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CASE REPORT

Diabetic ketoacidosis in vanishing white matter

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Key Clinical Message

Clinicians should consider the *EIF2B1* gene defect in any patient with diffuse white matter disease on an MRI of the brain and DKA.

Keywords

diabetic ketoacidosis, *EIF2B1*, hyperglycemia, vanishing white matter.

Introduction

Vanishing white matter (VWM) disease (OMIM #603896) is an autosomal recessive chronic and progressive leukodystrophy and is one of the most prevalent inherited childhood leukoencephalopathies [1, 2]. The symptoms of the disease can begin shortly after birth or in adulthood. The phenotypic variation is very wide and the most common features include neurological deterioration, optic atrophy, seizures, coma, and death [3, 4, 5]. VWM disease is diagnosed on the basis of the clinical symptoms in combination with MRI results and molecular testing [6].

Five Eukaryotic Initiation Factor "*EIF*" genes are known to be involved in VWM disease: *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B*. Of these, the *EIF2B5* gene accounts for more than one-half of the cases [7, 8]. Hyperglycemia and diabetic ketoacidosis (DKA) have never been reported before in patients with VWM disease. We are reporting on a case with both VWM disease and DKA, and so to the best of our knowledge, this is the first case of a similar presentation.

The proband was the product of a full-term normal delivery at a peripheral hospital with a birth weight of 2.2 kg (<3 percentile), and normal other growth parameters. He was discharged on the second day after birth with no perinatal health issues. He was admitted at the age of 8 months through the emergency department with irritability and vomiting and was found to have a blood glucose level (25 mmol/L; normal, 6–10 mmol/L), HbA1c (11.4%; normal 4–5.6%), as well as ketosis (Ketones +3; normal, Absent), metabolic acidosis (plasma bicarbonate 15 mEq/L; normal, 21–28 mEq/L), C-Peptide (22 pmol/L; normal, 366–1466 pmol/L), Glutamate decarboxylase Abs (4 IU/mL; Negative < 10.0 IU/mL, Positive ≥ 10.0 UI/mL), Islet Cells Abs (Negative; normal, Negative), and blood PH (7.1; normal, 7.35–7.45). Past medical history revealed hypotonia and delayed milestones involving gross, fine motor, vision, and hearing skills. Consequently, he was diagnosed and treated as a case of DKA and discharged on insulin injections of 0.30 IU/kg/day. At the age of 1 year, the patient was readmitted again with intractable seizures and generalized tonic–clonic convulsions, and a CT scan of

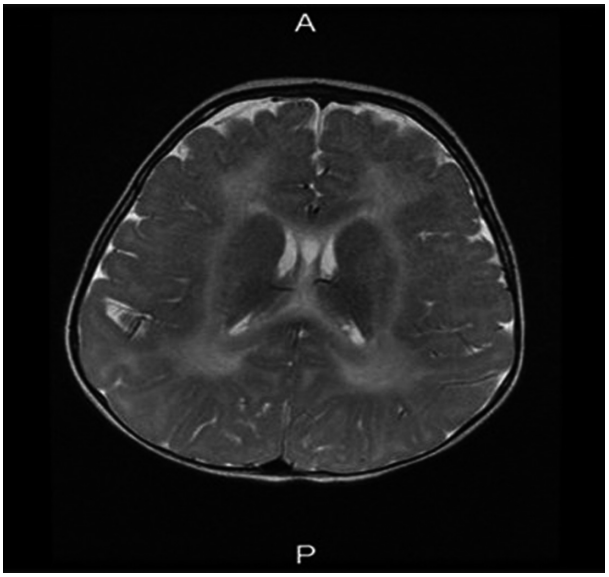

Figure 1. MRI of the brain showing the diffuse VWM changes.

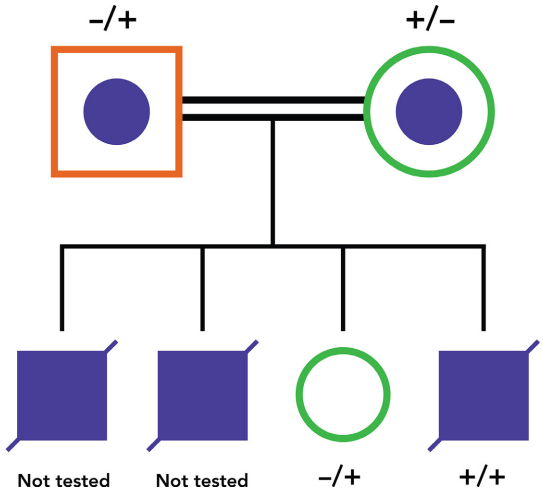

Figure 2. Family pedigree showing both parents and the affected children. ± signs indicate the status of the molecular testing (+) positive for the *EIF2B1* c.146T>G variant, (–) wild type.

