Title page

Complete recovery from psychosis upon miglustat treatment in a juvenile Niemann-Pick C patient

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Running head: Miglustat reverses psychosis in Niemann-Pick C

Abstract

Niemann-Pick disease type C is a rare lipid trafficking disorder characterized by the accumulation of cholesterol and glycosphingolipids in the brain and viscera. Perinatal, early infantile, late infantile, juvenile and adult forms are distinguished based on the age of manifestation. In the juvenile form, patients in their early years are usually, but not always, symptom free but present with neurodegeneration later in their lives. These include clumsiness, ataxia, seizures, motor and intellectual decline. Psychiatric manifestations may occur at any stage of the disease. These manifestations include schizophrenia, presenile dementia, depression or psychosis. In 2009, miglustat was approved for the therapy of the disease. We present a case of a patient with juvenile Niemann-Pick C whose psychosis was reversed, completely, by miglustat treatment. Based on our clinical experience we encourage the introduction of misgulustat in Niemann-Pick C patients even in the most advanced cases, with respect to psychiatric illness.

Keywords: Niemann-Pick C, miglustat, psychosis, cerebral atrophy.

Introduction

Niemann-Pick disease type C (NPC, OMIM 257220) is a rare lysosomal storage disease characterized by a defect in lipid trafficking within organelles. This is primarily due to the impaired functions of the NPC1 or NCP2 proteins. Several types of lipids including unesterified free cholesterol, sphingosine, sphingomyelin, phospholipids and glycosphingolipids accumulate in the lysosomes and late endosomes,[1] resulting in organomegaly, impaired liver function and progressive neurological damage. Neurological symptoms may include psychomotor retardation, clumsiness, ataxia, dysphagia, dysarthria, presenile dementia and vertical supranuclear gaze palsy. Psychiatric manifestations are often reported in adolescent and adult patients.[2] In general, the age of onset of neurological signs inversely correlates with progression rates. In the juvenile and adult onset forms, psychomotor development is usually normal in the early ages, but a gradual loss of previously acquired skills may suggest the underlying neurometabolic disease. It seems that visceral symptoms decrease and neuropsychiatric symptoms emerge with advancing age.[3] There is no causative therapy for NPC – slowing disease progression is the most promising option. In 2009, miglustat (Zavesca, Actelion Pharmaceuticals, Allschwil, Switzerland) was approved by European Union countries as the only specific therapy of the disease. The mechanism of action includes the inhibition of glycosphingolipid synthesis, thus reducing the accumulation of storage material in NPC1 deficient cells, resulting in partial improvement or stabilization of neurological symptoms. The latest guidelines recommend the initiation of miglustat following the appearance of neurological symptoms.[4] However, the extreme heterogeneity of the disease, the subtle clinical symptoms may hinder its recognition and severely delay the initiation of adequate therapy. Several cases presenting with psychosis and schizophrenia-like symptoms remain undetected.[5] In this paper, the authors present a case of a young adult patient with juvenile onset NPC who suffered from a severe psychotic episode but fully recovered following miglustat therapy.

