Niemann-Pick Disease Type C Initially Misdiagnosed as Gaucher Disease in a 6 Year Old Kazakh Girl

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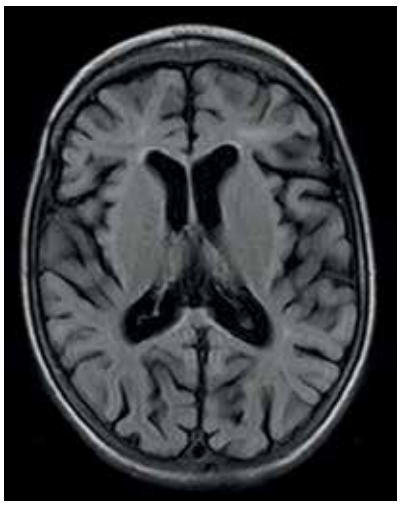
A girl aged 4 years 9 months was referred to the National Research Center for Maternal and Child Health in Astana, Kazakhstan in July 2015 because of seizures, gaze paralysis, hypotonia, intellectual development deterioration and splenomegaly. This patient had been healthy until the age of 2.5 years when she started to exhibit sloppy poor speech, gaze paralysis, ataxia, recurrent falls on her back, and loss of skills.

When she was 4 years old a provisional diagnosis of Lennox-Gastaut syndrome with atonic drop seizures was made. However, the finding of splenomegaly (11.5 x 4.7 cm) in addition to the neurological symptoms modified the initial clinical impression and suggested an underlying enzymatic disease. Niemann-Pick type A/B was ruled out as the acid sphingomyelinase activity was normal (282 pmol/spot x 20 hr; normal range 200–3500). A bone marrow aspiration showed numerous cells with eccentric nuclei, abundant bluish, fibrillary cytoplasm suggestive of Gaucher cells. Beta-glucosidase levels were 119 pmol/spot x 20 hr (normal range 200–2000) and even though molecular genetic testing failed to show characteristic mutations, a diagnosis of Gaucher type 3 disease was made. In February 2016 the patient therefore started treatment with imiglucerase 60 units/kg every 2 weeks and was discharged home.

Six months later a new neurological examination revealed inability to talk or produce any sound, lack of emotions, myoclonic-astatic and propulsive seizures, dystonia, hypotonia, cataplexy, somnolence, upward gaze paralysis and ataxia. Hypersalivation, dysphagia, hyperreflexia, clonus and positive plantar reflex (Babinski sign) were also noted.

A cerebrospinal fluid exam did not show any abnormality while a magnetic resonance imaging scan revealed diffuse brain atrophy, particularly in the frontal lobes [Figure 1]. Electroencephalography showed spike-waves from the left temporal lobe and slow basic activity. The clear failure to respond to the enzyme replacement therapy led us to question the diagnosis of Gaucher disease type 3.

Figure 1. Magnetic resonance imaging scan showing diffuse brain atrophy, particularly in the frontal lobes



A repeated bone marrow aspiration confirmed the presence of numerous cells with eccentric nuclei and abundant foamy cytoplasm while a new blood enzymatic analysis showed high lyso-sphingomyelin-509 (2.4 ng/ml, normal ≤ 0.9) with normal lyso-sphingomyelin-65. Two heterozygous mutations were found in the *NPC1* gene, the first located in intron 9, c.1554-1009G>A and the second in exon 18, c.2728G>A (p.Gly910Ser). Therefore, a diagnosis of Niemann-Pick disease type C (C1) was made and the treatment with imiglucerase was stopped.

Niemann-Pick disease type C is an autosomal recessive condition caused by mutations in the *NPC1* (95%) or *NPC2* (5%) gene and characterized by abnormalities of the intracellular transport of endocytosed cholesterol, with sequestration of unesterified cholesterol in lysosomes and late endosomes [1]. This rare condition (estimated minimal incidence of 1/120,000 live births) leads to progressive, irreversible, disabling neurological manifestations and premature death [2].

Our patient's clinical presentation with gaze palsy, seizures, hypotonia, ataxia and splenomegaly was compatible with both Gaucher disease type 3 and Neumann-Pick disease type C. Unfortunately the specific test to diagnose Niemann-Pick disease type C was not included in the initial panel of enzymatic analyses and the diagnosis was initially missed. This case confirms that Niemann-Pick disease type C can be misdiagnosed as Gaucher disease type 3 [3,4]. We suggest that enzymatic analyses for both diseases be conducted when Gaucher's cells are found in the

bone marrow and beta-glucosidase levels are low [3].

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“The force which makes for war does not derive its strength from the interested motives of evil men; it derives its strength from the disinterested motives of good men”

Sir Ralph Norman Angel (1872-1967), English lecturer, journalist, author, and Member of Parliament for the Labour Party. He was knighted in 1931 and awarded the Nobel Peace Prize in 1933