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Review article

Pyruvate dehydrogenase deficiency and epilepsy

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Abstract

The pyruvate dehydrogenase complex (PDHc) is a mitochondrial matrix multienzyme complex that provides the link between glycolysis and the tricarboxylic acid (TCA) cycle by catalyzing the conversion of pyruvate into acetyl-CoA. PDHc deficiency is one of the commoner metabolic disorders of lactic acidosis presenting with neurological phenotypes that vary with age and gender. In this mini-review, we postulate mechanisms of epilepsy in the setting of PDHc deficiency using two illustrative cases (one with pyruvate dehydrogenase complex E1-alpha polypeptide (PDHA1) deficiency and the second one with pyruvate dehydrogenase complex E1-beta subunit (PDHB) deficiency (a rare subtype of PDHc deficiency)) and a selected review of published case series. PDHc plays a critical role in the pathway of carbohydrate metabolism and energy production. In severe deficiency states the resulting energy deficit impacts on brain development in utero resulting in structural brain anomalies and epilepsy. Milder deficiency states present with variable manifestations that include cognitive delay, ataxia, and seizures. Epileptogenesis in PDHc deficiency is linked to energy failure, development of structural brain anomalies and abnormal neurotransmitter metabolism. The use of the ketogenic diet bypasses the metabolic block, by providing a direct source of acetyl-CoA, leading to amelioration of some symptoms. Genetic counseling is essential as PDHA1 deficiency (commonest defect) is X-linked although females can be affected due to unfavorable lyonization, while PDHB and PDH phosphatase (PDP) deficiencies (much rarer defects) are of autosomal recessive inheritance. Research is in progress for looking into animal models to better understand pathogenesis and management of this challenging disorder.

Keywords: Pyruvate dehydrogenase; Lactic acidosis; Epilepsy; X-linked; Autosomal recessive

Abbreviations: PDHc, pyruvate dehydrogenase complex; TCA, tricarboxylic acid; PDHA1, pyruvate dehydrogenase complex E1-alpha polypeptide; PDHB, pyruvate dehydrogenase complex E1-beta subunit; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; MPTP-1, methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 3-NP, 3-nitropropionic acid; rAAV2, recombinant adeno-associated virus 2 vector; LGS, Lennox–Gastaut syndrome; PS, partial seizures; Mos, months; Abs, absence; SMEI, severe myoclonic epilepsy in infancy; GTC, generalized tonic clonic; GSWC, generalized spike-wave complex; GPFA, generalized paroxysmal fast activities; MC, myoclonic; GLUT1, glucose transporter 1; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; DCA, dichloroacetate

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1. Background

The metabolic fate of pyruvate consists of cycling through biochemical reactions involving pyruvate dehydrogenase complex (PDHc), the Krebs cycle and the respiratory chain (Fig. 1). An enzymatic defect in any of these pathways leads to inadequate utilization of pyruvate in turn resulting in lactic acidosis [1]. PDHc is a multienzyme complex that catalyzes the irreversible conversion of pyruvate into acetyl-CoA, and functions as a gateway to the oxidative metabolism of carbohydrate within mitochondria. The proteins constituting the enzyme complex are coded for by nuclear genes and the disorder is inherited through both X-linked and autosomal recessive modes of inheritance. PDHc deficiency presents with wide variation in neurological presentations that are age and sex dependent. The neurological phenotype includes cerebral dysgenesis, encephalopathy and coma, epileptic seizures, motor deficits, dystonia, and ataxia [2]. The genetics, clinical and neurological features, EEG, and brain imaging findings are discussed using two illustrative cases of PDHc deficiency resulting from two different subtypes and different mutations and modes of inheritance. A detailed summary of published cases in the literature of PDHc and epilepsy is also listed in Table 1. This mini review will help with the understanding of the genetic aspects and key neurological features that characterize the nature of epilepsy and management challenges associated with this inborn error of metabolism.

