

Short communication

Dopa-responsive infantile hypokinetic rigid syndrome due to dominant guanosine triphosphate cyclohydrolase 1 deficiency

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Abstract

We report on a GTP cyclohydrolase 1 mutation-confirmed heterozygous case presenting with an infantile hypokinetic rigid syndrome and delay in attainment of motor milestones starting from the first year of life. He had a family history of dopa-responsive dystonia-parkinsonism. CSF neopterin, biopterin and HVA values were decreased. Molecular study of GCH-1 gene showed the Q89X mutation in exon 1. Treatment with L-dopa resulted in a complete remission of symptoms.

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1. Introduction

GTP cyclohydrolase 1 (GTPCH) is encoded by the GCH-1 gene, located on chromosome 14q22.1-q22.2. Patients heterozygous for GCH-1 mutations develop dopa-responsive dystonia (DRD) [1]. DRD may be classified into three groups: 1) *autosomal dominant GTPCH deficiency* (adGTPCH); 2) *tyrosine hydroxylase (TH) deficiency*; 3) *other forms of BH4 deficiency* (autosomal recessive GTPCH deficiency, 6-pyruvoyl-tetrahydropterin synthase, dihydropteridine reductase and sepiapterin reductase) [2]. DRD due to adGTPCH deficiency typically presents insidiously between the ages of 1 and 9 years with a diurnally fluctuating dystonia of one limb spreading to the other extremities after several years, together

with subsequent parkinsonian signs in adult ages. Some atypical cases presenting with an isolated parkinsonian state with onset in middle age have been reported [3–8]. Levodopa-responsive infantile hypokinetic rigid syndrome due to mutations in the TH gene has been described [9,10]. Nevertheless, to our knowledge, infantile hypokinetic rigid syndrome due to adGTPCH deficiency has not been previously reported. We describe a case of adGTPCH deficiency who presented with an infantile hypokinetic rigid syndrome and delay in attainment of early motor milestones, thus expanding the clinical spectrum of Segawa disease.

2. Methods

2.1. Neurological examination

Dystonia and parkinsonism were classified according to Nygaard et al. and Uncini et al. [3,7].

Samples from patients were obtained in accordance with the Helsinki Declaration of 1964, as revised in 2000. Informed

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consent for the study was obtained from the adult and adolescent patients themselves and from the parents of the children.

2.2. Biochemical studies

Biogenic amine metabolites (5-hydroxyindoleacetic and homovanilic acids) and pterines (neopterin and biopterin) in cerebrospinal fluid (CSF) were analysed by HPLC with electrochemical and fluorescence detection, as previously reported [11]. Results were compared with the reference ranges established in our laboratory.

2.3. DNA analysis

Genomic DNA was extracted from peripheral blood of patients using standard techniques. Each of the six exons of GCH-1 was amplified by PCR according to Ichinose and colleagues [1]. PCR products were analysed by single-strand conformation polymorphism followed by direct DNA sequencing [12]. DNA sequences were obtained with an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, California, United States).

3. Case report

The patient was born to healthy nonconsanguineous parents after an uneventful pregnancy at term and delivery (birth weight 3.130 g, length 49 cm, head circumference 34 cm). His mental and motor developments were considered normal until the age of 7 months, when a delay in attainment of early motor milestones became evident. At age 17 months he had generalized rigidity and had very little spontaneous movement. He could not sit, crawl, walk or stand by himself and was referred to our department because of a serious delay in motor development. At no time were there writhing movements, tremor or abnormal ocular movements. Symptoms showed a diurnal variation being more prominent in the afternoon and the evening.

The patient had a family history of DRD in the maternal aunt and uncle, and his older brother, who had been completely responsive to L-dopa (Fig. 1). His maternal aunt had a history of progressive gait difficulties due to dystonia since she was 7 years old. His maternal uncle developed a cervical dystonia, namely retrocolis, at the age of 38. His older brother had a history of toe-walking progressing to gait difficulties, beginning at the age of 1 year. No biochemical measurements or DNA analysis to confirm the clinical diagnosis of DRD had been performed previously on any of the family members.

On examination at age 17 months, our patient showed paucity of movement and bradykinesia. Examination of tone revealed rigidity of all limbs, slightly worse in the upper limbs, and trunk hypotonia. Hyperactive reflexes and a pseudo-Babinski sign (striatal-toe) were present. Drooling was marked. An expressionless face was also observed, while other cranial nerves were normal. Cognitive level, sensation and general examination were normal. There were no other rigid akinetic features, and aside from the toe posturing, no evidence of dystonia or spasticity was present. Magnetic resonance imaging scan of the brain was unremarkable.

Biogenic amine metabolite analysis and measurements of pterins in CSF revealed a decrement of HVA (268 nmol/L; reference values 334–906), neopterin (2 nmol/L; reference values 8–43) and biopterin (8 nmol/L; reference values 11–39) strongly suggestive of adGTPCH deficiency. Sequencing of the GCH-1 gene revealed that the patient was heterozygous for mutation Q89X in exon 1.

