Episodic dystonia and hallucinations due to dlat genes

Title: Carbamazepine responsive Episodic Dystonia and Hallucination due to Pyruvate Dehydrogenase E2 (DLAT) gene mutation

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ABSTRACT:

BACKGROUND: PDH E2 deficiency due to DLAT mutations is a very rare condition with only 4 reported cases to date.

METHODS: We describe a 15-year-old girl with mild intellectual disability, paroxysmal dystonia and bilateral basal ganglia signal abnormalities on brain MRI. Additional neurophysiological, imaging, metabolic and exome sequencing studies were performed.

RESULTS: Routine metabolite testing, and GLUT1 and PRRT2 mutation analysis were negative. A repeat brain MRI revealed “ Eye-of-the-tiger-sign”. Exome sequencing identified homozygous valine to glycine alteration at amino acid position 157 in the DLAT gene. Bioinformatic and family analyses indicated that the alteration was likely pathogenic. Patients ‘ s dystonia was responsive to low dose carbamazepine. On weaning carbamazepine, patient developed hallucinations which resolved after carbamazepine was restarted.

CONCLUSIONS: PDH E2 deficiency due to DLAT mutation has a more benign course compared to common forms of PDH E1 deficiency due to X-linked PDHA1 mutations. All known cases of PDH E2 deficiency due to DLAT mutations share the features of episodic dystonia and intellectual disability. Our patient’s dystonia and hallucinations responded well to low dose carbamazepine.

Introduction:

Pyruvate Dehydrogenase (PDH) E2 deficiency is a rare pediatric neurometabolic disease due to mutation in DLAT gene (Head et al., 2005; McWilliam et al., 2010). Only 4 cases with DLAT gene mutations have previously been reported (Head et al., 2005; McWilliam et al., 2010). All share the features of dystonia and some degree of developmental delay and characteristic globus pallidus signal abnormalities on brain MRI. This disease tends to have more benign course as compared to PDH E1 deficiency (Head et al., 2005; Huq et al., 1991; McWilliam et al., 2010; Patel et al., 2012). We report an additional case with DLAT mutation with new phenotype and treatment information.

Case Report

A 15-year-old girl presented with paroxysmal episodes of left lower extremity weakness and stiffening for the last 8 years. These episodes were triggered by exercise but no exacerbating or relieving factors were noted. There was no associated aura, alteration of consciousness, incontinence or other associated neurological symptoms. Her parents were second cousins, but family history was negative for known genetic disorders. Birth and past medical histories were also unremarkable. Patient had a speech delay but met her other childhood milestones appropriately. Later, she developed academic difficulties and at 15 years of age she was performing at a 4 th grade level. At presentation, the patient had a normal examination except for some cognitive and reading difficulties. At the time of initial presentation to a pediatric neurologist at 7 years of age, an MRI of the brain revealed bilateral T2 hyperintensities in the basal ganglia. In addition, she was found

to have decreased NAA peak and the suggestion of a lactate peak on MR spectroscopy. EEG, EMG and nerve conductions studies were unremarkable.

Over the years the patient was considered to have “ paroxysmal kinesiogenic dyskinesia” and was treated with carbamazepine (100 mg daily). The patient was initially evaluated by us at age of 14 years. Metabolic work up for serum lactate, serum amino acids, acyl carnitine profile, serum copper and ceruluplasmin and GLUT1 or PRRT2 mutation analysis were unremarkable. Repeat MRI revealed basal ganglia signal changes including “ Eye of the tiger” sign (Figure 1). MR spectroscopy studies were suboptimal.

Exome sequencing was performed through Ambry laboratory as previously described (Serajee and Huq, 2015). The patient had homozygous c. 470T> G (p. V157G) alteration in the DLAT (Dihydrolipoamide acetyltransferase (PDHC E2) gene suggesting the diagnosis of pyruvate dehydrogenase E2 deficiency, a rare cause of pyruvate dehydrogenase deficiency. Both parents and one brother were heterozygous carriers and another brother was homozygous normal. The p. V157G alteration (c. 470T> G), is in coding exon 3 of the DLAT gene, results from a T to G substitution at nucleotide position 470. The valine at codon 157 is replaced by glycine, an amino acid with dissimilar properties. The V157 amino acid position is highly conserved in all available vertebrate species. The p. V157G alteration is predicted to be probably damaging by Polyphen and deleterious by SIFT in silico analyses. The V157 amino acid is located within the biotin/lipoyl attachment domain of the DHAT protein. The DLAT c. 470T> G alteration was not observed in healthy cohort databases such as NHLBI Exome Sequencing Project (ESP) or the 1000 Genomes Project or the Database of Single Nucleotide Polymorphisms

(dbSNP). Based on data from the HGMD, only the four alterations reported by Head et al. (2005) and McWilliam et al. (2010) have been observed within the DLAT gene to date (Head et al., 2005; McWilliam et al., 2010). These include one missense alteration, two splice alterations, and one small in-frame deletion. Based on the above evidence, the homozygous c. 470T> G (p. V157G) alteration was considered pathogenic.