2. Illustrative cases

Both the cases below present unique aspects of clinical presentations of PDH deficiency and epilepsy. While case 1 (PDHA1 or X-linked form) presented with very severe intracranial abnormalities as shown in (Fig. 2a and b), lactic acidosis was modest. Her seizures have been significant and have required ongoing management with anticonvulsants and ketogenic diet. The patient in second case on the other hand presented with severe lactic acidosis and agenesis of corpus callosum and mild seizures. He carries a PDHB mutation (rare form of autosomal recessive PDHc deficiency).

2.1. Case 1

A female term infant was delivered by caesarian section to a 34 year old mother of Caucasian background. There were two previous siblings and a prior history of platelet antigen incompatibility, hypertension and gestational diabetes during pregnancy. Prenatal ultrasound scans suggested intrauterine growth retardation, absence of the corpus callosum and ventriculomegaly on ultrasound.

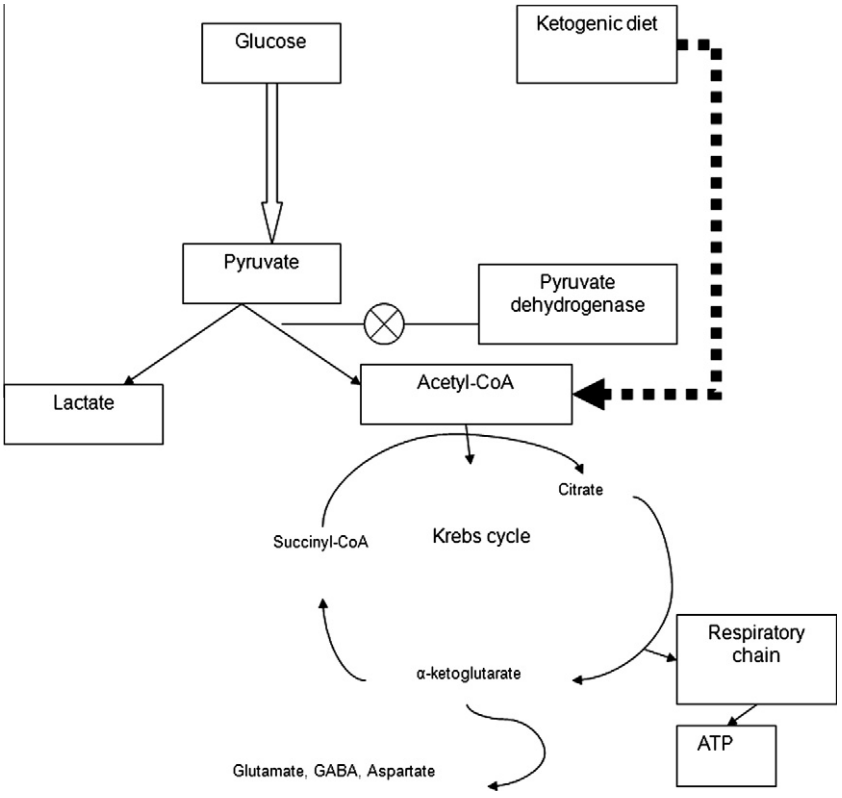

Fig. 1. A schematic flow chart of the metabolic pathways that links pyruvate dehydrogenase deficiency to energy production, neurotransmitter biosynthesis, and the mechanism of action of the ketogenic diet.

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Table 1
Summary of published case reports (PDHc deficiency and epilepsy).

