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The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, biochemical and genetic features in 371 patients

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Abstract

Context—Pyruvate dehydrogenase complex (PDC) deficiency is a genetic mitochondrial disorder commonly associated with lactic acidosis, progressive neurological and neuromuscular degeneration and, usually, death during childhood. There has been no recent comprehensive analysis of the natural history and clinical course of this disease.

Objective—We reviewed 371 cases of PDC deficiency, published between 1970 and 2010, that involved defects in subunits E1α and E1β and components E1, E2, E3 and the E3 binding protein of the complex.

Data sources and extraction—English language peer-reviewed publications were identified, primarily by using PubMed and Google Scholar search engines.

Results—Neurodevelopmental delay and hypotonia were the commonest clinical signs of PDC deficiency. Structural brain abnormalities frequently included ventriculomegaly, dysgenesis of the corpus callosum and neuroimaging findings typical of Leigh syndrome. Neither gender nor any clinical or neuroimaging feature differentiated the various biochemical etiologies of the disease. Patients who died were younger, presented clinically earlier and had higher blood lactate levels and lower residual enzyme activities than subjects who were still alive at the time of reporting. Survival bore no relationship to the underlying biochemical or genetic abnormality or to gender.

Conclusions—Although the clinical spectrum of PDC deficiency is broad, the dominant clinical phenotype includes presentation during the first year of life; neurological and neuromuscular

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degeneration; structural lesions revealed by neuroimaging; lactic acidosis and a blood lactate:pyruvate ratio≤20.

Keywords

Congenital lactic acidosis; Dichloroacetate; Neuroimaging; Ketogenic diet; Pyruvate dehydrogenase complex; Thiamine

1. Introduction

The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics [1,2] (Fig. 1). It comprises multiple copies of three enzymatic subunits: pyruvate dehydrogenase (E1), dihydrolipoamide transacetylase (E2) and dihydrolipoamide dehydrogenase (E3), as well as an E3 binding protein (BP). The E1 component is a heterotetramer of 2 alpha and 2 beta subunits. The gene for the E1α subunit is located on the X chromosome and all proteins of the complex are nuclear encoded. Rapid regulation of the complex is regulated mainly by reversible phosphorylation of the E1α subunit [3] that is mediated by a family of PDC kinases (PDK) and phosphatases (PDP) [4,5].

Although over 40 years have elapsed since the first description of a congenital deficiency of the PDC [6], the incidence and prevalence of this life-threatening condition remain unknown. Several excellent earlier reviews exist of the clinical and biochemical characteristics or of the molecular genetic etiologies of PDC deficiency [2,7–9]. However, there has been no recent comprehensive analysis of the natural history of the disease, nor attempts to discern phenotypic differences or predictable outcomes based on biochemical defects or mutations in specific components of the complex. Here we summarize the clinical, biochemical and genetic findings contained in published reports and personal experience of 371 individual cases of PDC deficiency. We sought associations among various pathological indices that could provide new insight into the pathobiology and clinical course of this disease.

2. Material and methods

2.1. Source material

We reviewed all English language publications under “pyruvate dehydrogenase deficiency” and deficiency of each individual subunit and component of the complex listed in PubMed and Google Scholar from 1970 through December, 2010 [6,10–163]. Additional publications were found by reviewing the references included in articles not identified by the search engines. We also included information on a previously unpublished case of PDC E1α deficiency.

2.2. Definition of PDC deficiency

To be included a report had to provide a quantitative assessment of overall PDC activity and/or of the activities of its component parts. In most cases, PDC specific activity was determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time. No case was

included unless a “normal” control mean value or range of control values was given. For cases in which only the range of normal values was provided, we used the minimum value of the range. For cases in which the values for enzyme activity were listed for more than one cell type, the default choice was: fresh or frozen skeletal muscle, then primary cultures of skin fibroblasts, then freshly isolated lymphocytes or transformed lymphoblasts, then other tissues (e.g., liver). This order was adopted because skeletal muscle is highly dependent upon mitochondrial oxidative metabolism and is thus a target tissue in PDC deficiency and because a skin biopsy was the most common source of cells used in making the biochemical diagnosis. If serial measurements were made in different tissue specimens, we used the lowest reported value, applying the same default strategy described above. If a publication described a patient with a clinical presentation consistent with PDC deficiency (e.g., psychomotor retardation, hypotonia, neonatal lactic acidosis) *who* was found to have a pathological mutation in a subunit or component enzyme of the PDC *or* who had a first degree relative who possessed a pathological mutation involving the complex, we accepted the patient as having PDC deficiency, even without confirmation by standard enzymological criteria. Thus, the total number of PDC cases exceeds the number of cases in which a measureable enzymological defect was obtained.

