A case report of 'variant' biochemical phenotype of Niemann-Pick C disease and a discussion of therapeutic options

Przypadek tzw. wariantu choroby Niemanna-Picka typu C i omówienie propozycji terapeutycznych

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Abstract

Niemann-Pick disease type C is a rare hereditary disorder caused by mutation-disrupted metabolism of cholesterol and low-density lipoprotein (LDL). In most patients, symptoms begin in childhood with severe clinical progression. We present a patient with heterozygote mutations 3001A>G and 3019C>G with late onset of the disease and positive response to treatment with miglustat. Behaviour and educational problems in childhood were probably related to the disease diagnosed later.

Key words: Niemann-Pick type C, heterozygote mutation, miglustat.

Streszczenie

Choroba Niemanna-Picka typu C jest rzadkim schorzeniem dziedziczonym autosomalnie recesywnie, spowodowanym zaburzeniem metabolizmu i transportu cholesterolu i LDL. Zachorowanie w większości przypadków dotyczy okresu dziecięcego i ma ciężki przebieg kliniczny. W artykule przedstawiono przypadek pacjenta z potwierdzoną złożoną mutacją 3001A>G i 3019C>G o późnym początku wystąpienia zaburzeń neurologicznych i korzystną odpowiedzią na leczenie miglustatem. Zaburzenia zachowania w wieku dziecięcym i trudności w nauce są najprawdopodobniej związane przyczynowo z później zdiagnozowaną chorobą.

Słowa kluczowe: choroba Niemanna-Picka typu C, mutacja złożona, miglustat.

Introduction

Niemann-Pick disease type C (NPC) is a rare hereditary disease transmitted as an autosomal recessive trait. Its incidence in the European population is estimated at 1 in 150 000 live births. More than 95% of patients with NPC harbor mutations in the *NPC1* gene on chromosome 18q11. Others have mutations in the *NPC2* gene on chromosome 14q24.3. Accumulation of non-esterified cholesterol, gangliosides and other glycolipids in lysosomes and endosomes is a biochemical hallmark of the disease [1-4]. Neurons and visceral organs (liver and spleen) are the main site of the lipid accumulation. The diagnosis may be difficult in patients with late onset (over 15 years of age) due to a low prevalence and variable clinical syndromes. Psychiatric symptoms, extrapyramidal syndromes and dementia dominate in the clinical picture of the late-onset cases.

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A 'variant form' of the disease with low accumulation of cholesterol in cultured fibroblasts is more common in adult cases, while the 'classical form' dominates among childhood and adolescence [3,5].

Case report

The patient, a 21-year-old male, was admitted to the Department of Neurology due to progressive ataxia recognized at the age of 18. In childhood, the patient was suspected of suffering from temporal epilepsy but that diagnosis was not confirmed. Then, activities of lysosomal enzymes measured in leucocytes were in the normal range. He also expressed aggressive and antisocial behaviour at school. He completed secondary school education. Progressive intellectual decline has been observed for the last three years (in annual Wechsler's test examinations scores of 80, 69 and 59, respectively). Family history did not reveal any neurological or psychiatric conditions.

During the first hospitalization in our department, his neurological examination revealed lower limb ataxia and speech ataxia. Decline in non-routine activities and avoidance of interpersonal relations were also observed. Psychological examination revealed mild cognitive impairment measured by WAIS-R/PL test (IQ verbal score was 68, non-verbal – 54; total – 59). Cube test and digit symbols indicated visuospatial disability. The patient also had impairment of abstract thinking and executive functions, and misunderstanding of social situations. Generally, the cognitive deficit resembles mixed cortical and subcortical pattern. The same test performed two years later showed no deterioration.

During multiple admissions to the hospital, spinocerebellar ataxias (SCA) 1, 2, 3, 6, 7 and 8, Friedreich disease, and vitamin E deficiency were excluded. Two years later, progression of the cerebellar and psychoorganic syndrome was noticed. At that time, the patient also suffered from two complex partial seizures that progressed to secondarily generalized seizures. Seizures were treated effectively with sodium valproate (600 mg/daily) for 5 months and then the treatment was discontinued possibly due to a lack of seizures.

Magnetic resonance imaging showed only mild cerebellar atrophy. Abdomen ultrasonography revealed hepatosplenomegaly. Lipidogram showed increased concentrations of total cholesterol (219 mg%) and triglycerides (275 mg%). Diagnostic tests excluded the following diseases: Huntington disease, Wilson disease, dentatorubral-pallidoluysian atrophy (DRPLA), spinocerebellar ataxia type 17 (SCA 17), metachromatic leukodystrophy, gangliosidoses GM1 and GM2, and Niemann-Pick disease type B. Increased chitotriosidase activity in the serum, tested three times ($>$ 525 nmol/ml/h, control $<$ 150 nmol/ml/h), combined with increased activity of sphingomyelinase in leucocytes (Table 1) and mild accumulation of free cholesterol in only a few of the cultured fibroblasts, suggested a diagnosis of NPC. That diagnosis was confirmed by molecular analysis. Two mutations in exon 20 of the *NPC1* gene (c.3001A>G and c.3019C>G) were found in the region coding for a cysteine-rich loop. In healthy parents and the younger brother, enzymatic tests and DNA test had not been performed.

Treatment with simvastatin (20 mg/daily), and ezetimibe (10 mg/daily) was ineffective in terms of progressive neurological and mental dysfunction [6]. The latter treatment was discontinued after publication of negative results in a clinical trial with ezetimibe performed in NPC patients. Finally, we recommended vitamin E and a low-cholesterol diet.