Number of patients	Age of onset (gender)	Type of PDHc deficiency	Clinical phenotype and neurological phenotype (based on Barnerias et al. [2]	Seizure types	Brain imaging	Ketogenic diet/ Treatment/Response	References
22	1 months–2 years (3F, 6M)	PDHA1	Non-progressive infantile epileptic encephalopathy	Only 9/22 had epileptic seizures clonic seizures (3) and IS (3) and three presenting beyond age 2 years with myoclonic absences, atypical absences or tonic clonic seizures	Micropolygyria (1) lesion on MRI abnormalities in CC (3), basal ganglia (1)	Not clear how many were put on ketogenic diet	[2]
3	6 months (F) 2 months (F) 3 months (M)	Not specified Not specified Not Specified	Non progressive infantile epileptic encephalopathy (all 3)	IS → LGS (MC → Abs, GTC) SMEI (PS → GTCS, MC) IS → LGS (Abs, MC)	Normal Leukomalacia Diffuse cortical atrophy	Yes/ineffective (Pt died during diet therapy Yes/ineffective Yes/ineffective	[41]
60	1 day–4 months (9F,1M)	PDHA1 deficiency	Non progressive infantile epileptic encephalopathy	Seizures 10/60 IS West syndrome in 33% of females and 3% of males	Not known	not known	[38]
1	6 months (F)	PDHA1 deficiency	Non progressive infantile epileptic encephalopathy	IS	Cerebral atrophy multiple cystic changes in brain partial agenesis of corpus callosum (enlargement of ventricles detected antenatally)	Yes/ineffective	[42]
7	Birth-13 months (7M)	PDHA1 deficiency	Non progressive neonatal encephalopathy Leigh syndrome relapsing ataxia	Seizures (2/7) clinical details regarding seizure type not provided	Cerebral atrophy demyelination (2/7)	Ketogenic diet. All patients died. Earlier introduction of ketogenic diet improved patient survival for some	[34]

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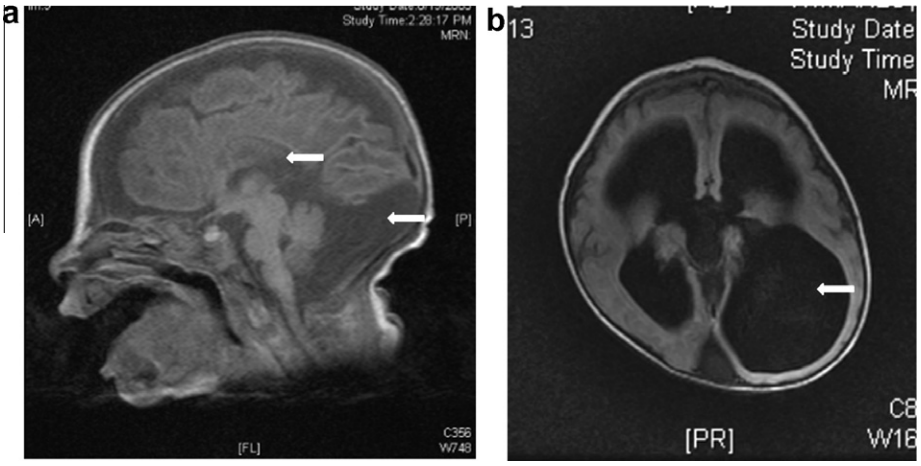

Fig. 2. Magnetic resonance imaging (panel). First exam was done at 5 days of age (a). Axial T1 weighted (TR1500, TE 15, and TI0). Sagittal cuts showing callosal dysgenesis (arrow), diffuse cerebral and cerebellar atrophy, loss of white matter, ventriculomegaly, and mega cisterna magna (arrow), while axial variable flip sequences show diffuse cortical atrophy, loss of white matter, and ventriculomegaly. Follow up study at 11 months of age (b) includes sagittal and axial cuts (sagittal T1 variable flip SE TR 550, TE 12, TI of 0, and axial FSE Dual TR 3600, TE 95.778, and TI 0) showing the progression of cortical atrophy and ventriculomegaly (arrow), loss of white matter bulk, and dysgenesis of the corpus callosum (arrow).

The older sibling was known to have a severe chromosomal abnormality (mosaicism for chromosomes 15 and 8). The mother reported excess *in utero* movements. Apgar scores were 8 and 9 at 1 and 5 min, respectively. The infant examination was notable for the growth parameters being relatively small for dates (birth weight 2.8 kg 10th percentile), and microcephaly (head circumference was 32.5 cm, <3rd percentile). Nonspecific facial dysmorphic features were noted with thin lips, smooth philtrum and anteverted nostrils. Within hours of birth, the infant developed episodes of recurrent apnea and bradycardia. On neurological assessment poor visual fixation, nystagmus and profound axial hypotonia were present. Cranial ultrasound examination disclosed microcephaly (plagiocephaly) and agenesis of corpus callosum. While the rest of the biochemical workup was normal, lactic acidosis with blood lactate levels in the 4–6 mmol/L range (reference values: 0.5–2.2 mmol/L) was documented repeatedly. Magnetic resonance imaging at age 5 days confirmed agenesis of the corpus callosum, ventriculomegaly (colpocephaly), thinning of the periventricular white matter, marked cerebellar hypoplasia, and a large retrocerebellar cyst (Dandy–Walker variant) (Fig. 2a). By age 7 months profound developmental delay was evident. Prominent pendular nystagmus in all directions of gaze suggested cortical visual impairment. The infant's hands were held fisted; muscle tone in the lower extremities was increased with hyperactive knee and ankle jerks. Follow up cranial MRI study at 11 months of age (Fig. 2b) showed further progression of cerebral atrophy, loss of white matter bulk, and absence of the corpus callosum.