2.3. Clinical features

Age of clinical disease onset was defined as the earliest reported clinical or biochemical sign or symptom consistent with a genetic mitochondrial disease. Quantification of intellectual, neuromuscular or peripheral nerve function or other clinical signs was seldom reported; therefore, we included them only as descriptive variables.

2.4. Metabolites

We combined data on whole blood, serum and plasma concentrations for lactate and pyruvate and chose the highest value reported for an individual case. We also used the highest reported values for cerebrospinal fluid (CSF) lactate and pyruvate. Circulating levels of alanine, which is in equilibrium with pyruvate and lactate (Fig. 1A), and other metabolites were frequently described as “elevated” but often were not quantified; consequently, we expressed the overall frequency of reported abnormalities in these molecules descriptively.

2.5. Neuroimaging

Findings derived from computerized tomography or magnetic resonance imaging of the brain, with or without the use of contrast material, were included in this category. “Leigh syndrome” (subacute necrotizing encephalomyopathy) was applied to cases in which patients had neuroimaging findings that included focal, bilaterally symmetric lesions in one or more parts of the basal ganglia, thalamus and brainstem.

2.6. Statistical analysis

Although this paper is mainly descriptive, we did conduct a number of comparisons. Qualitative associations were conducted by Fisher’s exact test. Comparisons between two groups for quantitative measures were conducted by the Satterthwaite *t*-test, which corrects for unequal population standard deviations. Associations between quantitative variables

were conducted by the Pearson's Correlation Coefficient. Readers are cautioned that, because a large number of statistical tests were conducted, some associations may be spurious.

3. Results

We found 159 full-length, peer-reviewed publications of 392 case reports of patients with PDC deficiency from the first reported case in 1970 [6]. A few papers reported complimentary details of the same patient [6,21,28,34,36,37,41,43,45,62,65,71,73,76,79,80,92,93,99,101,108, 110,124]. Twenty-one cases were omitted from our analysis, owing to lack of explicit enzymological or molecular genetic confirmation of disease [10–20]. Hence, this review summarizes the findings of 371 patients [6,12,21–163] (see Suppl. Table 1).

3.1. Clinical signs

Table 1 summarizes the most frequently reported clinical signs of PDC deficiency. We combined 211 cases in which patients were described as having "developmental delay", "mental retardation" or "psychomotor retardation" because of the ambiguity of these terms and the considerable overlap in their application to patients. This category was the most frequently reported clinical sign and was present in 57% of cases. Hypotonia and/or hypertonia (169 cases) were the next most frequently reported signs; most of these patients were hypotonic, whereas hypertonia was reported in a few instances. Ataxia was reported in 72 patients and was more common in males ($p=0.012$). Other frequently reported signs of motor dysfunction included spasticity, ptosis, and choreoathetoid movements. Reports of seizure activity frequently did not discriminate between focal and generalized convulsions, so this category includes both presentations. Microcephaly was usually reported without reference to a measured head circumference or in relation to a normative value. Respiratory distress typically occurred in the setting of acute acid–base decompensation and lactic acidemia, particularly in the neonatal period. Facial dysmorphism was reported to affect girls more frequently than boys and included such features as narrow head, frontal bossing, prominent philtrum and wide nasal bridge. Ocular manifestations of disease included optic atrophy, nystagmus and strabismus. The term "peripheral neuropathy" was used descriptively in most cases, even when formal nerve conduction testing was apparently undertaken during a patient's evaluation, and was reported more frequently in males ($p=0.004$).

3.2. Biochemical features

Among all patients, 326 (89%) reports provided enzymological data and, in most cases, additional biochemical investigation that identified the affected subunit (Table 2). The mean ±SD residual enzyme activity among cases was 37.0±34.6% of the normative data recorded in these reports. Most patients with PDC deficiency presented with clinical signs consistent with the disease (Table 1) before 1 year of age, regardless of the affected subunit or component. Seventy-six percent of patients had PDC deficiency due to a deficit in the α subunit of E1. Males slightly outnumbered females and consanguinity accounted for about 7% of all cases. A majority of patients with a deficiency of E1β [132,151,157], E2 [136] or

E3BP [12,58,78,126,128,140,143,171] were products of consanguinity, in which the disease often occurred in more than one family member.

