JIMD Reports
DOI 10.1007/8904_2011_60

RESEARCH REPORT

Efficacy of Vigabatrin Intervention in a Mild Phenotypic Expression of Succinic Semialdehyde Dehydrogenase Deficiency

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Received: 22 February 2011 / Revised: 11 April 2011 / Accepted: 12 April 2011 / Published online: 6 September 2011

Abstract We report a patient with succinic semialdehyde dehydrogenase deficiency who presented a mild phenotype including developmental language delay, in association with the typical elevations of 4-hydroxybutyric acid (GHB) in biological fluids and MRI alterations. Two pathogenic mutations were identified one transversion (c.278 G>T) in exon 1 and another (c.1557 T>G) in exon 10. Both parents are carriers of one of the mutations, confirming compound-heterozygosity in their affected child. To reduce the GHB levels in body fluids, a treatment with vigabatrin at low dose (25 mg/kg per day) was started, monitoring its efficacy by clinical and neurochemical follow-up. After 9 months of therapy with vigabatrin, a significant reduction of GHB concentrations in urine and CSF was observed; after 36 months, a significant improvement of communicative skills, not previously reported, was referred. These results support the hypothesis that the clinical improvement is correlated to the reduction in the GHB levels and the importance of considering the SSADH deficiency in the differential diagnosis of patients with mental retardation and language delay.

Communicated by: Ertan Mayatepek.

Competing interests: None declared.

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Introduction

Succinic semialdehyde dehydrogenase (SSADH) deficiency (OMIM 271980) is a rare autosomal recessive disorder of the 4-aminobutyric acid (GABA) catabolic pathway. In the absence of SSADH activity, succinic semialdehyde (SSA) is converted into 4-hydroxybutyric acid (GHB) that accumulates in plasma, urine, and cerebrospinal fluid (CSF) and represents the biochemical hallmark of this disorder. Patients are identified by detection of elevated GHB in body fluids and SSADH deficiency confirmed by enzyme assay in lymphocytes (Gibson et al. 1991, 1994, 1998).

The SSADH gene (*ALDH5A1*) has been mapped on chromosome 6p22 (Trettel et al. 1997; Blasi et al. 2002) and multiple different mutations have been identified (Gibson et al. 1997; Gibson and Jakobs 2001; Akaboshi et al. 2003) in approximately 450 patients thus far diagnosed (Jakobs et al. 1981; Kim et al. 2010). The clinical picture of SSADH deficiency is highly heterogeneous, characterized by neurological symptoms including such as varying degrees of mental retardation, seizures, hypotonia, ataxia, and developmental language delay. Other clinical features, including movement disorders, oculomotor apraxia, and nystagmus have been reported (Gibson et al. 1997; Gordon 2004).

The most common abnormalities on MRI consist of increased T2-weighted signal involving the cerebellar dentate nuclei, globus pallidus, and subthalamic nuclei

symmetrically as well as the subcortical white matter and brainstem (Ziyeh et al. 2002; Pearl et al. 2003). Proton spectroscopy has variably revealed elevated levels of GABA and GHB in the white and gray matter (Ethofer et al. 2004; Kim et al. 2010).

Currently, therapeutic intervention in patients with SSADH deficiency has been limited to antiepileptic drugs, mainly vigabatrin (GVG), which irreversibly inhibits GABA transaminase activity penultimate to the SSADH enzyme. The metabolic outcome of this inhibition should yield increased free and total GABA concentration in brain with concomitant reduction of SSA and GHB levels in biological fluids. Therapy with vigabatrin has been tried in a moderate number of patients with good results in some and little efficacy in others (Gibson et al. 1989, 1995; Jaeken et al. 1989; Matern et al. 1996; Gropman 2003; Ergezinger et al. 2003; Leuzzi et al. 2007).

We report an SSADH-deficient patient with a mild phenotype and the follow-up during treatment with vigabatrin, which revealed encouraging results.

