Case study

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

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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, pre-senile 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 disease whose psychosis was reversed completely by miglustat treatment. Based on our clinical experience we suggest considering Niemann–Pick C in cases of therapy-resistant psychosis and encourage the introduction of miglustat in Niemann–Pick C patients even in the most advanced cases, with respect to psychiatric illness.

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1. 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, 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. In general, the age of onset 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 cognitive and behavioural changes occurred: visual hallucinations, paranoid thoughts and distortion of the reality caused the parents to seek medical help for their child. He lost his 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 10 mg/die and clonazepam 2 mg/die were introduced. Brain MRI at this time showed moderate degree diffuse cerebro atrophy (Fig. 1B). IQ could not be measured because of incoherent thinking. After two weeks of ineffectiveness, the dose of olanzapine was increased to 20 mg/die, the maximum adult dose, and that of clonazepam was reduced to 0.5 mg/die. Seeing no improvement of symptoms after another two weeks of modified therapy, both drugs were gradually omitted and first-generation haloperidol 3 × 1.5 mg was introduced. This resulted in little partial improvement, but with respect to his best achievable status, the patient was emitted from hospital (10 weeks from the onset of psychotic symptoms). Haloperidol was maintained in a dose of 2 × 0.75 mg/die. However, only 5 weeks later a dystonic crisis appeared, and haloperidol had to be omitted. We tried aripiprazole (15 mg/die), another first-generation antipsychotic known to provoke fewer extra pyramidal 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 3 × 200 mg per day, and was given strictly throughout 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. 1C). 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, aged 24 years, the above mentioned fairly good psychomotor status is still preserved. The patient 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 have reappeared in the past 3 years.

3. 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. Recently, an NPC suspicion index was developed to help professionals enhance the early recognition of the disease. Reducing time interval between the onset of symptoms 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. 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. To date, a number of clinical research papers have reappeared in the past 3 years.

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. 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 a favourable change in the mental status of the patient is supported by the observations that 1) no significant improvement could be achieved with antipsychotic medications, 2) 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 3) 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 disease, thus 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 in NPC patients even in a more advanced stage of psychiatric illness.

Conflict of interest and financial disclosure

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