PDHc deficiency was confirmed by enzymatic studies on fibroblasts. PDH (native) activity was 0.15 ± 0.02 (controls 0.76 ± 0.14) nmol/min/mg/protein, pyruvate dehydrogenase (dichloroacetate activated) was 0.12 ± 0.02 (control 1.17 ± 0.12) and lactate/pyruvate ratio was reduced at 5.9 ± 0.38 (controls 17.5 ± 4.1). Molecular studies showed an R378C (1132C → T) mutation only on cDNA sequencing (not a common mutation). This mutation has been previously characterized [3]. A western blot with total PDHc antibody showed no E1α or E1β (enzymatic and molecular studies done at Dr. Brian Robinson's laboratory, Hospital of Sick Children, Toronto).

2.2. Natural history of epilepsy and neurodevelopmental progress

By the first year of life, the infant had developed tonic epileptic spasms as well as myoclonic seizures. These appeared to occur or coincide with sleep onset. Between the age of 2 and 4 years she had multiple hospitalizations for respiratory infections, seizures and aspiration pneumonia. A gastrostomy tube was inserted for feeding and medication use. She remains severely developmentally delayed, can only babble and make non-specific vocalizations. Her seizures remain reasonably well controlled on a combination of antiepileptic drugs (lamotrigine 6–10 mg/kg/day and clonazepam 0.1–0.2 mg/kg/day). She smiles often and appears to enjoy loud noises (banging of pots and pans). EEG findings at the age of 17 months were notable for the presence of slowing of background rhythms, predominantly over posterior quadrants and the presence of abundant focal independent epileptiform discharges over bilateral occipital regions with regional spread to parietal and central areas of both hemispheres. The focal spike and wave complexes occurred singly and repetitively without clinical accompaniments. At age 3 years, she developed

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simple, as well as complex partial seizures with staring, automatisms and focal clonic movements that were secondarily generalized. Follow up EEG recordings showed slowing of background rhythms over posterior quadrants, focal spike wave complexes maximal over the left hemisphere involving left central temporal and occipital regions and the vertex. Presently she is 5 years old, and her seizures are well controlled, except for continuing "startles" or myoclonic jerks. At age 5 years a posterior dominant rhythm of about 4 Hz is now seen, the background rhythms remain slow for age, focal spike and wave complexes are now seen over the left frontal, central parietal regions. A modified ketogenic diet was initiated when she was 17 months of age. Current caloric distribution is fat 65%, carbohydrates 19%, and protein 16% through gastrostomy tube and intravenous fluids for emergency access through portacath. The classic ketogenic diet in comparison includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1. Thiamine, lipoic acid, coenzyme Q, carnitine supplements and antiepileptic medications (lamotrigine and clonazepam) have been helpful. In addition, lorazepam (0.1 mg/kg/day) is being used as intermittent rescue therapy for the symptomatic management of acute seizure exacerbations.

