 years, the proband developed a severe writer's cramp at the age of 10 years, and persistent treatment limiting dyskinesias even with low doses of levodopa leading to treatment challenges. We conclude that dyskinesias as limiting side effects of levodopa should not preclude the diagnosis of dopa-responsive dystonia during diagnostic levodopa trials and that the diagnosis of Segawa disease should still be considered if there is partial improvement with levodopa, but dose limiting dyskinesias.

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Competing Interests

The authors report no conflicts of interest.

All other authors have nothing to disclose.

Keywords

Dopa-responsive dystonia; Segawa disease; Guanosine triphosphate cyclohydrolase I deficiency; *GCH1* gene; Dyskinesias

Introduction

Patients with heterozygous *GCH1* mutations present partial guanosine triphosphate cyclohydrolase I (EC 3.5.4.16) deficiency and develop the autosomal dominant Segawa syndrome (dopa-responsive dystonia); DYT5 dystonia (OMIM 128230) [1,2]. The disease responds well to levodopa therapy, and when dyskinesias are present, are usually present either at initiation of treatment [3,4] or at higher doses and do not lead to functional impairment [5]. We report an atypical phenotype, that of persistent treatment limiting dyskinesias, in a family with prominent brachial dystonia and a novel *GCH1* mutation.

Case reports

We examined two patients and two unaffected related subjects. The ethics committee of University Hospital Reina Sofía approved the study. The neuropsychiatric features of the index case and her mother were previously reported (Family B)[6], as was the phenylalanine loading in the index case (case 14) [7], although at the time of those reports no mutation had been identified. The index case was born to healthy parents and presented with congenital torticollis that resolved completely by one year of age with physical therapy. Her early psychomotor development was normal. She had gait difficulties since the beginning walking at age 15 months, with slight postural instability on turn. From the age of 4 years, mild laterocollis and postural scoliosis were evident. There was diurnal fluctuation including hand tremor and cervical stiffness, which were observed only during the evenings, and walking difficulties that improved after sleep. At the age of 7 years the child had prominent dystonia which was worse on the left than the right and included mild laterocollis and elevation of her right shoulder; diminished bilateral arm swing and right hand dystonic posturing, mild toe-walking, left foot eversion and poor balance. The tendon reflexes were normal and the plantar reflexes were flexor. Response to levodopa/carbidopa was initially good with only mild bilateral diminished arm swing persisting. However, even doses of less than 1 mg/kg per day of levodopa caused dyskinesias- which were characterized by choreic movements of the upper limbs while walking, at rest and with the arms outstretched. The child was then was maintained on 37.5 – 50 mg of l-dopa (1.1 – 1.6 mg/kg in the form of carbidopa/levodopa 25/100) with doses divided qid to decrease dyskinesias.

Evaluation at age 7 years included a normal brain MRI. Phenylalanine loading test [8] was abnormal (Table 1)[7]. Cerebrospinal fluid for biogenic amines and pterins was collected five days after discontinuation of treatment with levodopa and was analysed by high-performance liquid chromatography with electrochemical and fluorescence detection [9] and showed diminished pterin concentrations of both neopterin and biopterin (Table 1) which suggested autosomal dominant guanosine triphosphate cyclohydrolase I deficiency. Homovanilic and 5-hydroxyindoleacetic acids were normal. Although initial genetic studies by single-strand conformation polymorphism analysis and MLPA were negative, guanosine triphosphate cyclohydrolase I enzyme activity, measured in cytokine-stimulated fibroblasts, according to Bonafé et al. [10], showed a reduced activity of 0.39 μU/mg corresponding to 22 % enzyme activity of normal controls. Direct exonic sequencing of *GCH1* uncovered a novel mutation (c.235_240delCTGAGC[p.L79_S80del]) in exon 1 that was not present in 100 unrelated control subjects. The mother, who had intermittent postural tremor in the right arm, as well as right shoulder elevation and diminished right arm swing when walking, also

harboured the mutation and had abnormal phenylalanine loading test (Table 1). The asymptomatic father of the index case had a normal phenylalanine loading test, and the asymptomatic brother did not have the *GCH1* mutation.

