

CASE STUDY

Seizures and early onset dementia: D2HGA1 inborn error of metabolism in adults

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Introduction

D-2-Hydroxyglutaric aciduria type 1 (D2HGA1) (OMIM 600721) is a rare autosomal recessive neurometabolic

Abstract

D-2-hydroxyglutaric aciduria type 1 (D2HGA1) is a rare inherited metabolic disorder usually manifesting in infancy/early childhood with seizures and significant central nervous system involvement. We report two siblings with D2HGA1 presenting with mild intellectual disability, and the onset of seizures in adulthood. One of them was misdiagnosed as tuberous sclerosis due to her presentation and the presence of subependymal nodules on brain imaging. Both further developed early onset dementia. This report expands the phenotype of D2HGA1 to include late-onset seizures and early onset dementia in adults.

disorder caused by pathogenic variants in the D-2-hydroxyglutarate dehydrogenase (D2HGDH) gene. The biochemical hallmark of D2HGA1 is an increased level of D-2-hydroxyglutaric acid (D2HGA) in urine, plasma, and cerebrospinal

fluid (CSF). High levels of D2HGA are reported to have both cytotoxic and neurotoxic effects including: 1. Significant impairment of mitochondrial energy metabolism; 2. Increasing oxidative stress; 3. Induction of excitatory effects via NMDA receptor activation; and 4. Increasing synaptosomal glutamate uptake. Age of onset is usually within the first six years of life with heterogeneous clinical phenotypes from mild to severe neonatal presentation including intellectual disability (ID), hypotonia, seizures, cortical blindness, cardiomyopathy, and rarely, skeletal abnormalities. The life expectancy of these patients remains unknown.¹

Methods

A 53-year-old woman presented to the Toronto Western Hospital Memory clinic with a 2-year history of gradual cognitive decline. She had a history of mild ID and focal seizures with impaired consciousness evolving to bilateral tonic-clonic since the age of 33 years. Initially, her seizures occurred once a month and were well-controlled with Carbamazepine. There were occasional break-through seizures over the years and various medications were trialed such as topiramate and lamotrigine to try to improve seizure control but eventually, she ended up back on Carbamazepine. She continued to have a good response with one seizure every 4 to 5 months until the last year of her life when seizure frequency worsened to approximately 20 seizures over a 5-month period. She also had polycythemia rubra vera for which she underwent regular phlebotomies. At the age of 53, her neurological exam revealed bradykinesia with mild postural instability, bilateral postural tremor, mild bilateral ideomotor apraxia, dysdiadochokinesia, and difficulty in tandem gait.

At the time of referral, she had a diagnosis of tuberous sclerosis, due to the presence of subependymal nodules on brain MRI, seizures, and ID. At her first visit at the age of 53, neuropsychological assessment (Toronto Cognitive assessment (TORCA) score)² showed moderate-severe deficits in all cognitive domains, although worse in visual, executive, and language domains (Z-score -3.67 for total score) (Table 1). The cognitive decline progressed and by the age of 55, her driver's license was suspended. The z-score for the total TORCA score fell to -4.37 . At 56 she lost her job and became unable to perform instrumental activities of daily living (i.e. handling medications, doing laundry, using public transportation). The z-score for the total TORCA score fell to -5.2 . At age 58, she required assistance with some basic activities of daily living (i.e. grooming, toileting, dressing).^{2,3} Her ambulation also deteriorated and she began to have numerous falls requiring a wheelchair to travel long distances. She died at the age of 59.

The patient was born to non-consanguineous parents. Her father presented with late-onset dementia, as did a

Table 1. Z score for neuropsychology assessment

Toronto cognitive assessment score	Index patient			Sister 56 y
	53 Y	55 y	56 y	
297	200	183	162	¥
Z score	-3.67	-4.3	-5.2	

¥ There was only one assessment/visit that many of the subsets were not performed as the patient was not able to cooperate.

maternal uncle. The patient herself had two healthy children. The patient's only sibling, an older sister also presented with progressive cognitive and motor impairment.

Her sister was seen at the age of 56 years. Her mother provided the history: congenital (treated) hypothyroidism, and after falling out of her crib at age 1, suffered a "blood clot" resulting in cognitive delay (delayed speech and learning difficulties [completed grade 10 vocational school]). This sister lived independently and raised her three children. She developed her first seizure at the age of 43 years and during the workup was diagnosed with a subependymoma grade 1 tumor in the right frontal lobe, which was resected. She remained seizure-free thereafter on Carbamazepine and Valproic acid. A significant decline in cognitive functioning ensued at age 48, leading her to move in with her parents. At age 51, she was moved into a long-term care facility due to further neurocognitive decline. The index patient's sister's examination at the age of 56 revealed severe memory and executive deficits with the inability to do full TORCA, abnormal smooth pursuits, mild left-sided bradykinesia and dysmetria as well as mild left-sided lower extremity weakness, postural tremor, dysdiadochokinesia on her left side, and unsteady gait with retropulsion instability.