Table 3 summarizes the maximum reported lactate and pyruvate concentrations in blood and CSF and the blood lactate:pyruvate ratio. In some cases, only single values were reported; in others, serial blood levels were documented, although the time sequences varied greatly. Blood lactate was the most frequently reported value. The blood lactate: pyruvate ratio was calculated for those cases in which these measurements were obtained simultaneously. Virtually no temporal associations were described between measurements of blood and CSF chemistries; thus, we made no associations between blood and CSF lactate or pyruvate levels. These values were similar between genders and among the various biochemical diagnostic categories.

3.3. Neuroimaging findings

One hundred eighty-six patients had one or more imaging studies of the brain (Fig. 2). Seven subjects were reported to have normal imaging findings; all had E1α deficiency [80,110,125,137,145,147,156,163]. Ventriculomegaly was the most frequent abnormality, affecting 65 patients (35%) in whom an abnormal brain imaging finding was reported. Leigh syndrome was described in 50 patients (27%); autopsy confirmation of this condition was reported very rarely. The basal ganglia, brain stem and cerebellum are anatomical areas frequently reported in association with Leigh syndrome and were identified as isolated abnormalities in some patients. Hypogenesis or agenesis of the corpus callosum was reported in 57 patients (31%) and in slightly over one-third of E1α deficient individuals.

3.4. Molecular genetics

There were 237 cases (66%) that reported a mutation in a PDC component gene (Supplemental Table 1). Mutational data are listed chronologically and in relation to patient gender, residual PDC enzyme activity and age of clinical onset of disease. Missense mutations were more prevalent than frameshift mutations and occurred more often in males; most females harbored frameshift mutations (Table 4). Although patients possessing missense mutations were most likely to present clinically later in life (7.73±11.37 months vs. 3.60±7.64 months for frameshift mutations), there were no significant differences between these mutational classes in residual enzyme activity, maximum blood lactate concentration or survival at the time of case reporting. Not surprisingly, most mutations (84%) were located in the *PDHA1* gene. Among E1α deficient individuals, most missense mutations localized to exons 1–9 (77%), whereas most frameshift mutations localized to exons 10 and 11 (86.5%). Associations among *PDHA1* missense mutations, the amino acid sequence of the E1α subunit and residual PDC enzyme activities are described in the Supplemental Text and Supplemental Figs. 1–5.

3.5. Clinical outcome

We examined the cross-sectional relationship between PDC deficiency, based on biochemical diagnosis, and survival (Fig. 3). There were 294 cases (79% of total) in which the age of the patient at death was reported or in which the patient was said to be alive at the time the case was described. Table 5 shows that 108 patients (36.6% of total) died at the

time of reporting, with a mean age at death of 2.70±4.66 years. The remaining 187 patients were alive at the time of reporting, with a mean age of 7.10±6.15 years. There were 243 patients alive at 0.5 years of age, but only 10 patients were alive at age 20 years (Fig. 3). These statistics were closely matched by the data from the E1 and E1α patient subgroups. The only other category in which similar results could be compared was the group of E3BP deficient subjects. However, as noted in Table 2, over 60% of these patients were from consanguineous relationships. Patients who died before case reporting were 8 months younger at the time of clinical presentation, compared to those who were alive at the time of reporting (2.9±6.56 months vs. 11.3±19.8 months; $p=0.001$). Deceased patients also had higher maximum blood lactate concentrations (11.1±7.3 mmol/L vs. 6.2±3.8 mmol/L; $p<0.001$) and lower residual PDC activity (26.6±23.6% vs. 37.7±33.4%; $p<0.002$). However, these three variables were only weakly correlated with each other (range of r: 0.235 to 0.281).

Because E1α deficient patients represented the largest single subgroup in PDC deficiency, we undertook a similar cross-sectional comparison of age versus outcome in those E1α deficient patients in whom a mutation in the *PDHA1* gene was identified (Fig. 4). Of 187 patients with *PDHA1* mutations, the most frequently reported were at amino acid positions 302 (15 cases), 263 (15 cases) and 378 (14 cases); 35 were missense mutations. Note that a mutation affecting amino acid position 378 may be particularly lethal. Of those individuals with a mutation affecting this position, seven were dead within the first 2 years of life. In contrast, patients with an amino acid substitution at either position 263 or 302 appeared to have a less truncated life span. Males accounted for 29 (83%) of these common mutations.

We next examined the effect of gender on the outcome of all cases with PDC deficiency or E1α deficiency (Table 6). The proportion of males who died was greater than that of females in both groups. Unexpectedly, we also found that females who died presented earlier in life and died at a younger age than males, yet had higher residual enzyme activity. The reason for this apparent discrepancy is unclear.