In February 2009, miglustat was introduced at 300 mg daily. Improvement of coordination movements, gait, dysphagia, speech and normalization of mood

Table 1. Lysosomal enzyme activity in leucocytes

Enzyme	Activity	Units	Mean control values
Arylsulfatase A (37°C)	136	nmol/mg protein/hour	105 ± 30
α-Galactosidase	17	nmol/mg protein/hour	10 ± 2.5
β-Galactosidase	185	nmol/mg protein/hour	166 ± 99
Total β-glucosaminidase	905	nmol/mg protein/hour	665 ± 239
β-Glucosaminidase, % of the thermostable form	56	%	52 ± 8
α-Mannosidase	41	nmol/mg protein/hour	63 ± 35
Sphingomyelinase	279	nmol/mg protein/18 hours	70-108

disorders were observed. The rate of improvement fluctuated from day to day. One-month suspension of the treatment with miglustat brought about deterioration of cerebellar syndrome, loss of clinical fluctuation, repetitive falls, and apathy.

The most recent neurological examination revealed cerebellar syndrome with ataxic speech and gait, brisk tendon reflexes without pyramidal signs, and for the first time, mild periodic vertical oculomotor apraxia. The patient was cooperative, active and cheerful.

Discussion

Patients with late onset ataxia are often a diagnostic challenge. The patient described here was eventually diagnosed with NPC. NPC can develop at any age but late onset forms with clinically predominant ataxia are rather rare. Some clinical features can help in the diagnostic process: learning problems, psychiatric disorders (visual hallucinations, delusions and aggressive behaviour), gaze palsy, epilepsy, history of liver disease and splenomegaly, late onset ataxia and dystonia [5,7,8]. In our case, the patient lacked typical signs of NPC such as major psychiatric disorders or epilepsy at onset of the disease and, until the latest examination, there were no signs of gaze palsy. On the other hand, he suffered from learning problems, ataxia and hepatosplenomegaly. In our opinion, NPC should be taken into consideration in differential diagnosis in patients with late onset ataxia, especially with splenomegaly. Increased chitotriosidase activity may suggest, as in our patient, that a genetic test for *NPC* gene mutations is necessary [9,10]. To date neuroimaging findings play only a supplementary role in the diagnostic process [11,12].

Mutation c.3019C>G [P1007A] in the *NPC1* gene identified in a heterozygous state in our patient was described for the first time by Greer *et al.* in 1999. Since then, it has been found to be one of the most frequent mutations in late onset and variant cases of NPC1 [13]. The second mutation found in our patient is c.3001A>G [M1001V], a novel mutation. Both mutations result in amino acid substitutions located in the cysteine-rich luminal loop of the NPC1 protein, which serves as a signal target for lysosomes.

Treatment for NPC is currently under investigation, with many substances being scanned for potential beneficial results. Due to the dysfunction of cholesterol metabolism, statins were tried as one of the first therapies, but showed no benefit [14]. Significant but small improvement slowing down the dynamics of progression was found in Npc1–/– mice after treatment with tamoxifen and vitamin E [15]. Tamoxifen has multiple metabolic effects, among others on ceramide glycosylation. It also reduces oxidative stress damage. The latter is also obtained with vitamin E. Another substance which was proven effective in the treatment of NPC mice was allopregnanolone, which delayed the demyelination processes and prolonged survival [16,17], delayed cholesterol accumulation, reduced autophagic/lysosomal dysfunction and inflammation processes, and also enhanced myelination [18]. Another trial using anti-inflammatory therapy was also proven beneficial in mice [19]. Another substance tried was imatinib, a c-Ab-specific inhibitor used in treatment of certain types of leukemia, and was found to block cerebellar apoptosis and improve neurological symptoms in a mouse model of NPC [20,21]. Activation of pregnane X receptor (PXR) and a liver X receptor agonist also slowed neurodegeneration and increased the lifespan of NPC1 mice [22,23]. Neural stem cells implanted in NPC1 mice also showed benefit [24]. Trials of gene therapy in animals to inhibit cyclin-dependent kinase 5 reduced the number of axonal spheroids, delayed the death of Purkinje cells and significantly attenuated the hyperphosphorylation of tau proteins [25]. These animal studies show that improvement can be achieved using many different approaches at a metabolic level.

So far, only one randomized controlled study in humans has been published showing effects of treatment of NPC disease with miglustat [26]. Miglustat is an iminosugar that reversibly inhibits glucosylceramide synthase, which catalyses the first step of glycosphingolipid synthesis. Miglustat was originally approved for treatment of another lysosomal storage disorder – Gaucher disease. In this trial, 29 patients aged 12 years or older were randomized to receive either miglustat 200 mg three times a day or standard treatment. The primary endpoint of that study was horizontal saccadic eye movement (HSEM) velocity, which corresponded with disease progression. At the observation after 12 months, miglustat showed improvement or stabilization of HSEM. That result suggested that ganglioside accumulation was partially responsible for the neurological symptoms in NPC patients [27]. Another possible option to treat NPC1 is ganaxolone, a GABA-A agonist and a derivative of pregnenolone, currently being tested in clinical trials as an antiepileptic drug with clinical efficacy and mild side effects [28].

Recent reports show that the role of NPC1 protein is more complex than just the control of lipid metabo-

lism. It may also regulate copper metabolism and vitamin E status, suppress oxidative stress, and even participate in Alzheimer disease pathology [29-32].

Disclosure

Authors report no conflict of interest.

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