Results

Investigations performed in the index patient: brain MRI (Figure 1) showed subependymal nodules and white matter changes, CSF biomarkers for Alzheimer's in the borderline range: AT index of 0.8 (<1.0), P-Tau of 62.35 pg/mL (>61 pg/mL).

Microarray, TSC1&TSC2 gene sequencing (tuberous sclerosis 1 and 2, respectively), GFAP gene sequencing (Alexander disease) were negative, but she was found to carry two APOE4 genotypes. The patient's sister was also homozygous for the APOE4 genotype. Whole exome sequencing (WES) in both sisters revealed two novel heterozygous variants in D2HGDH: c.1486C>T (p.Gln496*) a frameshift variant resulting in premature truncation) and c.451G>C (p.Ala151Pro) a likely pathogenic missense variant, considered deleterious in multiple in silico models, including SIFT and Mutation Taster.

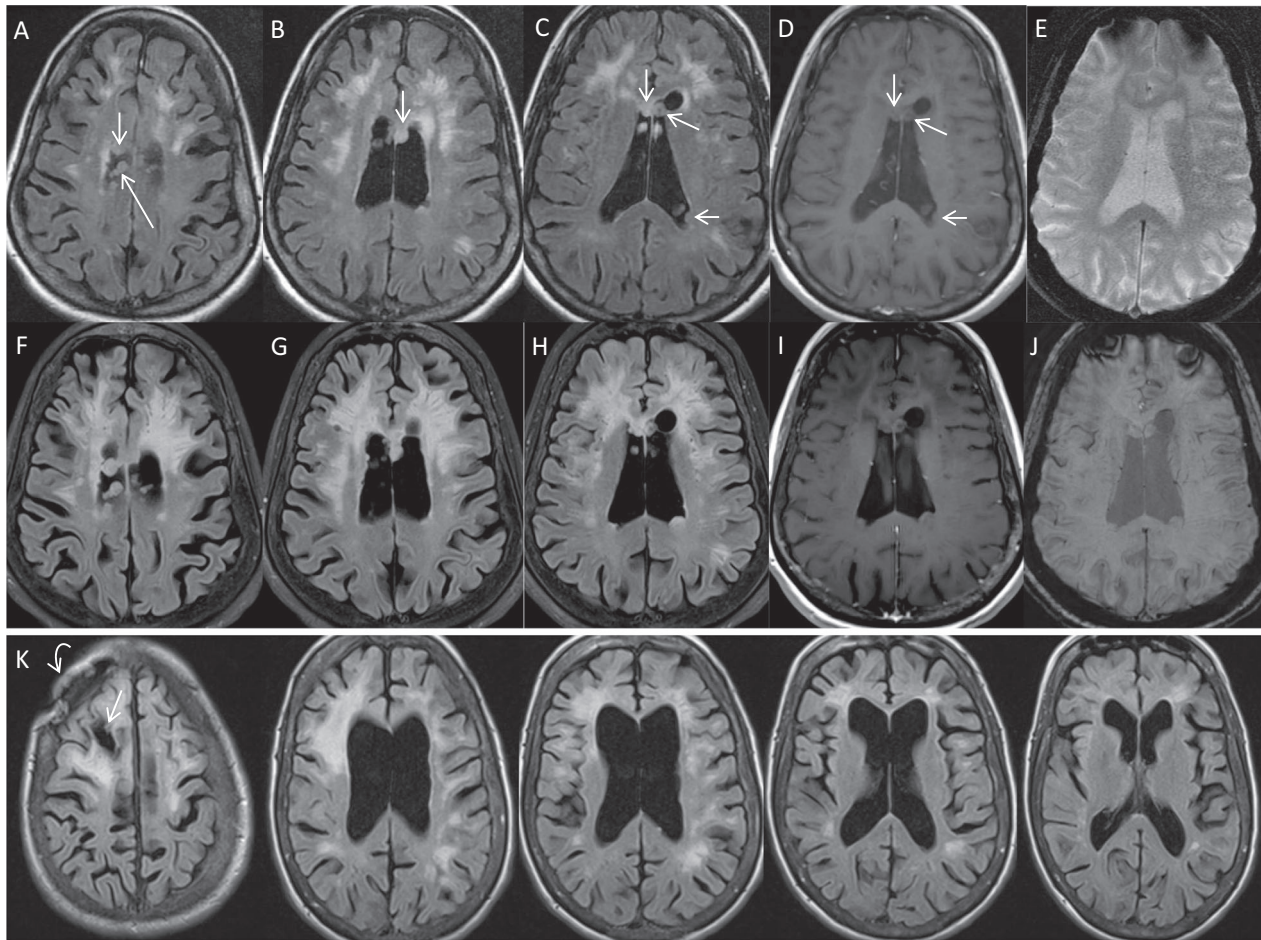


Figure 1. Selected images from MRI performed at age 46 (A-E) demonstrate multiple subependymal nodules that are slightly hyperintense to gray matter on FLAIR imaging (arrows in A-C), without significant enhancement post-gadolinium (D), and no hypointensity on gradient echo imaging to suggest significant calcification (E). There are FLAIR hyperintense white matter changes that are most pronounced in the frontal white matter. There is mild cortical atrophy without evidence for focal cortical lesions (no cortical tubers). Selected images from MRI performed at age 55–56 (F–J) demonstrate progression in confluent FLAIR hyperintense white matter changes (F–H), as well as marked interval progression in atrophy. Subependymal nodules are stable, without significant enhancement (I) or susceptibility effect (J). Bottom panel (K): selected FLAIR images from MRI of the patient's sister at age 56 demonstrate marked atrophy with frontal-predominant hyperintense white matter changes. There is right frontal encephalomalacia (straight arrow) underlying a right frontal craniotomy (curved arrow), presumably related to remote surgery.