3.6. Other associations

We found no statistically significant associations between genders regarding the following variables: survival outcome at the time of case reporting; mental retardation/developmental delay/psychomotor retardation; hypotonia/hypertonia; microcephaly; facial dysmorphism; corpus callosum hypogenesis or agenesis; Leigh syndrome; basal ganglia involvement; or brainstem and cerebellar involvement. There was also no significant difference between the individual enzyme component deficiencies and the categories above and no significant association between corpus callosum agenesis or hypogenesis and Leigh syndrome, or between microcephaly and ventriculomegaly.

3.7. Treatment

Finally, we sought information relating to the clinical management of PDC deficiency. Alkali, usually as sodium bicarbonate, was administered often but sporadically, usually as a temporary treatment for acute acid–base decompensation. The most common interventions used chronically were thiamine (vitamin B1; 73 cases), a ketogenic diet, comprising at least

65% of total calories (19 cases), and dichloroacetate (DCA; 15 cases). Thiamine doses varied, from a few milligrams per day to doses exceeding 1 g/day. These latter cases typically involved patients in whom PDC deficiency was considered due to a mutation affecting the interaction of thiamine pyrophosphate with the E1α subunit. The frequency with which ketogenic diets were employed may be underrepresented because many reports failed to specify the proportion of fat calories. Some patients received intravenous DCA for acute treatment of lactic acidosis but the majority of patients received DCA for chronic oral treatment at doses usually of 25 mg/kg/d or more. No intervention for PDC deficiency has been evaluated in a randomized controlled trial.

4. Discussion

PDC deficiency has been considered one of the most common biochemically proven causes of congenital lactic acidosis [2]. Our review of 371 cases of biochemically and/or genetically established PDC deficiency supports this notion. Regardless of which subunit or component of the complex is defective, most patients present within the first few months of life with both clinical and biochemical evidence of disease. The dominant presenting phenotype of PDC deficiency includes impairment of neurological and motor function; structural abnormalities of the brain, particularly ventriculomegaly, collossal dysgenesis and findings consistent with Leigh syndrome; hyperlactatemia; and a circulating lactate:pyruvate ratio≤20. Nevertheless, the clinical spectrum of PDC deficiency is broad, ranging from neonatal death with overwhelming lactic acidosis to a relatively benign course early in life with few overt signs.

Inhibition of PDC activity impairs the mitochondrial oxidation of pyruvate and promotes its cytoplasmic reduction to lactate or transamination to alanine. Diminished flux through the PDC also decreases the availability of acetyl CoA for the TCA cycle. In turn, reduction of both PDC and TCA cycle activities decreases the generation of reducing equivalents (as NADH and $FADH_2$) that donate electrons to the respiratory chain to complete the process of oxidative phosphorylation. Consequently, potentially any congenital or acquired defect in any PDC component may give rise to lactic acidosis and to cellular energy failure, the latter most commonly expressed as progressive neurological and neuromuscular deterioration. Thus, it is not surprising that we found no clinical, neuroimaging or biochemical signs that distinguish patients with the most commonly reported E1α deficiency from patients with defects in E1β, E2, E3 or the E3BP of the complex. In general, those who died were younger, had earlier clinical onset and had lower PDC activity.

The natural history of PDC deficiency appears generally very similar between genders. However, boys may die proportionately more often than girls, yet at an older age, a phenomenon that may reflect the impact of lyonization of the *PDHA1* allele. Although significant gender differences were observed for ataxia and peripheral neuropathy, we caution against overinterpreting these findings. Ataxia has been reported in response to carbohydrate feeding in a subset of males who exhibited an otherwise mild phenotype during the first 2 decades of life [57,111]. However, gross motor abnormalities occur in affected patients of both sexes (Table 1) and it is difficult to rationalize why one of these features should necessarily afflict one gender more than another. Electrical evidence of

peripheral neuropathy, when sought, is a very common finding in patients with genetic mitochondrial diseases, including PDC deficiency [164–168], as would be expected for a tissue reliant mainly on oxidative metabolism for energy. Most of the published reports in our series that described the presence of peripheral neuropathy provided little or no objective documentation of sensory or motor nerve dysfunction and subtle abnormalities probably were either not sought or missed in many other patients. Thus, we tentatively conclude that the apparent gender discrepancy for this clinical sign is probably spurious and will not be confirmed by future studies in which formal peripheral nerve conduction testing is undertaken.