his brain showed diffuse confluent bilateral symmetrical low attenuation in white matter consistent with leukodystrophy, which was confirmed by an MRI of the brain revealing diffuse white matter disease (Fig. 1). An electroencephalogram showed diffuse slow waves that reflected the fact that the patient was on midazolam infusion treatment, and an eye exam showed bilateral optic nerve atrophy. Full metabolic work-up revealed persistent mild lactic acidosis (3 mmol/L; normal, 1.0–1.8 mmol/L), normal ammonia (40 μmol/L; normal, 10–47 μmol/L), normal acylcarnitine profile, and urine organic acid (semiquantitative analysis). Further investigations for Anti-Parietal Cell Abs (APCA), five genes that associated with neonatal and infantile diabetic syndromes (KCNJ*11, ABCC8, INS, GCK*, and *PDX1)*, and muscle biopsy for defects in mitochondrial respiratory chain complexes were all negative. Eventually, the child died at the age of 2 years while he was on insulin injections due to severe hypotonia, gastroesophageal reflux, and recurrent chest infections.

His parents are first cousins and healthy. They have one daughter who is alive and at the time of writing is 18 years old. There is a history of two other sons who died at 1 year of age with insulin-dependent diabetes mellitus, white matter disease, and spastic quadriplegia (Fig. 2). Also, there was a history of abortion at 2 months of gestation and premature death of a baby boy at 6 months gestation. Further investigations including Whole Exome Sequencing (WES) revealed a homozygous likely pathogenic variant in *EIF2B1* NM_001414: c.146T>G p.(Leu49Arg) in the proband; both parents were heterozygous, and the healthy older sister was heterozygous of this variant.

Discussion

VWM disease is an autosomal recessive chronic and progressive white matter disorder [1, 2], with symptoms capable of beginning shortly after birth or in adulthood. Five clinical subtypes have been described (antenatal, infantile, early childhood, late childhood, or juvenile and adulthood). Phenotypic variation in VWM disease is extremely wide and affects almost all the human body systems. The reported endocrine manifestation in VWM disease is limited to ovarian dysgenesis including primary and secondary amenorrhea, ovarian failure with high serum gonadotrophin level, and low levels of serum estrogen and progesterone. However, there is no previous report of an association between VWM disease and diabetes mellitus; yet, our patient was found to have a disease-causing variant of VWM disease and he also met the consensus statement from the International Society for Pediatric and Adolescent Diabetes (ISPAD) in 2014 for the biochemical diagnostic criteria for DKA [9]. Additional investigations for the other possible causes of DKA were negative. Based on the segregation analysis, ruling out other possible disorders, and the MRI manifestations, the missense variant in *EIF2B1* explains the phenotype. However, we have no DNA from the two previously affected siblings for segregation analysis as they were born in a peripheral hospital. This variant has not been previously reported in a large-scale exome sequencing database such as Exome Aggregation Consortium (ExAC), dbSNP/1000 genome, or Exome Sequencing Project (ESP). The leucine residue is highly conserved through evolution among *EIF2B1* homologs, including

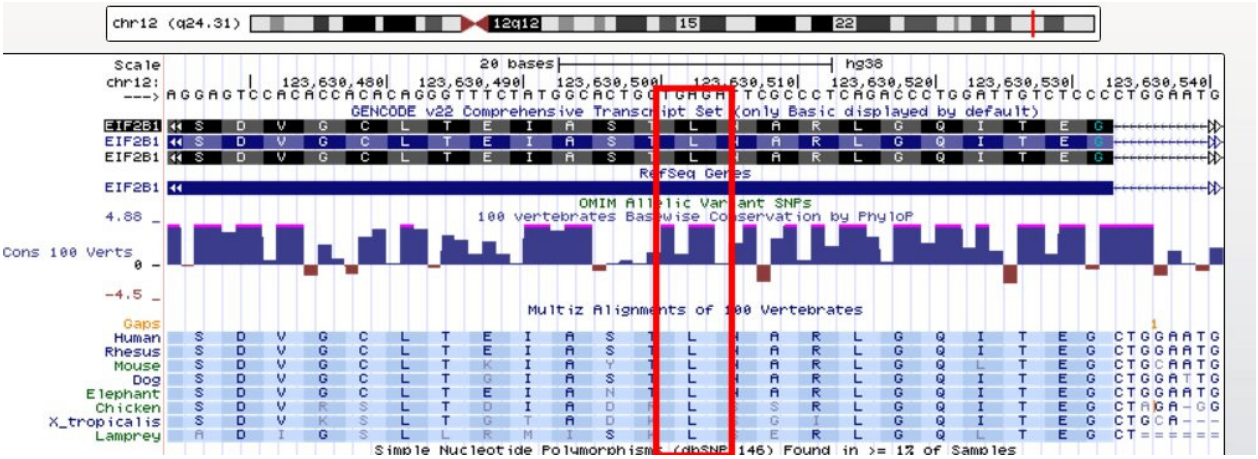

Figure 3. Screenshot of UCSC Genome Browser https://genome.ucsc.edu, showing the location of the residue and comparative genomic tracks multi alignment [Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833].

