The spectrum of pyruvate oxidation defects in the diagnosis of mitochondrial disorders.

Abstract:

Pyruvate oxidation defects (PODs) are among the most frequent causes of deficiencies in the mitochondrial energy metabolism and represent a substantial subset of classical mitochondrial diseases. PODs are not only caused by deficiency of subunits of the pyruvate dehydrogenase complex (PDHC) but also by various disorders recently described in the whole pyruvate oxidation route including cofactors, regulation of PDHC and the mitochondrial pyruvate carrier. Our own patients from 2000 to July 2014 and patients identified by a systematic survey of the literature from 1970 to July 2014 with a pyruvate oxidation disorder and a genetically proven defect were included in the study (n=628). Of these defects 74.2% (n=466) belong to PDHC subunits, 24.5% (n=154) to cofactors, 0.5% (n=3) to PDHC regulation and 0.8% (n=5) to mitochondrial pyruvate import. PODs are underestimated in the field of mitochondrial diseases because not all diagnostic centres include biochemical investigations of PDHC in their routine analysis. Cofactor and transport defects can be missed, if pyruvate oxidation is not measured in intact mitochondria routinely. Furthermore deficiency of the X-chromosomal PDHA1 can be biochemically missed depending on
the X-inactivation pattern. This is reflected by an increasing number of patients diagnosed recently by
genetic high throughput screening approaches. PDHC deficiency including regulation and import
affect mainly the glucose dependent central and peripheral nervous system and skeletal muscle.
PODs with combined enzyme defects affect also other organs like heart, lung and liver. The spectrum
of clinical presentation of PODs is still expanding. PODs are a therapeutically interesting group of
mitochondrial diseases since some can be bypassed by ketogenic diet or treated by cofactor
supplementation. PDHC kinase inhibition, chaperone therapy and PGC1? stimulation is still a matter
of further investigations.