Case Report

A 8.2 years old girl, second child of unrelated healthy parents, was admitted in our department at 4.5 years to evaluate idiopathic mental retardation with a severe speech delay. She was born at term after an uneventful pregnancy; APGAR score after 1 and 5 min was 9–10; she weighed 3,040 g and was 50 cm long; OFC was 35.5 cm. There was no family history of epilepsy, motor or psychiatric disorders. Her brother, 16 years old, presented an isolated speech delay but he graduated from high school. The child started to walk alone at 14 months demonstrating mild hypotonia with joint hyperlaxity and insufficient coordination. Her language development showed impressive delays, especially in expressive language with sufficient speech comprehension.

At first examination, the child presented clumsiness and difficulties in execution of oral and ideomotor praxis, severe language deficit with verbal dyspraxia, mild mental retardation and hyperactive behavior. Spontaneous language production was limited to few incomplete words. Verbal expression was integrated with a production of iconic, deictic and some referential gestures.

Karyotype (550 band level) and basal neurometabolic workup (aminoacids, creatine, organic acids) were performed. The organic acids analysis revealed a marked increased excretion of GHB (311 mmol/mol creatine; controls < 5), while the other investigations were normal. EEG showed rare paroxysmal abnormalities; motor-sensitive nerve conduction velocity of the lower limbs was normal.

MRI with proton spectroscopy (^{1}H-MRS), carried out based upon a suspicion of an SSADH deficiency, showed the typical neuroradiological pattern above described. There were abnormalities involving globus pallidus bilaterally and symmetrically, as well as abnormalities of the subcortical white matter and cerebellar dentate nucleus. No significant alterations were detected by ^{1}H-MRS.

SSADH activity in the patient's lymphocytes was strongly decreased (48 pmol/min per mg protein; controls 1,907–3,901 pmol/min per mg protein) confirming the suspected diagnosis.

DNA investigation of the SSADH gene (*ALDH5A1*) performed in the patient and her family identified two pathogenic mutations: a G>T transversion (c.278 G>T) in exon 1, which results in the substitution of cysteine by phenylalanine at position 93 (p.Cys93>Phe); the other a T>G transversion (c.1557 T>G) in exon 10 which results in the replacement of tyrosine by a termination codon at position 519 (p. Tyr519X). Both healthy parents carried one of the mutations, confirming compound-heterozygosity in their affected child; the brother is a carrier of the maternally inherited allele.

The assessment of cognitive abilities was performed using the Leiter International Performance Scales (Leiter 1997, Italian translation 2002). Language evaluation was performed using: the Italian version of the Infant's and Toddler's MacArthur Bates Communication Development Inventories (CDI) (Caselli and Casadio 1995) for productive vocabulary, the Peabody Picture Vocabulary Test (PPVT) for receptive vocabulary (Dunn and Dunn 1997, Italian standardization, Stella et al. 2000) and the Rustioni test (Rustioni 1994) for sentence comprehension. Voluntary oral praxis movements were evaluated on verbal request and on imitation too.

To reduce the GHB levels in body fluids, a treatment with vigabatrin at low dose (25 mg/kg per day) was started, monitoring its efficacy by clinical and neurochemical follow-up. The GHB and aminoacids (AA) levels in CSF and blood were monitored before starting therapy (T0), at T2 (6 months), T4 (12 months), T6 (30 months), and T7 (36 months).; the MRI-MRS was performed at the same times except for the T7 measurement. A more frequent monitoring of urinary concentrations of GHB and AA were performed at T1 (3 months), T2 (6 months), T3 (9 months), T4 (12 months), T5 (18 months), T6 (30 months), and T7 (36 months). To evaluate the possible side effect of irreversible constriction of the visual field under vigabatrin therapy (Gordon 2004), the child underwent periodic ophthalmologic evaluation (fundus oculi and visual field examinations).