At age 18 months treatment with 1 mg/kg per day L-dopa combined with carbidopa was started. Within days the patient was less rigid and hypokinetic, and he showed a more vivid facial expression. He was able to walk unsupported at age 20 months. Motor performance did progressively normalize. The current L-dopa dosage is 5.2 mg/kg per day at age 3 years, which has resulted in complete remission of symptoms. There has been no evidence of levodopa-induced dyskinesias or other adverse effects. There is no developmental delay. On examination there are no abnormal findings.

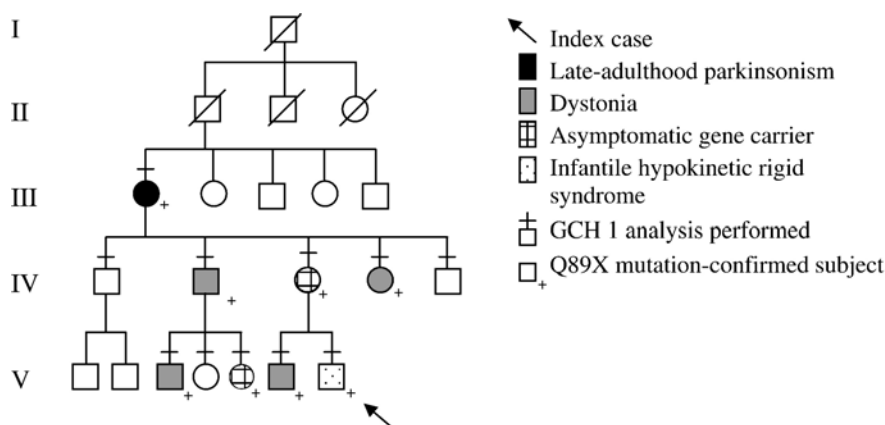


Fig. 1. Pedigree of DRD family: circles denote females, squares designate males, filled symbols are asymptomatic gene carriers or patients affected with dystonia or parkinsonism, open symbols are unaffected, and arrow indicates proband.

Family history and clinical examination revealed DRD in other family members. Seven further GTPCH mutation-confirmed heterozygous subjects were found (Fig. 1). A first cousin of our patient suffered from leg stiffness during exercise with otherwise normal clinical examination, and his grandmother presented an isolated late adulthood-onset parkinsonism not preceded by dystonia, which responded to L-dopa.

4. Discussion

We describe a case of DRD presenting with infantile hypokinetic rigid syndrome and delay in attainment of motor milestones. The patient was heterozygous for the mutation Q89X in exon 1 of GCH-1. This mutation was first described and confirmed with restriction-enzyme digestion by Hoenicka et al. in an unrelated Spanish family from the same region of southern Spain, affected with DRD and parkinsonism and studied in our center [13]. Q89X consists of a 265C to T transition that creates a premature TAA stop codon and abolishes a *Bst*API restriction site. The predicted consequence of Q89X mutation is the lost of 177 C-terminal amino acids in the protein [13]. No other mutations in either the coding region or the splice sites of GCH-1 were found in our patient.

Presentations of DRD with a clinical onset in middle age as isolated parkinsonism have been reported [3–8]. Nygaard et al. reported a family with DRD in which three members developed a parkinsonian syndrome [3]. In another family with DRD reported by the same group, 5 women presented with a hypokinetic rigid syndrome [4]. Harwood et al. described a family with DRD in which some members presented adulthood parkinsonism [5]. Grimes et al. reported one affected member belonging to a family with DRD presenting with parkinsonism [6]. Uncini and colleagues confirmed in 2 subjects that late-adulthood parkinsonism is part of the spectrum of clinical presentation of GCH-1 gene mutations [7]. Tassin and co-workers reported three late-onset cases of DRD with parkinsonism [8].

Postuma et al. described a case of young-onset DRD presenting with an isolated bilateral resting leg tremor from the age of 15 years, with no other features of parkinsonism [14].

Our patient developed a progressive hypokinetic rigid syndrome with diurnal fluctuation completely responsive to L-dopa starting during the first year of life. This strongly suggests that adGTPCH deficiency may present as an infantile hypokinetic rigid syndrome. In families with mutations in exons 1 and 2, the ages at onset tend to be earlier in the younger generation [15]. The ratio of mutant messenger RNA to wild messenger RNA of GCH-1 differs depending on the loci of mutation [15]. This ratio might contribute to enzymatic and clinical variations. The adGTPCH deficiency results in reduced striatal TH [7], and according to the degree of this enzymatic deficiency the clinical presentation might be either as a dystonia or as a

hypokinetic rigid syndrome. Similarly, among TH deficiency cases the residual TH activity seems to determine the variability of the clinical picture: those cases with relatively high residual TH activity present as a dystonia, whereas patients with lower residual activity have a hypokinetic rigid syndrome [9,10].

In conclusion, the diagnosis of adGTPCH deficiency should be considered in any infant presenting with infantile hypokinetic rigid syndrome. As with other presentations of DRD, this clinical picture is completely responsive to L-dopa.

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