Facial dysmorphism is both an uncommon and curious finding in PDC deficiency, affecting only 11% of patients (mostly girls) in this review. Intriguing comparisons have been made between the dysmorphic features in PDC deficiency and fetal alcohol syndrome [reviewed in 2], given that the latter condition can potentially inhibit PDC activity and disrupt energy metabolism. However, it is likely that newborns with congenital PDC deficiency have suffered a degree of cellular energy failure at least as protracted and severe as children born to mothers who consume alcohol during pregnancy. Therefore, if PDC deficiency is the dominant biochemical mechanism underlying facial dysmorphism in both disorders, it is surprising that its prevalence is not higher in our series.

Structural brain lesions have long been noted as a common feature of PDC deficiency, but none of the findings reported here is unique to the disease. Moreover, their true frequencies are probably underestimated because only 186 (51%) of the cases contained evaluable neuroimaging details. In addition, given the high prevalence of ventricular enlargement in our series, it is probable that the true prevalence of cerebral atrophy is underreported.

Mosaicism in the *PDHA1* gene due to variability in the pattern of X chromosome inactivation may make it difficult to diagnose PDC deficiency in females [148] and a few cases of somatic mosaicism have also been reported in males [144,169]. Consequently, cells obtained by biopsy for enzymological diagnosis could falsely overestimate global residual PDC activity in E1α deficient girls. It might be assumed that the amount of residual E1α activity measured in cells would correlate more closely with clinical phenotype in males who are heterozygous for a mutation than in females, in whom the biochemical expression of the defect depends on the degree of lyonization. However, as we and others [2] have found, there is generally a poor correlation between measured enzyme activity and clinical presentation and course, a conclusion applicable to PDC deficiency in general, regardless of the underlying component defect. This discrepancy between enzyme activity and the clinical phenotype of PDC deficiency is at least partly explained by both random X inactivation (in cases of E1α deficiency) and the dependency of the tissue used to diagnose the disease on PDC activity for supporting its energy needs.

PDHA1 gene mutations have been subdivided broadly into 1) missense point mutations, with loss of PDC catalytic activity only; 2) deletions or exon skipping mutations, resulting in loss of E1α mRNA and protein; and 3) deletions, missense or nonsense mutations, resulting in loss of E1α protein without loss of E1α mRNA (unstable E1α) [10,23,138,147,154,170,172,178]. Despite the variable nature of these mutations, we found

it difficult to draw sharp distinctions between specific mutations of the PDC and the natural history of the disease, although mutations affecting position 378 in *PDHA1* may be particularly lethal. As a whole, missense mutations occur more frequently in boys, whereas frameshift mutations are more common in girls. However, this difference does not appear to be translated into biochemically or clinically meaningful differences.

Treatment of most patients with PDC deficiency has been disappointing and no intervention specific to this disease has been evaluated in a randomized controlled trial [173]. Nutritional mixtures of various cofactors and vitamins are commonly provided to patients with PDC deficiency, usually, with limited biochemical rationale. In the majority of cases we reviewed, the doses of these modalities were omitted from the reports. Thiamine doses ranged from a few mg/d to >1 g/d. Thiamine pyrophosphate is an obligate cofactor for the E1 component of PDC, and most cases in which higher thiamine doses were administered involved cases in which a pathological mutation affecting the thiamine pyrophosphate binding site of E1 was assumed or established.

Patients with PDC deficiency do not oxidize carbohydrates efficiently; hence, the pyruvate derived from glycolysis is more likely to be reduced in the cytoplasm to lactate. This has led to the widespread use of high fat diets, typically with a caloric ratio of 3–4 fats to 1 carbohydrate plus protein, which induce ketosis and provide an alternative source of acetyl CoA, particularly for the nervous system. Reports of a few children with PDC deficiency whose clinical course improved dramatically while following a high fat diet [23,111] are consistent with this postulate and have resulted in the incorporation of such diets in the routine care of many patients with PDC deficiency [111,174]. However, most of the reports reviewed here described the administration of a “ketogenic,” “high fat” or “low carbohydrate” diet without providing information on the caloric distribution of metabolizable fuels. Therefore, we included under the category of ketogenic diet only those cases in which fat comprised at least 65% of total calories. No controlled trials have prospectively evaluated any type of “ketogenic diet” in the treatment of PDC deficiency.

DCA increases PDC activity by inhibiting the activity of PDKs in virtually all tissues, thereby maintaining E1α in its phosphorylated, catalytically active, state [175,176] and by stabilizing the complex and decreasing its rate of turnover [176]. When DCA was administered to PDC deficient patients, doses frequently varied over time in a given patient and, among subjects, in duration of treatment. The drug has been evaluated in randomized controlled trials in patients with various genetic mitochondrial diseases [177–179] in which a few children with PDC deficiency participated. These and other open label reports [10] have suggested that chronic DCA may benefit patients with PDC deficiency.