Parental testing confirmed that these variants were inherited in trans, one from each carrier parent. The organic acid profile showed significantly elevated D-2-HGA, confirming the diagnosis of D2HGA1. Amino acid assay in serum showed high glutamine, normal ammonia, and lower than normal lysine levels.

Discussion

D2HGA1 is a rare neurometabolic disorder described mainly in children. Very little is known about the long-term outcome of this condition. Rare asymptomatic children up to the age of 10 years were reported in the literature who had normal intelligence or mild intellectual disability, suggesting the possibility of some protective

factors working against the toxicity of D2HGA.⁴ However, to our knowledge, this late-onset seizures and early onset dementia phenotype reported in our patients has not previously been observed.

Diagnostically, this case presented a challenge: despite mild ID, the index patient was able to complete high school, have a family, and be gainfully employed for a number of years. When the seizures started at the age of 33 years, she was misdiagnosed with a mild form of tuberous sclerosis due to the presence of subependymal nodules on imaging, along with the late-onset seizures and mild ID. It was not until the signs of dementia prompted further investigation that another unifying diagnosis was considered. Furthermore, it was only during the subsequent investigation for dementia that it was

revealed that her sister had a similar phenotype although the family had always attributed the sister's symptoms to her falling from the crib causing a "blood clot" in her brain.

Macrocephaly, multifocal cerebral white matter abnormalities with variable involvement of basal ganglia, and subependymal pseudocysts were reported in D2HGA1. Subependymal pseudocysts result from the persistence of the germinal matrix usually around the caudate nucleus and in combination with other brain abnormalities can be seen in a variety of metabolic and chromosomal abnormalities.^{3,5}

Subependymal nodules in our patient, however, are likely hamartomatous changes in subependymal tissue which is a common finding in tuberous sclerosis patients. We suggest that D2HGA1 should be added to the differential list of subependymal nodules especially in the absence of significant calcification or enhancement of the subependymal nodules, absence of cortical tubers, and presence of confluent white matter changes that do not resemble the typical radial white matter bands described in tuberous sclerosis.⁶ Furthermore, depending on the patient's age, other known neuro-imaging findings of D2HGA1 such as delayed cerebral maturation, subdural effusions, and enlargement of the lateral ventricles³ can further elucidate the diagnosis. White matter involvement in D2HGA1 is not specific and has a wide range of differential diagnosis. In this case, preferential involvement of the frontal white matter could raise an imaging differential diagnosis of Alexander disease, frontal variant of x-linked adrenoleukodystrophy, metachromatic leukodystrophy or leukoencephalopathy with axonal spheroids and pigmented glia. However, the absence of typical clinical or additional imaging features specific for these entities would help to exclude them; also, the presence of subependymal nodules is a unique feature that has not been described in these other leukodystrophies.⁷ Childhood cases of D2HGA1 have shown subcortical leukodystrophy with variable basal ganglia involvement³ which still differs from white matter involvement in TS.

The late-onset seizures and early onset dementia in these sisters is atypical for D2HGA1. One could speculate that there are genetic or epigenetic factors that may have played a protective role. For instance, the novel missense pathogenic variant in these siblings may confer a milder phenotype, even with the co-occurrence of a premature truncating variant. Also, both sisters were homozygous for APOE4 alleles, which may have conferred protection in this metabolic condition. Taking into consideration that tricarboxylic acid cycle intermediates and ketone bodies are elevated in D2HGA1³ and that APOE4 carrier cells were reported to have overexpression of genes related to ketone body uptake and utilization.⁸ APOE4

homozygosity may attenuate the adverse effects of high levels of D2HGA1 on brain metabolism. In addition, there are reports showing that APOE4 genotype may improve neuronal performance and survival during fetal development, infancy, and youth at the expense of decreased capacity in old age.⁹

Dementia has not been described as a symptom of D2HGA1, perhaps because the patients described so far have not lived long enough, no formal natural history studies have been carried out for D2HGA1 or because the diagnosis of dementia is difficult in patients with ID. This report serves to shed light on the importance of a multi-disciplinary approach to patients with unclear diagnosis, the importance of updated family histories, genetic investigations, and expanding the differential diagnosis to include inborn errors of metabolism in adults. Finally, this case highlights the potential similarities between tuberous sclerosis and D2HGA1.

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Conflict of Interest

All the authors declare to have no potential conflicts of interest.

Ethics Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study included only tests derived from routine clinical practice and therefore did not require specific ethics committee approval at our Institution.

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