2.3. Case 2

A 9.5 years old male born at term to consanguineous parents of northern Iraqi background has been followed in our metabolic clinic with microcephaly (head circumference 47 cm; $\ll$3rd percentile) and developmental delay. Prenatal ultrasound scans had confirmed the agenesis of corpus callosum. The infant presented with severe lactic acidosis soon after birth (plasma lactate levels ranged 8.2–22 mmol/L) (normal 0.5–2.2 mmol/L) with a normal lactate to pyruvate ratio. Urine organic acids showed excretion of large amounts of lactate and pyruvate. A prior sibling of this infant had died of lactic acidosis in the neonatal period. Post mortem studies had confirmed an absent corpus callosum. PDHc deficiency in the proband was suspected and confirmed by the enzymatic assay of PDHc in skin fibroblasts. PDHc was found to be very low (11% of the mean of prior controls). The residual activity showed some activation/inactivation after incubation with DCA/fluoride of 0.27 (control 2.03 nmol/min/mg protein in skin fibroblasts). Activity of E3 component of PDHc was normal (128% of prior controls). The ratio of PDHc/E3 was very low (9% of the mean). Molecular analysis showed a homozygous missense mutation 106 C > T causing R36C change in PDHB gene which encodes the protein E1 beta subunit of the pyruvate dehydrogenase complex (biochemical and molecular analysis (Dr. D.S. Kerr's laboratory: Center for Inherited Disorders of Energy Metabolism (CIDEM), Cleveland, Ohio)). Molecular genetics aspects of this case are previously published [4].

2.4. Natural history of epilepsy and neurodevelopmental progress

Initial seizure-like episodes reported in this patient included generalized tonic posturing and myoclonic jerks during the acute phase. During the newborn period phenobarbital was used for seizure control (stopped after infancy). Since the institution of a ketogenic diet at 6 months of age, his condition improved dramatically, his seizures have remained well controlled. In addition the lactate levels have normalized. The patient is sociable and very interactive, maintaining motor skills and has gained a vocabulary of a few words. Currently, the treatment regimen consists of supplements of carnitine 100 mg/kg (divided into three dosages), thiamine 100 mg once a day, ketogenic diet (80% calories as fat, 10% carbohydrate, and 10% protein). Recent neurological evaluation disclosed a left-handed dominant boy, with microcephaly, motor findings consistent with mild spastic diplegia, global developmental delay, intermittent dystonic posturing of his right hand, and congenital nystagmus. His developmental age is approximately 2 years, with a vocabulary of about 10 words. Initial brain imaging showed agenesis of corpus callosum and generalized brain atrophy. Repeat EEG at age 7 years does not show any significant epileptiform activity.

3. Discussion

3.1. Etiology, biochemical, and molecular basis of pyruvate dehydrogenase deficiency

Human PDHc is a multienzyme complex of 6 subunits, pyruvate dehydrogenase (E1), dihydrolipoyl acetyl transferase (E2), dihydrolipoyl dehydrogenase (E3), an E3-binding protein (E3BP), and two dedicated regulatory components—pyruvate dehydrogenase kinase (PDK) and pyruvate dehydrogenase phosphatase (PDP) [5,6]. The E1 component of the PDH complex contains a conserved TPP binding motif that helps catalyze the thiamine pyrophosphate (TPP)-dependent decarboxylation of pyruvate. In addition, the PDH complex is regulated by phosphorylation/dephosphorylation of the PDHA1 subunit [7]. The PDHA1 gene (MIM300502) is located at Xp22.2-p22.1 and is the most frequently encountered inherited defect that leads to impaired PDHc activity. A majority of the mutations involving the PDHA1 encode the E1α subunit of the PDHc which impairs either polypeptide stability or catalytic efficiency [7–9]. E1β subunit of PDH has been mapped to 3p13-q23. PDHB encodes E1β subunit of PDHc and accounts for only a minority of cases of PDHc deficiency. In a recently published report on PDH deficiency, there were four

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cases of PDHB (MIM 179060) among 83 cases [4].The R36C mutation (detected in case 2) causes a reduction of the number of internal hydrogen bonds that in turn affects the interaction of several amino acids resulting in conformational changes leading to instability of the E1β subunit. Though the severity of enzyme deficiency is similar to PDHA1, PDHB mutations also present with considerable phenotypic variability and severity [4]. Other rare subtypes include PDP deficiency which can cause severe metabolic acidosis in the neonatal period. These cases can present with lactic acidosis, nystagmus and gastrointestinal involvement [10–12].