Table 1 Laboratory findings during vigabatrin treatment

	T0	T1	T2	T3	T4	T5	T6	T7	Controls
Vigabatrin (mg/kg per day)	None	25	25	25	25	25	25	25	–
GHB urine (mmol/mol creatine)	311	298	95	71	71	51	52	60	< 5
GHB blood (μmol/L)	204	–	170	–	–	–	107	121	< 2
GHB CSF (μmol/L)	357	–	102	–	–	–	60	–	< 2

Results

At T0, GHB levels were markedly increased in urine (311 mmol/mol creatine), blood (204 μmol/L) and CSF (357 μmol/L) (Table 1). After 3 months (T1) of therapy with vigabatrin a mild reduction of GHB concentrations in urine was observed, with a further dramatic fall at T2 and T3; the same decrease was observed in CSF, whereas the levels in blood remained high even after 30 months of treatment.

Aminoacids levels in plasma, urine, and CSF were consistently normal, except for a mild increase in ornithine in the blood at T7.

The MRI abnormalities remained unchanged after more than two years of treatment; the EEG performed during follow-up disclosed sharp waves and spikes upon the central parietal regions, especially on the right hemisphere. Intermittent photic stimulation did not provoke photoparoxysmal response and no epileptic seizures were observed. At T7 the fundus oculi was still normal but a visual field constriction developed in the right eye.

The assessment for language skills performed at T0, T1, T5, and T7 showed a mild improvement in communicative abilities (Table 2). Moreover a more pronounced recovery in the behavior with reduction of hyperactivity and attention deficit was observed, while the cognitive abilities, evaluated at T4 and T7, remained stable.

Table 2 Raw scores obtained with neuropsychological test

	T0	T1	T5	T7
Rustioni test	32.7	47.7	56.4	95
PPVT	38	38	51	72
Oral praxis (on request/on imitation)	8 + 1	8 + 1	8 + 5	9 + 6
MacArthur questionnaire	12[a]	–	38[a]	46[a]

[a] Any level of referential expressions, including syllabes and simplified words

Discussion

SSADH deficiency is an autosomal recessive rare disorder caused by mutations in *ALDH5A1* gene, which maps to chromosome 6p22. Since the first report in 1981 (Jakobs et al. 1981), several other patients have been identified (Ziyeh et al. 2002; Pearl et al. 2003; Gropman 2003; Leuzzi et al. 2007; Di Rosa et al. 2009), showing marked differences between them regarding GHB concentrations in body fluids, residual enzyme activity, clinical symptoms, and efficacy of therapy. Neurological findings are predominant in SSADH deficiency but the clinical picture shows a wide spectrum from mild to severe developmental delay, especially involving the language. Other typical signs and symptoms include axial hypotonia, ataxia, movement disorder such as dystonia or choreoatetosis and epilepsy (Knerr et al. 2007). Psychiatric symptoms may be the most disabling and are manifest by hyperkineticism, inattention and sometimes aggression in early childhood, anxiety, and obsessive–compulsive disorder in adolescence and adulthood (Kim et al. 2010).

The clinical phenotype above reported, in which the mental retardation with prevalent involvement of communicative skills represents the core of the disease, is less severe than the majority of other patients described in the literature. So far the patient has never experienced movement disorders or psychiatric symptoms, despite the presence of the prototypical alterations in the basal ganglia.

In addition, we have performed the neuropsychological profile before and during vigabatrin treatment to better characterize the potential effectiveness of GVG therapy.

The first speech evaluation showed that the child was able to use 12 referential expressions including onomatopoeia and simplified words and to perform only few verbal and nonverbal oral movements. Imitation of oral movements did not bring any quantitative and qualitative improvement. During the treatment the verbal production increased and the child learned new verbal expressions even though referentiality was unstable. After 36 months of GVG therapy, lexical and phrasal comprehension had significantly improved. The vocabulary includes 46 words; some of them are juxtapositions of syllables but are still not fused; however, referentiality is stabilized. Imitation of oral praxis movements has also improved. Table 2 summarizes the raw scores obtained with the communication and cognition testing we employed.