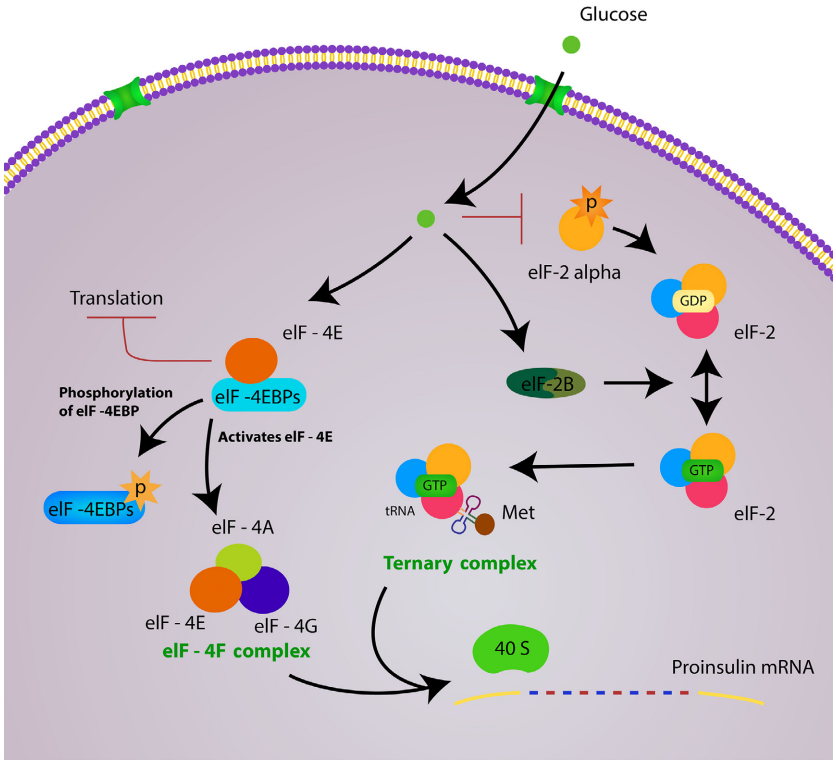

Figure 4. Glucose stimulates insulin synthesis largely by promoting insulin translation initiation. (1) Glucose promotes the phosphorylation of eIF-4EBP and activates eIF-4E; eIF-4E, eIF-4A and eIF-4G form eIF-4F, a complex whose functions include recognition of preproinsulin mRNA and recruiting 40S ribosome to mRNA. (2) eIF2 is a critical factor regulating protein biosynthesis. Glucose causes the dephosphorylation of eIF2α, and induces an increase in the availability of the translational ternary complex for protein translation [Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833].

rhesus, mouse, dog, and lamprey (Fig. 3), and this substitution was predicted to be damaging by computational prediction tools (PolyPhen2, MutationTaster, FATHMM, PROVEAN, and SIFT). Furthermore, WES revealed only one disorder and the chances of co-occurrence and recurrence in the two siblings with similar clinical presentation

(VWM + DKA) make the possibility of one monogenic autosomal recessive disorder more likely. β-cells improve the protein translation, which is controlled by dephosphorylation of eukaryotic initiation factor 2a (eIF2a) via protein phosphatase 1 (PP1). When β-cells are exposed to high glucose it decreases the ratio of phosphorylated eIF2a to eIF2a. In addition to that, the *EIF2B1* gene encodes one of five subunits of eukaryotic translation initiation factor 2B (eIF2B) protein complex, which plays a critical role in the initiation of protein synthesis and the cellular response to stress by activating the initiation factor eIF2, which interacts with the glucose response stimulus (Fig. 4), so a defect in the pathway could lead to hyperglycemia and possible DKA.

In conclusion, this is the first case of an association between VWM disease and DKA which yields additional observations regarding the role of *EIF2B1* in glucose regulation and expands the phenotype of VWM disease. However, the relation between the eIF2B protein complex and glucose level is unclear and requires further research.

Conflict of Interest

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. To the best of our knowledge, no conflict of interest, financial or other, exists.

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