3.2. Clinical and neurological phenotypes of PDHc deficiency

PDHc deficiency is remarkable primarily for its effects on cerebral metabolism. This further affects both structure and function of the brain without involvement of other organ systems. Initial descriptions of the neurological phenotype in PDHc deficiency (PDH1A) by Robinson et al. identified three patterns: (1) a neonatal encephalopathic pattern with facial dysmorphic features and cerebral developmental defects affecting females, (2) Leigh syndrome-like presentation with symmetric necrotic lesions of the basal ganglia in males, and (3) a chronic relapsing ataxia in males compatible with prolonged survival [13,14]. A recent review reinforces the great variability in neurological phenotypes and also reconfirms the age dependent presentation and four patterns of neurological features [2] (Table 1). In addition to the above three, a fourth pattern includes a static encephalopathy/cerebral palsy like motor deficits associated with paroxysmal dystonia. The presentation of relapsing ataxia is currently attributed to a chronic axonal neuropathy [2]. PDHC deficiency and other mitochondrial disorders of oxidative phosphorylation show overlapping neurological phenotypes whether it be Leigh's syndrome [15], West syndrome [16], or morphological abnormalities of the developing nervous system [17].

PDHc plays a critical role in maintaining energy homeostasis within the nervous system that is essential during the development of the nervous system, as well as its function [18]. As a normal level of pyruvate dehydrogenase (PDH) enzyme activity is a key prerequisite of aerobic metabolism, PDH deficiency is often associated with both developmental as well as encephaloclastic lesions [17,19].

The chronic energy deficit from PDHc deficiency likely leads to perturbations of the normal sequence of development, neuronal migration and differentiation resulting in callosal dysgenesis (Fig. 2a and b), as well as the formation of grey matter heterotopias in the periventricular white matter and in the cerebellum [20]. Magnetic resonance imaging as well as cranial ultrasound can detect structural brain anomalies such as agenesis of corpus callosum, diffuse cerebral and cerebellar atrophy, loss of white matter, ventriculomegaly and mega cisterna magna as seen in our case 1. The cranial structural abnormalities can be asymmetrical particularly in females [2] [17,19]. Acute energy failure in PDH deficiency can also lead to neuronal injury and cell death, and progressive neuronal loss resulting in encephaloclastic lesions of the grey matter of the tegmentum, the dentate nuclei, and the thalami in a pattern reminiscent of the features of Leigh syndrome [2].

3.3. Pathogenesis of epilepsy (EEG and brain imaging)

The developmental lesions mentioned above lay the foundation for the occurrence of lesional epilepsy as a cause for epileptic seizures. Furthermore prominent pathological neocortical involvement due to PDHc deficiency probably accounts for the epileptogenic susceptibility associated with defects of pyruvate metabolism [21]. In a study of epilepsy associated with infantile onset mitochondrial encephalopathies, PDHc deficiency accounted for 41% of patients with epilepsy [22]. Early onset presentations include infantile spasms and subsequent evolution into one of the intractable epilepsy syndromes associated with developmental lesions, while generalized seizures presenting in later life tend to be pharmacosensitive or at least partially responsive to the introduction of the ketogenic diet and thiamine supplementation [2] (Table 1). Atypical absence and myoclonic seizures are also described in association with paroxysmal dystonia. In our illustrative cases, the seizures reported in the second case were mild and self-limiting, while in the first case, the seizures continue to be pharmacosensitive and responsive to conventional antiepileptic medications, with periodic exacerbations during infections and metabolic stress.

Epileptogenesis in PDHc differs from other disorders of energy metabolism according to the presence or absence of structural and functional brain abnormalities. There is a vast body of *in vivo* and *in vitro* literature linking mitochondrial dysfunction with the epileptic state. Clinical evidence suggests a strong relationship of defects in mitochondrial energy metabolism as a cause of epileptic seizures (e.g., MELAS, and MERRF) [22]. Experimental evidence on the other hand suggests that mitochondrial energy metabolism is affected as a consequence of epileptic seizures resulting in both neuronal death, as well as altered neuronal function leading to epileptogenesis [23,24]. Numerous correlates of the electrophysiological measures of epilepsy link energy metabolism with enhanced excitability of the brain, and the generation of conditions that are capable of sustaining abnormal neuronal firing, leading eventually to epileptogenesis [25].