Antiepileptics, mainly vigabatrin, are the most frequently used drugs in the treatment of SSADH deficiency aimed at reducing seizures and behavioral symptoms. The response to treatment varies greatly, as well as the severity of clinical phenotype and the residual SSADH activity in relation to the GHB levels. Moreover, the effects of vigabatrin on GABA transaminase are not entirely predictable, depending on the differences between brain and peripheral forms of the enzyme (Ergezinger et al. 2003). The partial effect on peripheral GABA transaminase would lead to an increase of GABA in the CNS, with the resultant clinical ineffectiveness. This could be one of the mechanisms to explain the lack of clinical response in some patients under vigabatrin therapy. Ergezinger et al. (2003) reported a significant improvement in a patient employing vigabatrin at a low dose (25 mg/kg per day) in parallel with a drop of the levels of GHB in body fluids and suggested that others monitor vigabatrin treatment not only by clinical assessment but also by repeated controls of GHB in body fluids. According to Ergezinger, the GHB concentrations in CSF of our patient decreased by 7 times during treatment with vigabatrin up to 30 months, and less markedly in urine and plasma (Table 1). These results appear to support the hypothesis that the clinical improvement is correlated with the reduction in the GHB levels, although the values remain always above the normal range. Unfortunately, not all patients reported in the literature have been subjected to plasma and/or CSF monitoring of GHB, so such a correlation remains unproven at this time. The mild increase of GHB levels in blood and urine of our patient after 36 months of therapy could be related to a slight reduction of the dose per kilogram per day due to a body weight gain. The clinical improvement of the child, after a static course period and speech therapy, and the absence of the onset of other neurological symptoms of the disease can be ascribed to the vigabatrin effect. The 3-year period may be still too short to clarify whether our patient truly benefits from vigabatrin the long run, although there is no doubt that the reduced levels of GHB depend on the therapy, which may have influenced the course of the disease.

After 36 months of treatment, biochemical analyses revealed higher levels of blood ornithine (102 μmol/L; 37–96 μmol/L n.v.) than at T0 (57 μmol/L) or in all previous examinations. The visual field constriction was observed for the first time at the final examination, coincident with the ornithine increase, seems to suggest a correlation between these observations. Recently, it has been suggested that increase of ornithine levels might be involved in vigabatrin-associated visual field defects (Roubertie et al. 1998; Sorri et al. 2010) as a result of ornithine-δ-aminotransferase (OAT) impairment. In some patients with gyrate atrophy, vitamin B6 substitution has been successfully employed to prevent the loss of vision (Wang et al. 2000; Ohkubo et al. 2005; Sorri et al. 2010). In line with this observation, and in order to prevent a worsening of the visual defect, we implemented a pyridoxine supplementation (300 mg/day) in conjunction with the same dosage of vigabatrin.

To the best of our knowledge, no other patients with an identical genotype as our have been described in the literature. The p.Cys93Phe mutation has been identified in several patients with SSADH deficiency; overexpression of the p.Cys93Phe allele in mammalian cells results in 3% SSADH activity as compared to overexpression of wild-type SSADH (Akaboshi et al. 2003). Therefore, the mutation should be considered pathogenic. The p.Tyr519X mutation results in a premature stop and may be subjected to nonsense mediated decay; it has not been reported before, but should be considered pathogenic due to the nature of the mutation. Both mutations were not detected in 210 control chromosomes.

In conclusion, we suggest that SSADH deficiency should be considered in the differential diagnosis of patients with mental retardation and language delay, and we confirm the clinical efficacy of vigabatrin treatment. However, careful monitoring of the visual field over time, together with measurement of ornithine plasma concentrations, should be considered to prevent the vigabatrin ocular toxicity and to evaluate the effectiveness of vitamin B6 supplementation.

Take-Home Message

SSADH deficiency should be considered in the differential diagnosis of patients with mental retardation and language delay; we confirm the clinical efficacy of vigabatrin treatment.

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