Her parents refused treatment with the ketogenic diet. When carbamazepine was weaned off due to parental concerns of side effects, within few weeks, patient developed hallucinations. Parents reported resolution of symptoms after carbamazepine was restarted.

Discussion:

The Pyruvate Dehydrogenase Complex functions in the oxidative decarboxylation of pyruvate to acetyl coenzyme A. The complex contains three subunits: E1, E2 and E3 (Patel and Roche, 1990). The most common form of pyruvate dehydrogenase deficiency is due to mutations affecting the E1 subunit, and results in a variety of clinical manifestations depending upon the residual function of the enzyme (Huq et al., 1991; Patel et al., 2012). E1 subunit is encoded by PDHA1 gene of X chromosome. Most patients present in infancy with lactic acidosis, ataxia and hypotonia, either chronically or episodically (Huq et al., 1991; Patel et al., 2012). The mutation in our patient is in the E2 subunit (dihydrolipoamide acetyltransferase), which forms the structural core of the enzyme and functions in accepting the acetyl groups and transferring them to coenzyme A, an essential step preceding the entrance of glucose into the TCA cycle (Head et al., 2005; Patel and Roche,

1990). E2 subunit is encoded by DLAT gene located on chromosome 11q23. 1.

To date, however, there are only four reported cases of pyruvate dehydrogenase deficiency caused by alterations in the DLAT gene, making it a very rare cause of the condition (Head et al., 2005; McWilliam et al., 2010). In addition, Robinson et al reported an additional patient with reduced E2 dihydrolipoyl transacetylase enzyme activity (32% of the control and undetectable E2 immunoreactive protein (Robinson et al., 1990). For this patient, no gene mutation data is available (Robinson et al., 1990). The patient reported by Robinson et al. had a different phenotype compared to our patient and four other genetically confirmed DLAT mutation cases and had profound retardation and microcephaly (Robinson et al., 1990).

Head *et al.* (2005) first described two unrelated individuals with PDH deficiency caused by homozygous non-protein truncating mutations in the *DLAT* gene (Head et al., 2005). One patient demonstrated a deletion of glutamic acid in the outer lipoyl domain of the protein, whereas the second expressed a missense mutation in the catalytic site, leading to a substitution of leucine for phenylalanine. Both patients were male children born of first-cousin parents. These patients presented with a less severe phenotype compared to individuals with the more common type of PDH caused by alterations in the *PDHA1* gene encoding the E1 subunit, and their common features included episodic dystonia, hypotonia, ataxia, and developmental delay(Head et al., 2005). Episodes of dystonia were often triggered by stress or fever, and developmental progress appeared to slow after the episodes as well. Additional reported features included inconsolable crying, nystagmus

and abnormal eye movements, ptosis, drooling, jerky head movements, arching of the body, “ bottom shuffling”, stiffening of the limbs, episodic clenching of the hands, head lag and hypotonia. Brain MRI findings in each patient included “ focal signal abnormality in the basal ganglia with high T2 signal and low T1 signal in the globus pallidus” which was compatible with an abnormality of energy metabolism (Head et al., 2005). The authors concluded that mutations in the *DLAT* gene are an extremely rare cause of PDH deficiency and that patients with this type of PDH may be more likely to respond to a ketogenic diet (Head et al., 2005). McWilliam et al. (2010) also described two sisters born of non-consanguineous parents affected with pyruvate dehydrogenase E2 deficiency caused by compound heterozygous splice mutations in the DLAT gene (McWilliam et al., 2010). Clinical features were like those described in Head et al. (2005), including progressive episodic dystonia, cognitive impairment, and globus pallidus hyperintensity on brain MRI. Both patients were treated with a modified ketogenic diet and the parents reported improvements in concentration, fine motor control, and decreased fatigue (McWilliam et al., 2010).

