UNILATERAL PERIVENTRICULAR LEUKOMALACIA IN ASSOCIATION WITH PYRUVATE DEHYDROGENASE DEFICIENCY
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ABSTRACT: PURPOSE: The purpose of this study was to review the MRI findings in patient with unilateral periventricular Leukomalacia in association with Pyruvate dehydrogenase deficiency.

KEYWORDS: MRI, Unilateral periventricular Leukomalacia.

INTRODUCTION: Pyruvate Dehydrogenase (PDH) deficiency is a major cause of primary lactic acidosis and neurological dysfunction in infancy and early childhood. A deficiency of PDH E1 alpha, a subunit of the PDH complex, is a prominent cause of congenital lactic acidosis. We describe a female infant born at term and delivered by emergency Caesarean section. She presented at 9 months of age with failure to thrive and developmental impairment. Her plasma and cerebrospinal fluid lactate were raised. She had raised plasma Pyruvate with a normal lactate–Pyruvate ratio. Magnetic resonance imaging of the brain showed left periventricular Leukomalacia. Skin fibroblast culture assay revealed PDH deficiency, confirmed by mutation analysis of the E1 alpha subunit. She has been treated with dichloroacetate and a ketogenic diet with out any side effects.

Various clinical presentations have been described, including congenital lactic acidosis, callosal agenesis, infantile spasms, and other types of early-onset epilepsy, Leigh encephalopathy, recurrent ataxia, and chronic neuropathy. Our female infant has left unilateral periventricular Leukomalacia (PVL) in association with PDH deficiency. Consent has been obtained the family for publication of the case report.

CASE REPORT: A term female infant her healthy non-consanguineous parents. At 9 months of age, she was referred to hospital for failure to thrive and motor development. On examination she had upper limb hypertonia and global developmental impairment. Investigations included normal toxoplasmosis, rubella, cytomegalovirus, and herpes screening, skull radiograph, karyotype, and a coeliac screen. Urinary organic acid analysis showed increased lactate excretion together with increased fumarate, glutarate, and 2-ketoglutarate. Her fasting and post feed lactate was high. Her plasma pyruvate levels were 210 lmol/L. Cerebrospinal fluid lactate was 3.2 mmol/L. This strongly suggested the possibility of a defect in energy metabolism. Magnetic resonance imaging (1.5T) of the brain showed left unilateral PVL (Fig. 1). Skin for fibroblast culture and muscle biopsy for histology, electron microscopy, and respiratory chain enzymes were undertaken for mitochondrial disorders. Skin fibroblast culture assay revealed PDH deficiency.

She was reported to be more active while taking dichloroacetate, and did not have any adverse effects. A ketogenic diet (classic, with a fat to carbohydrate and protein ratio of 2:1) was introduced successfully with good tolerance and no side effects. The family was referred for genetic counseling.
DISCUSSION: PDH deficiency is a severe inborn error of metabolism that affects mainly the nervous system. PDH is a huge multicomponent enzyme complex made up of multiple units of four enzymes: pyruvate decarboxylase (E1, 30 units), dihydrolipoil transacetylase (E2, 60 units), dihydrolipoamide dehydrogenase (E3, six units), and protein X (six units). Most individuals with PDH deficiency have mutations of the X-linked E1 subunit of the pyruvate decarboxylase component of the enzyme complex. The clinical course of PDH deficiency is highly variable, with the most severe cases presenting in the newborn period as severe persistent lactic acidosis, resulting in death within a few weeks or months. This variant of the disease is often associated with agenesis of the corpus callosum. Various neuroradiological findings have been described in PDH deficiency (Table 1). In males, three clinical presentations are encountered: neonatal lactic acidosis, Leigh encephalopathy, and intermittent ataxia. The more severely affected infants die before 6 months of age and have low residual activity of the PDH complex and chronic severe lactic acidaemia. Children with mild to moderate deficiency usually present in infancy with a history of developmental impairment, hypotonia, failure to thrive, and seizures. The course of the diseases is often punctuated by bouts of severe lactic acidosis, often precipitated by inter current illnesses. Presentation with relapsing intermittent ataxia is also described in males. Females with PDHE1 alpha deficiency tend to have a more homogeneous clinical presentation, although with variable severity.