Case Study

Patient (male) was born from unrelated, healthy Caucasian parents. He has a healthy older sister. The perinatal and infantile period was uneventful. No prolonged neonatal jaundice was noted. Psychomotor development was normal until adolescence, although attention deficit and delayed reactions to environmental stimuli was reported since preschool age. Involuntary torsion-like movements of the arms were first noted at 10 years of age but were misjudged as a bad habit or tick. At age 14, a consultation with a pediatric neurologist took place due to symptoms such as slurred speech and coordination problems. The parents reported frequent falls and loss of balance. On physical examination, slight swaying to the right in Romberg's test and right deviation of the tongue was described. Audiological examination revealed central hypacusis at high frequencies. Brain MRI was normal. Later, dyslexia and dysgraphia developed, but the patient fulfilled the normal curriculum with satisfactory grades until he was 17 years old. A pediatric psychologist estimated his intellect to be normal, with verbal performance in the average range and motor performance slightly below average. Fine motor skills started to decline more rapidly at age 17, and dysphagia developed. A repeated neurological examination disclosed mild central facial paresis, diminished pharyngeal reflexes, dysarthria, subjective dysphagia, mild cerebellar ataxia, dystonia of the hands and fingers and vertical supranuclear gaze palsy when looking downwards. The possibility of a neurodegenerative disease was raised, but a repeated MRI showed no abnormality (Fig. A). However, brain-stem auditory evoked potentials signalled diffuse brain stem dysfunction. Abdominal ultrasonography showed isolated splenomegaly, the estimated volume of the spleen was 440 mL, which, together with the vertical supranuclear gaze palsy and the gradual decline of motor skills suggested Niemann-Pick C disease. A bone marrow biopsy was performed and confirmed the presence of CD68 positive foamy macrophages, also staining positive with Oil Red O. Fibroblast filipin staining was performed at the Mayo Clinic, Rochester, MN, USA according to standard protocol but it could not confirm and neither rule out NPC, cholesterol esterification rate was 17% of the normal control but higher than in control NPC-deficient fibroblasts. For mutation analysis, NPC1 exons were individually amplified and sequenced. Compound heterozygous missense mutations in the NPC1 gene were found: c.3019 C>G mutation in exon 20 (p. Pro1007Ala), and c.3182 T>C in exon 21 (p. Ile1061Thr) resulting in the genotype of [c.3019 C>G] + [c.3182 T>C] (Fig. D). Both mutations were described previously in the literature, their pathogenicity is proven.[6,7] Testing

of the parents' sample revealed that the c.3019 C>G mutation was inherited from the mother while the c.3182 T>C mutation from the father. At age 20.5 years remarkable cognitive and behavioral changes occurred: visual hallucinations, paranoid thoughts and distortion of the reality caused the parents to seek medical help for their child. He lost ability of spatial orientation and reacted inadequately in everyday situations. Attention span was reduced. MMSE was 30/23 suggesting dementia and cognitive decline. Over the next four weeks, persecutory delusions, sleep disturbance, anxiety, bizarre paranoid doxasmas developed, for which psychiatric inpatient care was needed. Olanzapine 10mg/die and clonazepam 2mg/die (0.5-0.5-1mg) were introduced. Brain MRI at this time showed moderate degree diffuse cerebral atrophy (Fig. B). IQ could not be measured because of incoherent thinking. After two weeks of ineffectiveness, the dose of olanzapine was increased to 20mg/die, the maximum adult dose, and that of clonazepam was reduced to 0.5mg/die. Seeing no improvement of symptoms after another two weeks of modified therapy, both drugs were gradually omitted and fisrt-generation haloperidol (3x1.5mg) was introduced. This resulted in little partial improvement, but with respect to his best achievable status, the patient was exmitted from hospital (10 weeks from the onset of psychotic symptoms). Haloperidol was maintained in a dose of 2x2.5mg/die. However, only 5 weeks later a dystonic crisis appeared, and haloperidol had to me omitted. We tried aripiprazole, another first-generation antipsychotic known to provoke fewer extrapyramidal side effects, yet the movement disorder was so severe that aripiprazole could not be continued. The dystonic storm was successfully treated with intravenous diazepam and biperiden, carbamazepine suppository and oral baclofen. Right after the approval of the drug in Hungary (six weeks from the onset of psychotic symptoms), miglustat was introduced in a dose of 3x200 mg per day, and was given strictly troughout the course of the psychotic disease independent from other medications. Its side effect was temporary diarrhoea resolving spontaneously after six months of therapy. Three months after the initiation of miglustat and two weeks after cessation of all antipsychotics from necessity in a non-symptom-free psychiatric status, psychotic symptoms gradually resolved and did not recur ever since. Brain MRI performed at age 22 and also at 23 years showed no progression of cerebral atrophy (Fig. C). At age 23 years, after 3 years of follow-up, the patient had an overall IQ of 79, certain skills were more severely affected than others: verbal intelligence was in average range (VQ=92), performance intelligence reflected mild mental subnormality (PQ=68). MMSE is 30/26. He recognized social and moral norms above average level, logical thinking, reasoning, mathematical skills and visuomotor coordination were severely impaired.