In situations with later onset and milder epilepsy phenotypes, the epileptogenic process may be similar to the

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situation encountered in other disorders of energy failure that are associated with epilepsy (GLUT1 transporter defect and mitochondrial encephalopathies such as MELAS and MERRF). There is strong evidence of metabolic coupling that exists between energy metabolism and neurotransmitter synthesis and turnover cycles within neurons and the supporting cells of the glial network [26–28]. A biologically plausible hypothesis would be to suggest that PDHc deficiency could destabilize the neurotransmitter balance in the glioneuronal unit and wider neuronal network through effects on glutamate and GABA, as these compounds are sourced from the TCA cycle through alpha ketoglutarate. Published clinical data would suggest that energy failure could target different regional networks and other neurotransmitter systems (dopaminergic) producing the variable neurological phenotypes (paroxysmal dystonia from basal ganglia injury and cerebellar ataxia in late onset PDHc deficiency) [2]. Animal models of mice deficient in dihyrdrolipoamide dehydrogenase, a critical component of the PDHc complex, are more vulnerable to striatal injury induced by MPTP, malonate as well as other mitochondrial toxins such as 3-NPA [29]. As has been shown in vitro experiments, normal PDHc protein is itself likely to be a target for oxidative stress induced loss of activity under conditions of ischemia and reperfusion or other forms of metabolic stress [30]. It is conceivable that mutant PDHc could also be similarly susceptible leading to a loss of PDHc activity below a critical threshold required to maintain neuronal membrane stability and integrity. Such an effect, however, remains to be convincingly demonstrated in animal model of PDHc deficiency. Further, lowered intracellular Pcr (phosphocreatine)/ATP ratios result in an inability to maintain ionic gradients across neuronal membranes efficiently, as these processes are energy dependent (e.g., Na-K pump) [25]. Intracellular homeostasis of calcium is handled by mitochondria and plays an important role in regulation of several critical cellular neurophysiological processes including aerobic metabolism and cell death [31–33]. Thus, one could speculate that the energy deficit in PDHc deficiency targets not only excitatory/inhibitory neurotransmitters, but other neurotransmitters systems as well leading to dysfunction in different pathways (pyramidal and extrapyramidal) in the brain. The putative mechanisms linking energy deficit in mitochondrial disorders to heightened seizure susceptibility and ictogenesis are summarized in Fig. 3.

3.4. Metabolic management

Cofactor supplementations with thiamine, carnitine, and lipoic acid have been used in patients with PDHc deficiency. High doses of thiamine may be most effective in some mutations causing thiamine-responsive PDHc deficiency. Ketogenic diets consisting of fat, carbohydrate and protein caloric intakes of 80%, 10%, and 10%, respectively, have been used to control lactic acidosis and seizures with some success [34]. Dichloroacetate (DCA) reduces the inhibitory phosphorylation of PDHc and has been used to treat lactic acidosis. Resolution of lactic acidosis is observed in patients with PDHA1 enzyme subunit mutations that reduce enzyme stability [35] when treated with DCA, however, it does not appear to reverse the disease process [36].