4.1. Conclusions

In summary, our analysis of 371 cases of proven PDC deficiency found that neither gender nor any biochemical or clinical feature differentiates the various enzymological or molecular genetic etiologies of the disease. The clinical spectrum of PDC deficiency is broad, but typically presents in early childhood with neurodevelopmental and neuromuscular compromise. Hyperlactatemia is a frequent, but not universal, finding early in the disease process, is associated with a blood lactate:pyruvate ratio≤20 and often portends an early

demise when present during the neonatal period. Boys and girls may differ in a few clinical characteristics and in the type of PDC mutation they harbor, but otherwise share a fairly common clinical course. Although many cases in our series described the administration of thiamine, a ketogenic diet and DCA, singly or in combination, such uncontrolled studies involving one or a few subjects provide no new insight into the potential safety and efficacy of these interventions. Rigorous, prospective evaluation of promising therapies is needed for PDC deficiency. Such controlled trials should incorporate a standardized approach to the longitudinal study of the natural history of this devastating disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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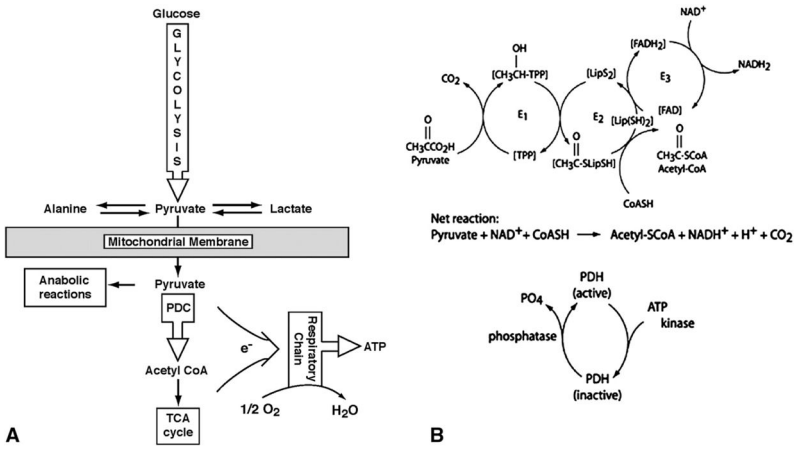

Fig. 1.

A. Central role of PDC in cellular energetics. B. PDC multi-enzyme complex. Abbreviations: TCA, tricarboxylic acid; e^{-}, electrons; E1, pyruvate decarboxylase; E2, dihydrolipoamide transactylase; E3, dihydrolipoamide dehydrogenase; TPP, thiamine pyrophosphate; Lip, lipoate (reduced and oxidized).