This includes dysmorphic features (Narrow head with frontal bossing, wide nasal bridge with upturned nose, long philtrum, and flared nostrils), microcephaly, moderate to severe intellectual disability, and a spastic diplegia or quadriplegia resembling a non-progressive encephalopathy. Seizures are reported in almost all affected females. These usually present within the first 6 months of life and are often present as epileptic spasms or severe myoclonic seizures. Our infant has not been affected by seizures to date. Plasma lactate levels in PDH deficiency are usually persistently elevated. The lactate pyruvate ratio is characteristically normal. Urinary organic acid analysis in patients with E1 alpha defects is unremarkable apart from the presence of excess lactate and some 2-hydroxybutyrate. In children with mitochondrial encephalopathies, the most common magnetic resonance imaging features are bilateral symmetric abnormalities in the basal ganglia and brainstem. The presence of white matter abnormality has been described only in a few cases. PVL and parenchymal venous infarction complicating germinal matrix intraventricular haemorrhage have long been recognized as the two significant white matter diseases responsible for the majority of cases of cerebral palsy in survivors of preterm birth.

| White matter abnormalities | Brainstem | Cortical | Cerebellar | Other |
|----------------------------|-----------|----------|------------|-------|
| Periventricular pseudocysts | Palladi and caudate nuclei abnormalities | Abnormalities of corpus callosum including agenesis, hypoplasia and partial dysgenesis | Vascular proliferation on cerebellum | - |
| Periventricular white matter demyelination | Abnormalities of thalamus, putamen, and dentate nuclei | Cortical atrophy, absent pyramids | - | Subdural effusions |
Sub cortical white matter involvement & - & Polymicrogyria & - & - \\
Enlargement of lateral ventricles and brain atrophy & - & Heterotopic nodule of grey matter in subependymal regions & - & - \\
Progressive vacuolization of affected white matter & - & Decreased cortical sulcation and gyration & - & - \\
Large subependymal cysts & - & - & - & - \\

Table 1: Neuroradiological findings described in Pyruvate dehydrogenase deficiency

CONCLUSION: To our knowledge, unilateral PVL as a neuroradiological feature has not been described in children with PDH deficiency. PDH deficiency should be considered as a differential diagnosis if PVL is unilateral and if the perinatal history is not typical of PVL.

REFERENCES:
1. Robinson BH. Lactic acidemia: disorders of Pyruvate carboxylase and Pyruvate dehydrogenase. In: Scriver CR, Beaudet AL, Sly WS, editors. The Metabolic and Molecular Basis of Inherited Disease, Vol. 2, 8th edn. London: McGraw-Hill Professional, 2011; 2278–82.
2. Wada N, Matsuishi T, Nonaka M, Yoshino M. Pyruvate dehydrogenase E1 alpha subunit deficiency in a female patient: evidence of antenatal origin of brain damage and possible etiology of infantile spasms. Brain Dev 2004; 26: 57–60.
3. Barnerias C, Saudubray JM, Touati G, et al. Pyruvate dehydrogenase complex deficiency: four neurological phenotypes with differing pathogenesis. Dev Med Child Neurol 2010; 52: e1–9.
4. De Meirleir LJ, Vancoster R, Lissens W. Disorders of pyruvate metabolism and the tricarboxylic acid cycle. In: Saudubray J-M, van den Berghe G, Walter JH, editors. Inborn Metabolic Diseases, 5th edn. New York: Springer, 2011: 167–8.
5. Moroni I, Bugiani M, Castelli G, Lamantea E, Uziel G. Cerebral white matter involvement in children with mitochondrial encephalopathies. Neuropediatrics 2002; 33: 79–85.
CASE REPORT

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