Previous reports noted the phenotypic overlap to patients with PKAN, and suggested investigation for PDH E2 deficiency in patients suspected to have atypical PKAN with negative genetic testing (Head et al., 2005; McWilliam et al., 2010). PKAN is one of several diseases classified under the umbrella of “ neurodegeneration with brain iron accumulation” (NBIA). It is caused by a mutation in the pentothenate kinase 2 gene, an abnormality of coenzyme A metabolism (Zhou et al., 2001). CoPAN (Coenzyme A synthetase protein-associated neurodegeneration) is another NBIA that affects the synthesis of

coenzyme A. It is caused by a mutation in coenzyme A synthetase (COASY) gene (Schneider, 2016; Tonekaboni and Mollamohammadi, 2014). Clinical features of PKAN and CoPAN also include ataxia, dystonia, chorea and Parkinsonism, cognitive decline and psychiatric manifestations (Schneider, 2016; Tonekaboni and Mollamohammadi, 2014). In NBIA, whether iron accumulation is a cause or an effect of the disease process is still not known (Schneider, 2016; Tonekaboni and Mollamohammadi, 2014).

In our patient, the pattern of MRI changes in the bilateral globus pallidus is remarkably like that seen in PKAN and CoPAN, revealing “ the eye-of-the-tiger sign “. On brain MRIs of patients with PKAN and CoPAN, the central hyperintensity of the eye-of-the-tiger sign is thought to be due to the tissue necrosis, while the surrounding hypointensity is attributed to the iron accumulation (Dusi et al., 2014; Kumar et al., 2006). Other diseases including cortical basal degeneration, multisystem atrophy, multiple sclerosis and neurofibromatosis may have similar neuro-radiological findings. However, these diseases differ from PKAN in their clinical behavior and pattern of MR abnormalities (Kruer et al., 2012). PKAN and CoPAN also affect the substantia nigra (Kruer et al., 2012); however, the involvement of the substantia nigra has not yet been reported in cases of PDH E2 deficiency due to DLAT mutations. Out of the four previously reported cases of PDH E2 deficiency due to DLAT mutation, only two patients had serial MRI scans. In one patient, the brain MRI was normal at one year of age but follow up at 6 years-old showed an abnormal hyperintense T2 signal in the bilateral globus pallidus. In the other patient, similar lesions were noticed at 15 months-old that remained unchanged on follow up at 2 and 6 years of age (Head et al.,

2005). As opposed to the eye-of-the-tiger sign seen in our patient, all the previously reported cases showed homogenous basal ganglia hyperintensities (Head et al., 2005; McWilliam et al., 2010). As discussed above, PKAN and CoPAN result from a defect in coenzyme A synthesis (Schneider, 2016; Tonekaboni and Mollamohammadi, 2014). PDH E2 deficiency due to DLAT mutations, on the other hand, affects the transfer of acetyl group formed by decarboxylation of pyruvate to coenzyme A (Kumar et al., 2006; McWilliam et al., 2010; Patel and Roche, 1990). It is possible that the clinical and radiological similarities of PKAN, CoPAN and PDH E2 deficiency are due to shared abnormalities in the acetyl-CoA metabolism.

Like our patient, the 4 previously reported DLAT mutation cases presented with dystonia and intellectual disability, with a more benign course than those affected with the PDH E1 subunit deficiency (Head et al., 2005; McWilliam et al., 2010) . In this regard, PDH E2 deficiency due to DLAT mutation is like PDH deficiency due E3 binding protein deficiency (Head et al., 2005). Serum and CSF lactate were elevated in only one patient, but all demonstrated characteristic hyperintense T2 and hypointense T1 signal in the bilateral globus pallidi on brain MRI. In 3 out of the 4 patients, ketogenic diet was helpful in alleviation of the disease symptomology(Head et al., 2005; McWilliam et al., 2010). Our patients had hallucination, which was not described in other 4 reported patients. Her dystonia and hallucinations responded to low dose carbamazepine. Our case thus expands upon the phenotype for PDH E2 deficiency associated with the DLAT gene mutation.

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Figure 1 Legend:

MRI of the brain:

A. Axial T2 image showing hyperintensity in bilateral globus pallidus, which is surrounded by a hypointense signal

B. Axial T1 image showing hypointensity in bilateral globus pallidus

C. Coronal T2 FLAIR image showing hyperintensity in bilateral globus pallidus, which is surrounded by a ring of hypointense signal (eye-of-the-tiger sign)