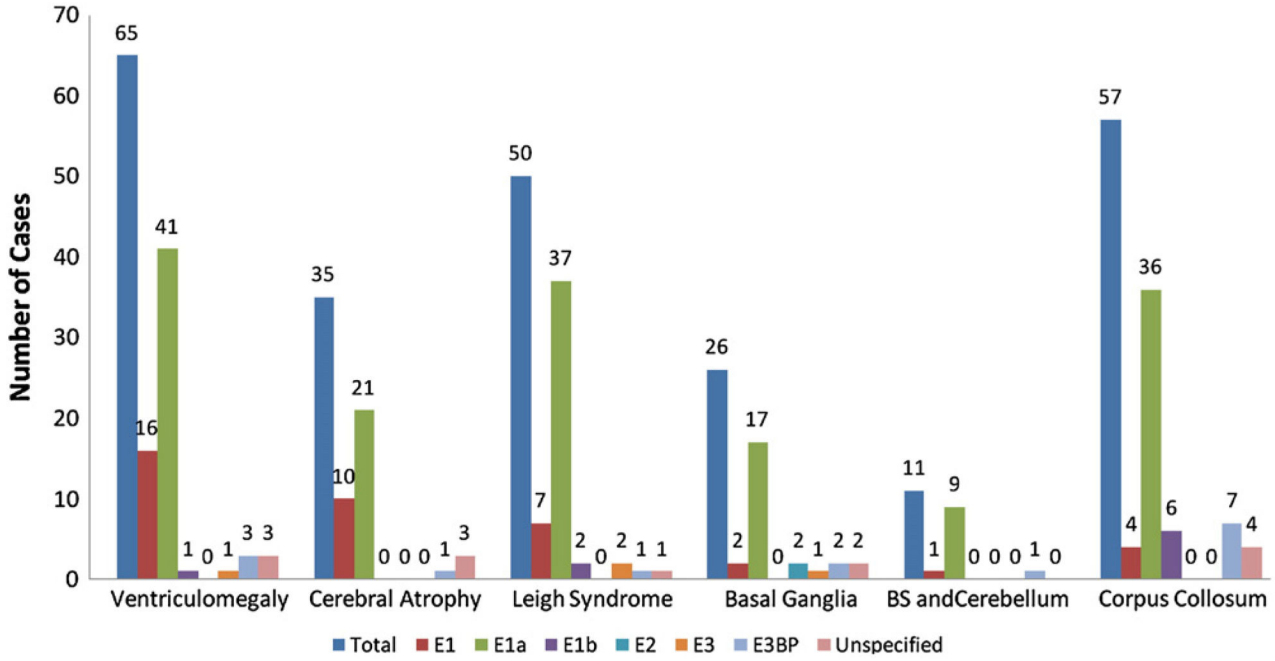

Fig. 2.

Brain imaging findings in 186 patients with PDC deficiency. Abbreviation: BS, brain stem.

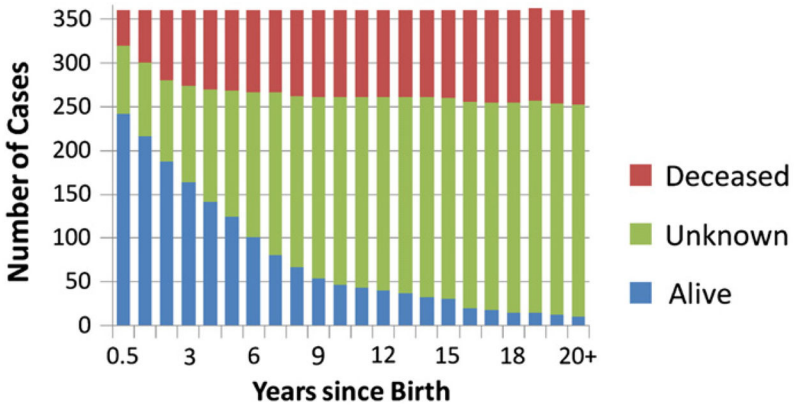

Fig. 3.

Outcome of 371 patients with PDC deficiency. There were 294 patients in whom death or survival was documented at the time of reporting and 77 patients whose outcome was unknown at the time of reporting.

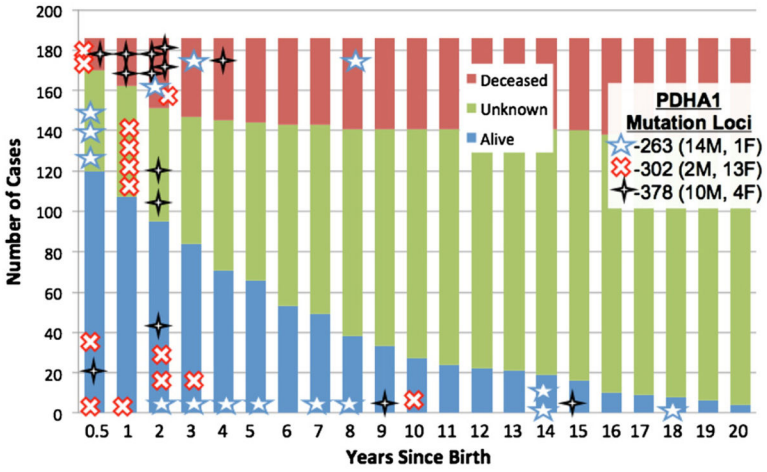

Fig. 4.

Outcome of 187 patients with PDC deficiency due to an identified biochemical and/or molecular genetic defect in E1α.

Table 1

Clinical signs associated with PDC deficiency.

Sign	No. of cases (% of total)	% Males
DD/MR/PMR	211 (57)	45
Hypotonia/hypertonia	169 (46)	51
Seizures	95 (26)	47
Microcephaly	83 (22)	23
Ataxia	72 (19)	78
Respiratory distress	51 (14)	59
Facial dysmorphism	44 (11)	34
Spasticity	38 (10)	34
Peripheral neuropathy	26 (7)	88
Optic atrophy	15 (4)	60
Nystagmus	11 (3)	64
Ptosis	9 (2.5)	89
Choreoathetoid movements	8 (2)	88
Strabismus	6 (1.6)	100

Table 2

Enzymological classification and age of clinical presentation in PDC deficiency.

