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Case Report

Neurocognitive assessments and long-term outcome in an adult with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency

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ABSTRACT

Background: 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBDD) is a rare X-linked disorder associated with the accumulation of 2-methyl-3-hydroxybutyric acid in body fluids as a consequence of a disruption in isoleucine metabolism. The clinical presentation is heterogeneous, including a neurodegenerative course with retinopathy and cardiomyopathy leading to death in early childhood and a slowly progressive disease associated with learning disability and survival into adulthood. The condition is often diagnosed in childhood.

Results: This paper outlines the long-term neurocognitive outcomes in a 38-year old man with MHBDD. Several psychometric tests were used to assess his cognitive ability and adaptive functioning in childhood during an acute illness and in adulthood when the patient showed deterioration in the ability to walk or speak.

Conclusions: There is an increasing demand for an accurate and objective measure of cognitive functioning that can be used to follow the natural progression of MHBDD. Psychological assessment may enable the identification of organic problems. The application and interpretation of psychometric tests used in children may vary from those used in adults.

1. Background

2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency (MHBDD) is a rare X-linked disorder associated with the accumulation of 2-methyl-3-hydroxybutyric acid in body fluids due to abnormal activity of MHBDD which is involved in isoleucine degradation [1]. Degradation of the branched-chain amino acid isoleucine in humans takes place in mitochondria via the concerted action of a series of enzymes, during which isoleucine first undergoes transamination to 2-keto-3-methylbutyrate, followed by oxidative decarboxylation to 2-methylbutyryl-CoA [2].

Almost 30 patients with MHBDD have been reported worldwide. To date, seven pathogenic variants in *HADH2* have been reported to result in MHBDD. Among missense pathogenic variants, p.Arg130Cys is the most common [2–5].

The classical infantile form of MHBDD disease is characterized by a progressive neurodegenerative course with retinopathy and cardiomyopathy, leading to death at the age of 2–4 years or later [6]. Clinical presentation, however, can be very heterogeneous [7], ranging from diarrhoea, vomiting, lethargy, disturbance of consciousness, dyspnea and metabolic acidosis during acute illness, to slow neurocognitive decline in adulthood [5, 8]. Some patients may present with developmental delay or neurologic problems without regression and patients without neurologic regression during youth may develop neurologic problems and/or other symptoms later in life. Indeed Lorea et al. (2015) reported a patient who had a *HADH2* p.Ala158Val variant and developed Parkinsonism at the age of 27 years [9].

Most patients with MHBDD described so far presented in childhood; in a few cases diagnosis was not established until adulthood [9, 10]. This paper presents the long-term neurocognitive outcomes in an adult patient affected with MHBDD.

2. Results (CASE)

A 23-year old man was biochemically diagnosed with juvenile MHBDD, as described previously by Olpin et al. [10]. Ten years later, sequence analysis of *HADH2* led to identification of a novel, likely

Abbreviations: MHBDD-2, Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency; IMD, Inherited Metabolic Diseases; ABAS, Adaptive Behaviour Assessment System; WISC, Wechsler Intelligence Scale for Children; WAIS, Wechsler Adult Intelligence Scale; TONI, The Test of Nonverbal Intelligence; IQ, Intelligence Quotient

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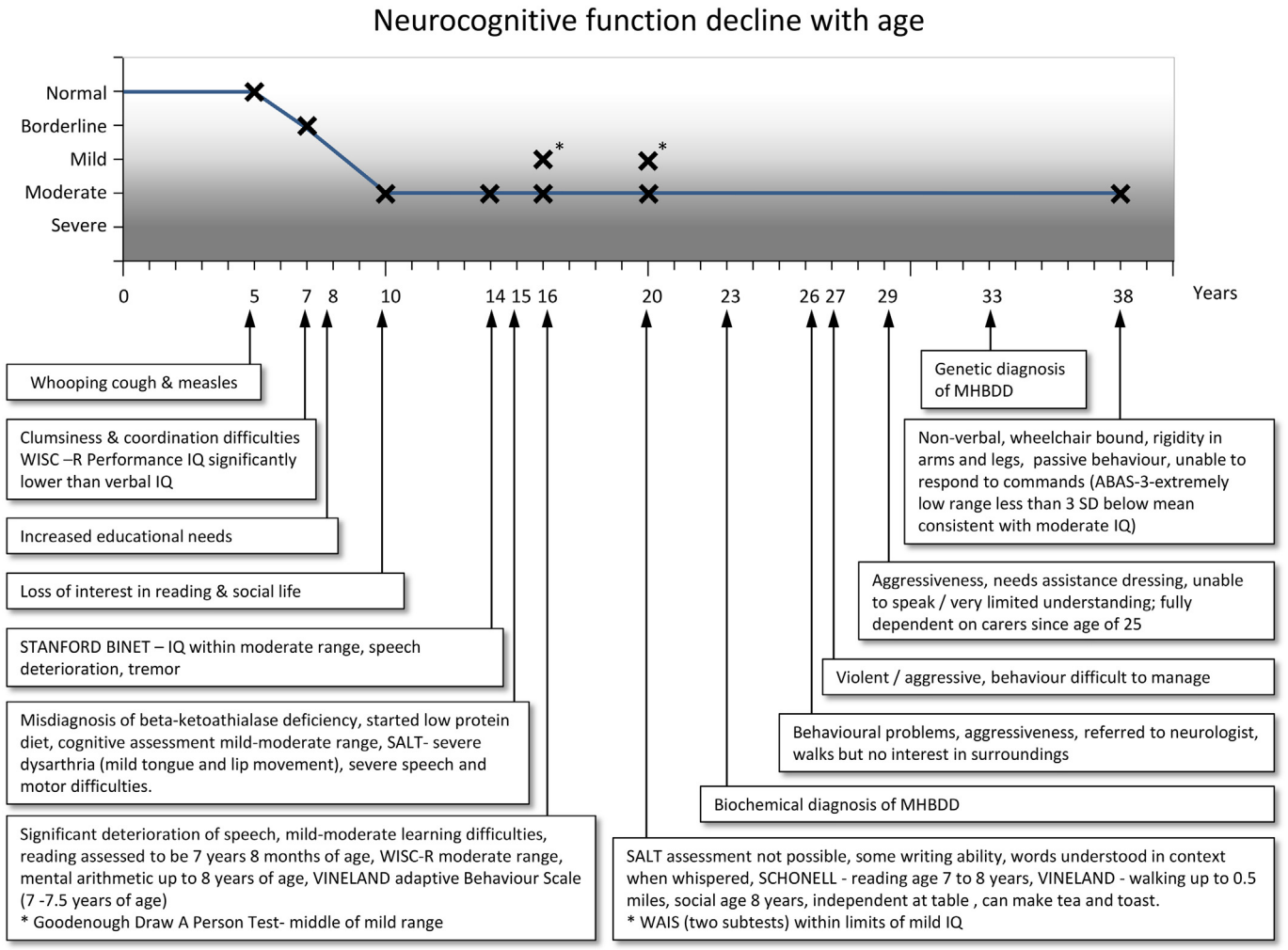

