Enzymatic testing sensitivity, variability, and practical diagnostic algorithm for Pyruvate Dehydrogenase Complex (PDC) Deficiency

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Introduction

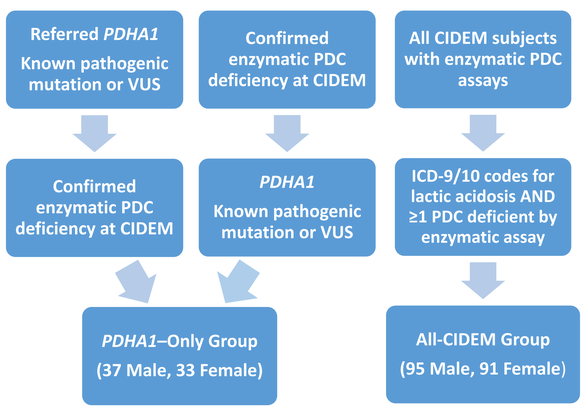
Pyruvate dehydrogenase complex (PDC) deficiency is a major cause of primary lactic acidemia in children. Prompt, correct diagnosis of PDC deficiency (and differentiating between specific, generalized, or secondary deficiency) has important implications for clinical management and therapeutic interventions in neonates, infants, young children, and selected adults. Both genetic (molecular) and enzymatic (functional) testing approaches are being used in the diagnosis of PDC deficiency. The diagnostic efficacy of each of the above testing approaches for neonates and children affected with PDC deficiency has not been systematically investigated because of the rarity of this disorder.

Aims

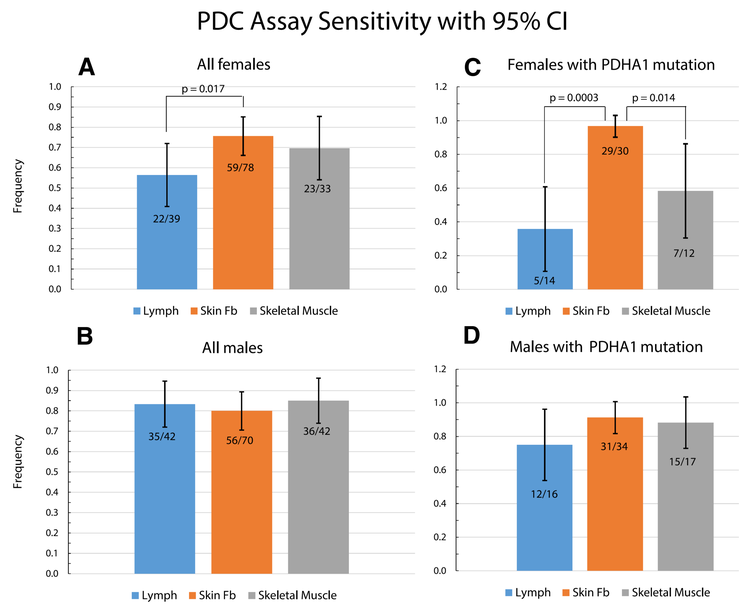
We sought to evaluate the diagnostic sensitivity and variability (for repeat testing, gender, and cell/tissue type) of the various biochemical PDC assays available at the Center for Inherited Disorders of Energy Metabolism (CIDEM) and, based on such data, propose a practical diagnostic strategy for clinical use.

Methods

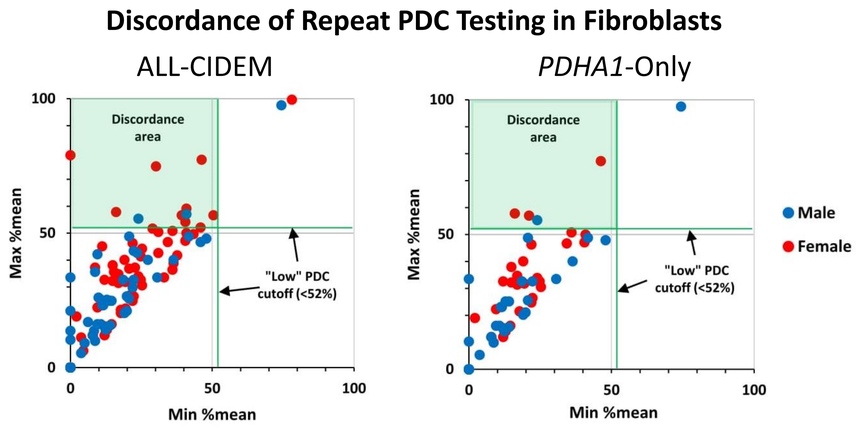
We retrospectively analyzed the sensitivity of the PDC assay in a cohort of de-identified patients referred to CIDEM with lactic acidosis and functional PDC deficiency, with or without a known pathogenic *PDHA1* mutation, in at least one of either blood lymphocytes, cultured fibroblasts or skeletal muscle. CIDEM data identified 186 subjects (51% male and 49% female), about half of whom were genetically resolved. Of these, 78% had a pathogenic *PDHA1* mutation. CIDEM data were filtered as follows:



Results



PDC assay sensitivity for blood lymphocytes, cultured fibroblasts and skeletal muscles. 95% Confidence intervals (CI) are indicated along with statistical significance ($p < 0.05$) when applicable.