Despite persistent l-dopa therapy of 1.1 – 1.4 mg/kg, at the age of 10 years, the patient developed a mild postural tremor of the hands and worsening of her previously mild right arm dystonia, with severe writer's cramp involving hand, forearm, proximal upper arm and limb girdle musculature. An improvement of the task-specific dystonia was achieved by increasing levodopa to 2 mg/kg; however, more than this dose again caused dyskinesias characterized by choreic movements of both upper limbs distally along with the persistence of the disabling writer's cramp. Levodopa was reduced to 1.5 mg/kg and the dopamine agonist pramipexole was added, which only partially improved the symptoms, and was withdrawn after 3 months because of somnolence and irritability. At the age of 12 years, the addition of botulinum toxin injections of wrist and finger flexors to the levodopa dosage of 1.8 mg/kg per day improved the velocity and quality of handwriting lasting four months, when a second injection session was administered. Two months later, trihexiphenidyl was initiated, two and a half years after writer's cramp onset. The dose was increased slowly by 2 mg/2 weeks up to 10 mg/day together with levodopa 75 mg/day (1.6 mg/kg per day). Although the velocity of handwriting and the dystonic spasms improved, the patient experienced drowsiness and for that reason, trihexiphenidyl and levodopa were slowly reduced, to 6 mg per day and to 37.5 mg per day (0.8 mg/kg per day) respectively. She did not require botulinum toxin injection for eight months and she did not suffer from further dyskinesias during this period.

Discussion

The development of a severe writer's cramp as a levodopa-resistant symptom in the presence of dyskinesias even with low doses of levodopa led to treatment challenges in our index case. Classically, it has been reported that patients with dopa-responsive dystonia show an excellent and sustained response to small doses of levodopa without any relationship to the longevity of the clinical course and without unfavourable side effects [3,4]. We have described a similar experience in 14 *GCH1* gene mutation manifesting-carriers detected in our community due to a possible founder effect [11]. Partial or lack of response to levodopa, as well as drug-induced dyskinesias have also been reported [12–16]. While levodopa-induced dyskinesias have been considered a symptom present at initial treatment of l-dopa, or of overdosage, disappearing by reduction of the dosage and slow titration to the optimal doses [4,11,14], lowering the dose in our patient caused re-emergence of postural dystonia and aggravation of action dystonia.

The development of treatment limiting dyskinesias with levodopa has not been, to our knowledge, previously described in dopa-responsive dystonia. The pathophysiologic basis for the dyskinesias is unclear, as dyskinesias are usually attributed to abnormalities in the striatal post-synaptic receptors [17], and most [18–20], but not all [21–23] functional dopaminergic imaging studies suggest preservation of dopaminergic nerve terminals in dopa-responsive dystonia. Although present in dopa-responsive dystonia, dyskinesias are more prominent in *parkin* related dystonia [13], and are often suggested to distinguish dopa-responsive dystonia from other early onset dystonia/parkinsonism syndromes. The proband's course supports that dyskinesias in response to empiric treatment with levodopa may be consistent with diagnosis of dopa-responsive dystonia, and that further diagnostic testing is warranted in these unusual cases.

It is of interest that not only was the writer's cramp apparently refractory, brachial dystonia was the primary feature in both the proband and her mother. In the proband, it is likely that

the dystonia could have persisted because we were unable to obtain a sufficiently high dose due to the limiting dyskinesias. Both familial brachial-predominant dystonia, as well as levodopa resistant writer's cramp have been previously reported [16], yet this is a new mutation, suggesting that these are not effects attributed solely to the genotype in this family. The phenotype in both cases was also notable for sternocleidomastoid hypertrophy ipsilateral to the most prominent limb dystonia. The presence of early toe-walking in the child is commonly seen in doparesponsive dystonia, and in this patient likely correlated with bilateral leg dystonia even though the dystonia was more pronounced on one side.

Segawa disease has been separated into action and postural type dystonia, which reflect symptoms relative to postulated maturation of the basal ganglia [4]. In this classification schema, this family would most likely belong to the action dystonia type of Segawa disease: the mother presented during adulthood with focal dystonia, and there was incomplete response to l-dopa, albeit, as noted above, it is unclear how much the dystonia appeared non-responsive, when we could not achieve an adequately high dose because of dyskinesias.