Fig. 1. Neurocognitive function decline with age; x axis-age (years), y axis- neurocognitive function; NORMAL- similar to peers of the same age; BORDERLINE- IQ 70-85; MILD-IQ 50 -55 to 70; MODERATE-IQ 35-40 to 50-55; SEVERE- IQ 20 -25 to 35 -40.
SALT- Speech and Language Therapy; WISC-R- Wechsler Intelligence Scale for Children; ABAS 3- Adaptive Behaviour Assessment System; WAIS- Wechsler Adult Intelligence Scale.

deleterious pathogenic variant, c.745G > C (p.Glu249Gln). His mother was an asymptomatic carrier.

At the age of 38, he presented to the Adult Metabolic Clinic with significant speech and motor impairment. He displayed a passive behaviour, and although he was unable to verbally communicate, he smiled when engaged. The clinical course of his mild condition and his steady neurocognitive impairment are presented in Fig. 1.

On examination he exhibited tremor and signs of dystonia treated with carbidopa and levodopa (Sinemet 62.5 mg daily). He had marked contractures in his knee and ankle joints and was unable to walk independently. He had marked muscle atrophy (sarcopenia), attributed to lack of mobility and chronic wheelchair use and intake of a low protein diet (0.7 g/kg) since childhood. Audiometry showed he had normal ipsilateral acoustic reflexes indicating healthy VIIIth nerve pathways and hearing was assessed as not worse than mild loss.

His biochemical tests showed plasma ammonia, renal function and liver function tests within normal reference ranges. Plasma amino acids showed leucine 121 μmol/L (38–83), isoleucine 64 μmol/L (77–162) and valine 205 μmol/L (151–302). Acylcarnitine profile was normal and free carnitine was 16.6 μmol/L. His most recent urine organic acids profile showed a mild increased excretion of 2-methyl-3-hydroxybutyrate, a moderate increase in excretion of tiglylglycine with no 2-methylacetoacetate detected. A slight increase in vanillactate and vanilpyruvate acids detected were likely to be secondary to carbidopa and levodopa intake prescribed for tremor and dystonia.

Table 1 outlines psychology assessments that were performed at different stages of his life.

The patient completed the Wechsler Intelligence Scale for Children (WISC) at 7 and 16 years of age and the Wechsler Adult Intelligence Scale (WAIS) at age 20 years. His scores on these tests were reported to be within the mild, moderate and mild range respectively. At 7 years, there was statistically significant discrepancy between his Performance Intelligence Quotient (IQ) (mild range) and his Verbal IQ (low average range). The patient completed the Stanford Binet at 10 years indicating an IQ within the Moderate range.

It was not possible to re-administer the WAIS at 38 years due to the patient's limited receptive capacity and significantly limited motor and verbal skills. Information was gathered from clinical interview with his mother, and his adaptive functioning was assessed using the Adaptive Behaviour Assessment System-Third Edition (ABAS-3). The patient's general Adaptive Composite Score on the ABAS-3 was reported to be in the extremely low range (< 0.1 percentile). This score is consistent with a moderate IQ in the absence of a comprehensive IQ assessment. His reading was assessed at 16 and 20 years using the Schonell Reading Test, and his level when retested remained stable between 7 and 8 years. His social functioning as assessed on the Vineland Adaptive