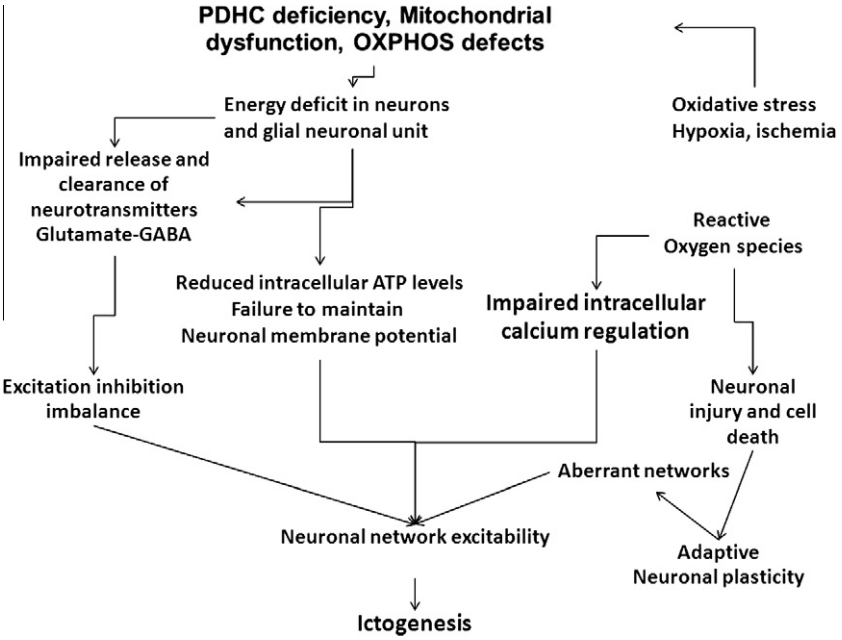

Fig. 3. Putative mechanisms underlying ictogenesis in mitochondrial disorders.

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3.5. Inheritance and genetic counseling

PDHA1 is the commonest defect of the PDHc. PDHA1 exhibits X-linked inheritance. It is thought to be X-linked dominant as heterozygous females can manifest severe symptoms, although males are typically affected to a much greater extent [37]. Severe lactic acidosis with early demise and Leigh syndrome are more commonly observed in males with PDHc deficiency. West syndrome has been encountered more frequently in females with PDHc deficiency. Of 60 patients with PDH deficiency, one male infant and nine female infants were found to have West syndrome [38] (Table 1). The factors that lead to this relative female preponderance are not completely understood. One possible explanation for this phenomenon may be attributed to a random and unfavorable inactivation of the normal allele in females. It has been suggested that such random inactivation (lyonization) would give rise to a form of somatic mosaicism with two populations of cells in the developing nervous system, one with a mutant allele, and one with a normal allele. On the other, in males all cells in the nervous system would be uniformly affected in carrying the mutant allele. Affected cells carrying the mutant allele would be prone to an energy deficit and lactate accumulation. It is proposed that this imbalance in ATP pools within the two populations of neurons could account for the propensity to develop infantile spasms in females with PDHc deficiency [38]. Progressive neurological degeneration is observed more commonly in females with PDHc deficiency. A family history is potentially informative in identifying the autosomal recessively inherited PDHB and PDP deficiencies. Prenatal diagnosis based on mutations is preferred because of difficulties in interpreting PDHc enzyme assay results in females. Families need to be provided with formal genetic counseling.

3.6. Animal model

A zebra fish model exists with two alleles of the recessive lethal mutant 'no optokinetic response a' (*noa*) [39] that exhibits phenotypes similar to human PDHc deficiency. To rescue the deficiency, the researchers added ketogenic substrates to the water in which the embryos developed. This treatment successfully restored vision, promoted feeding behavior, reduced lactic acidosis, and increased survival. Gene therapy has also been tried using rAAV2 vectors that expressed PDH E1α. *In vitro* studies demonstrated a correction of approximately 30% of wild-type PDH activity in PDH deficient patient fibroblasts. Vectors were tested *in vivo* with stereotaxic injection into rat striatum and expression persisted for 1 year without evidence of toxicity. More research is required into role of gene therapy in humans [40].

4. Summary and conclusion

PDHc is a critical enzyme essential for normal neuronal function; however, it is interesting to note that there appears to be little to no extra-neurological consequences of its deficiency. Structural brain anomalies are common in this condition along with varying severity of epilepsy. Different forms of inheritance are seen with PDHc deficiency with X-linked inheritance being most frequently encountered. Other subtypes are inherited in an autosomal recessive manner. Clinical presentations of various subtypes can be similar. Diagnosis is available both by biochemical and molecular means. Management is still far from ideal although early institution of a ketogenic diet may be helpful in some cases. Dichloroacetate has not found universal acceptance due to its side effects of peripheral neuropathy and that it does not reverse the central nervous system problems. More research is needed for the optimal management of epilepsy and pathogenesis of epilepsy in the setting of PDHc deficiency. Families require formal genetic counseling and psychosocial support as PDHc deficiency is a complex disorder and can be associated with a poor prognosis.

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