At present, by age 24 years, this fairly good psychomotor status is still preserved. He requires round the clock supervision by his parents but remained ambulatory, capable of self-care and does sports on an everyday basis. No signs of psychosis has reappeared in the past 4 years.

Discussion

Neuropsychiatric manifestations of Niemann-Pick C disease may occur at any stage of the disease and are most likely to define clinical outcome over other symptoms. Apart from early dementia and cognitive decline, schizophrenia, depression or psychosis are often reported, especially in adolescent and adult patients.[2] Recently, an NPC suspicion index was developed to help professionals enhance the early recognition of the disease.[8] Reducing time interval between the onset of symtoms and the definitive diagnosis appears to be of paramount importance. Emerging treatments should be more efficient at the visceral or cognitive/psychiatric stages of the disease, before the occurrence of widespread deep brain neurological lesions.[9,10] In 2009, miglustat was approved as the only specific therapy of NPC and was found to achieve stabilization or partial improvement of neurological symptoms. According to the recommendations of the NPC Guidelines Working Group, patients without neurological manifestations should not receive miglustat as some can remain asymptomatic for a considerable period of time. In cases where severe neurological impairment is already present at the time of diagnosis, particularly in very young patients, miglustat is less likely to provide substantial therapeutic benefits.[11] To date, a number of clinical research focus on the beneficial therapeutic effect of miglustat upon the neurological manifestations of the disease, but only a few deal with its favourable influence upon psychiatric symptoms, social behaviour and quality of life from the patients' and caregivers' perspectives.[5] Here we presented a case of a patient with juvenile-onset NPC who suffered from a severe psychotic episode that resisted to all administered antipsychotic medications but was ameliorated by miglustat within three months, and a fairly good quality of life was regained. Our conviction that miglustat is responsible for such an improvement of psychiatric symptoms is supported by the observation that improvement occurred when no conventional antipsychotics could be given due to severe dystonia and miglustat was the only medication the patient received apart from oral anticholinergic pyridostigmin as long as the dystonic crisis lasted, and that psychotic symptoms have not recurred in 3 years of follow up. We also aim to point out that vertical supranuclear gaze palsy, isolated splenomegaly, bulbar signs and gradual psychomotor decline of a previously symptom-free young patient were key features suggesting Niemann-Pick C, and providing a basis for clinical and molecular diagnosis. In patients where psychiatric symptoms occur earlier than the knowledge of the underlying metabolic disease is gained, there is a greater chance that physicians focus on treating the mental illness and miss

important signal signs that could indicate its organic origin and direct health care professionals to initiate a specific – although not curative – therapy. Based on our clinical experience we suggest a careful revision of the anamnesis and checking for vertical supranuclear gaze palsy and bulbar symptoms such as difficulties in swallowing and articulation in all patients with schizophrenia and psychosis, and encourage the introduction of miglustat to NPC patients even in a more advanced stage of psychiatric illness.

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Conflict of interest and financial disclosure

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Figure legend

T2 weighted axial images performed at age 17 (A), 20.5 (B), and 23 (C) years. At age 17 no signs of atrophy can be detected, while moderate degree atrophy developed between ages 17-20.5 years (A and B). Between ages 20.5 and 23, closely from the introduction of miglustat therapy, atrophy showed no progress. Electropherogram of patient showing compound heterozygote mutations c.3019 C>G in exon 20, (p. P1007A), and c.3182 T>C in exon 21 (p. I1061T) (D).