Discordance of successive repeat PDC testing in fibroblasts. Plot of minimum *vs* maximum fibroblast PDC activity noted as % control mean (%mean) for the All-CIDEM and *PDHA1*-Only groups. "Low" PDC cutoff values (<52%, corresponding to <3rd percentile of the control range) noted as green lines along with the area of discordance noted (green box). Y-axis (Max %mean) and X-axis (Min %mean) represent maximum and minimum PDC activities for a subject as % control mean, respectively. Control fibroblast activity (nmol/min/mg protein): 2.42 ± 0.88, range 1.26-4.42, n = 329.

Cell/tissue type-specific discordance. Cell/tissue-specific discordance in males with known *PDHA1* mutations (37 cases) was 15% ± 11% and in All-CIDEM males (95 cases), irrespective of their genetic etiology for PDC deficiency, was 23% ± 8% (data not shown).

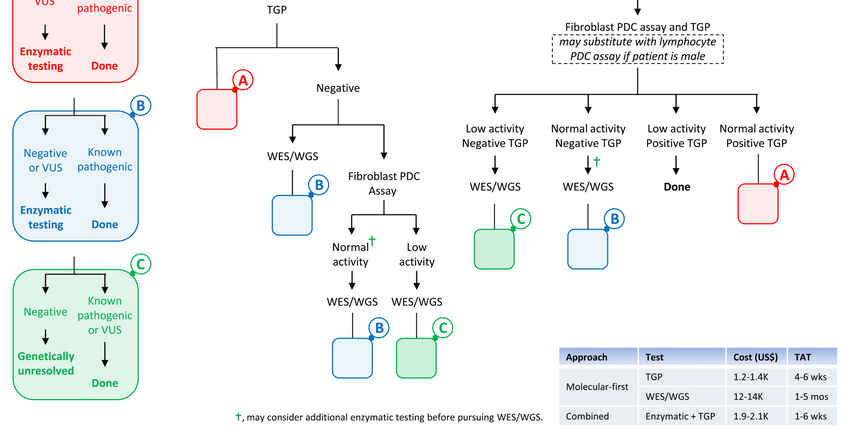
Discussion

Based on these results, we propose a practical diagnostic approach for when PDC deficiency is suspected, for use by pediatricians, neonatologists, neurologists, intensivists, child development specialists, clinical geneticists and biochemical geneticists, who encounter cases with non-specific clinical features such as hypotonia, seizure, developmental delay, ataxia, gait disturbances and/or "cerebral palsy."

PDC deficiency would be suspected if,

1. lactate (L) and pyruvate (P) in plasma and/or CSF are above their respective reference ranges, with normal or slightly elevated L:P ratio (10-25),
2. alanine in plasma and/or CSF is above the reference range,
3. plasma lactate and alanine concentrations are higher in a post-prandial state than a fasting state,
4. abnormal brain MRI or CT (e.g., ventriculomegaly with microcephaly, corpus callosum abnormality, basal ganglia or midbrain lesions, etc..), and/or
5. an abnormal MR spectrometry (with a significant lactate peak).

Recommended Algorithm for Diagnosis of Pyruvate Dehydrogenase Complex (PDC) Deficiency



Approach	Test	Cost (US$)	TAT
Molecular-first	TGP	1.2-1.4K	4-6 wks
	WES/WGS	12-14K	1-5 mos
Combined	Enzymatic + TGP	1.9-2.1K	1-6 wks

Conclusions

1. Assaying PDC in cultured fibroblasts in cases where the underlying genetic etiology is *PDHA1*, was highly sensitive (>90%) irrespective of gender.
2. In contrast to fibroblast-based testing, lymphocyte- and muscle-based testing were <u>not</u> sensitive for identifying known PDC deficient females with pathogenic *PDHA1* mutations.
3. In males with known PDC deficiency with or without a known genetic etiology, the sensitivity of the various cell/tissue assays were not statistically different.

Acknowledgements

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