	Patients (%)	Males (%)	Consanguinity (%)	PDC activity (% of nl)	Age of clinical onset (mos)
Total	371 (100)	52.1	6.8	37±34.6	8.0±15.8
E1	65 (17.5)	58.4	0	38.8±25.9	7.3±15.7
E1α	210 (56.6)	50.4	1	41.7±39.2	8.9±17.3
E1β	9 (2.4)	55.6	55.6	24.2±22.2	3.1±6.2
E2	4 (1.1)	50	66.7	48.5±16	9.0±8.6
E3	20 (5.1)	66.7	13.3	48.5±21.2	5.9±9.5
E3BP	23 (6.2)	60.8	60.8	18.1±13.2	5±10.2
Unclassified	40 (10.8)	46.9	0	42.3±30.2	9.3±16.6

Cases included as E1 deficiency were those in which a defect in the alpha or beta subunit was not described.

Table 3

Blood and CSF lactate and pyruvate concentrations in patients with PDC deficiency.

	Blood lactate (mmol/L)	Blood pyruvate (mmol/L)	Blood L:P ratio	CSF lactate (mmol/L)	CSF pyruvate (mmol/L)
Total	7.8±5.6 (216)	0.76±2.3 (118)	19.6±22 (45)	6.1±3.04 (123)	0.47±0.27 (43)
E1	9.9±8.2 (16)	0.67±0.99 (15)	18.6±7.2 (5)	5.90±4.5 (9)	0.57±0.4 (4)
E1α	7.02±5.8 (115)	0.56±0.83 (66)	20.1±25.6 (32)	6.07±3 (74)	0.48±0.27 (26)
E1β	11.8±6.6 (8)		20.2±0.28 (2)		
E2	2.58±2.1 (3)	0.137 (1)		1.4±0.39 (2)	
E3	11.3±4.6 (15)	4.37±8.6 (7)		3.01±1.47 (4)	
E3BP	10.3±6.9 (21)	0.56±0.43 (10)	13.4±4.7 (5)	6.03±2.3 (6)	0.53±0.06 (2)
Unclassified	6.0±2.6 (38)	0.37±0.19 (19)	17.6 (1)	6.9±2.8 (28)	0.40±0.26 (11)

Table 4

Mutational classification in relation to various clinical indices.

Mutation	% Males	% Females	Enzyme activity	Age of clinical onset	Max. blood lactate	% Alive	% Deceased
Missense	62.7 (96)	36.3 (57)	37.8±35.20 (142)	7.78±12.90 (111)	7.81±5.70 (95)	65.6 (86)	34.3 (45)
Frameshift	38.6 (27)	61.4 (43)	32.7±29.30 (64)	3.60±7.70 (47)	7.41±4.20 (35)	63.5 (33)	36.5 (19)

The number of cases is in parentheses.

Table 5

Outcome of 294 patients with PDC deficiency.

	Deceased			Alive		
Subunit (no. of cases)	**Percent**	**Mean age in years**	**Range in years**	**Percent**	**Mean age in years**	**Range in years**
Total (294)	36.2 (108)	2.71±4.53 (107)	0.1–35	63.8 (186)	7.1±6.11 (167)	0–21
E1 (57)	42.1 (24)	0.98±1.69 (24)	0–8	57.9 (33)	6.65±5.17 (31)	0.1–22
E1α (163)	36.8 (60)	3.22±5.22 (60)	0–21	63.2 (103)	7.5±6.43 (92)	0.2–35
E1β (9)	44.4 (4)	0.65±0.48 (4)	0.1–1.1	55.5 (5)	9.14±10.3 (5)	0.3–27
E2 (4)	0			100 (4)	7.5±4.77 (3)	3.5–11
E3 (13)	50.0 (9)	2.40±2.16 (8)	0.3–5.5	50.0 (9)	4.01±2.86 (8)	0.8–5
E3BP (22)	22.7 (5)	4.88±6.67 (5)	0.1–16	77.2 (17)	7.8±7.08 (17)	0.9–24
Unclassified (21)	28.6 (6)	4.5±6.58 (6)	0–16	71.4 (15)	5.78±4.72 (14)	0.8–15

Table 6

Gender differences in clinical presentation and course.

Gender	Number of deceased (%)	Age of onset (mos)	Age of death (years)	PDC activity (% nl)
Male	62 (64)/*37 (64)*	3.5/*4.1*	3.2/*3.8*	23.5/*26.1*
Female	38 (36)/*21 (36)*	1.1/*0.9*	2.1/*2.4*	32.7/*41*

Standard font represents total number of cases, while italicized text represents E1α cases.