Pramipexole, a dopamine D3 receptor-preferring agonist, improves the efficacy of levodopa therapy in the treatment of 6-pyruvoyl tetrahydropterin synthase deficiency, [24], and a similar benefit might be expected in other forms of inherited tetrahydrobiopterin deficiency. While our patient did not significantly improve with the addition of pramipexole to levodopa, we cannot exclude that this was due solely to a lack of effect because side-effects at lower doses of pramipexole were noted. Trihexyphenidyl, as expected [4], did improve writer's cramp, and did not induce dyskinesia, but this too, was limited by tolerability. The addition of botulinum toxin injections to the treatment with levodopa resulted in improved handwriting that was sustained for four to eight months.

The identified *GCH1* mutation was likely pathogenic, as amino acids L79 and S80 are located at the end of the alpha-helix 2, forming part of the N-terminal antiparallel helix pair alpha2/alpha3 that is responsible for dimer formation by a four-helix bundle generating the active guanosine triphosphate cyclohydrolase I decamer from two pentamers [25]. Further, using two independent Protein Structure Prediction Servers: APSSP2 (www.imtech.res.in/raghava/apssp2; [26]) and PSIPRED (http://bioinf.cs.ucl.ac.uk/psipred/), two main structural changes: (1) reduction of alpha helix 2, and (2) shortening of the inter-helical space between alpha2 and alpha3 were associated with the predicted protein sequence, and these would be predicted to decrease guanosine triphosphate cyclohydrolase I enzyme activity. Interestingly, although guanosine triphosphate cyclohydrolase I enzyme activity was proved to be low, cerebrospinal fluid homovanilic and 5-hydroxyindoleacetic acids concentrations were normal after 5 days off levodopa. Although there should not be a persistent levodopa effect at this time, we cannot exclude that this is the case. However, it is not clear that this profile explains the propensity to dyskinesias; a similar dissociation between cerebrospinal pterins and homovanilic acid was noted in two symptomatic patients with dopa-responsive dystonia [12] who did not show treatment limiting dyskinesias.

Thus, we both demonstrate a novel mutation that further expands the mutational spectrum of *GCH1* gene associated with dopa-responsive dystonia, and report limiting side effects of levodopa dyskinesias in a child despite being treated early in life. As up to 20% [27] of dopa-responsive dystonia cases do not have mutations, this has implications for diagnostic levodopa trials: the diagnosis of dopa-responsive dystonia should still be considered in cases without an apparent mutation, as should additional testing including either phenylalanine loading, measurement of guanosine triphosphate cyclohydrolase I activity in fibroblasts, and/or cerebrospinal pterins, if there is partial improvement with levodopa, but dose limiting dyskinesias.

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Table 1

Results of cerebrospinal fluid analysis of biogenic amines and pterins, phenylalanine loading test results, enzyme guanosine triphosphate cyclohydrolase I activity and molecular analyses of the family with DYT5 dystonia

	CSF*				Oral Phe loading test Phe/Tyr ratio			Enzyme activity GTPCH in fibroblasts	Molecular diagnosis Sequencing *GCH1*
	5-HIAA (nmol/L)	HVA (nmol/L)	Neopterin (nmol/L)	Biopterin (nmol/L)	1h	2h	4h		
Index case	173	318	3	8	6.6**	5.9**	2.2**	0.39 μU/mg	c.235_240delCTG AGC [p.L79_S80del]
Ref. values (child)	87–366	158–596	9–55	10–52	1.6–5.4	0.9–2.8	0.6–1.5	22 % enzyme activity of normal controls	
Mother					7.7	8.2	2.8		c.235_240delCTG AGC [p.L79_S80del]
Father					5.1	2.6	1.4		Negative
Ref. values (adult)					2–6.3	1.17– 4.15	0.6– 1.88		

CSF = cerebrospinal fluid, Phe = phenylalanine, Tyr = tyrosine, 5-HIAA = 5-hydroxyindoleacetic acid, HVA = homovanilic acid, GTPCH = guanosine triphosphate cyclohydrolase I

*CSF was collected five days after discontinuation of treatment with levodopa.

**Described as patient 14 in the reference by López-Laso et al. [11]