The progressive intellectual and neurological deterioration study: a game changer

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Progressive intellectual and neurological deterioration (PIND) requires rapid recognition as well as accurate diagnosis of the underlying condition to minimize its devastating consequences. The patient and family deserve information on the underlying disease so that optimal quality of life can be achieved with the advanced care planning and appropriate support. Accurate genetic counselling on recurrence risk and identification of other affected family members is paramount to avoid additional suffering. More urgently, we must intervene before injury to the brain is irreversible. For a limited yet increasing number of inborn errors of metabolism (IEM) causing PIND, therapy targeting the underlying disease mechanism can prevent further regression, halt disease, and in a few cases improve functioning. A recent review reported 85 IEM causing PIND, 35 (41%) of which were amenable to treatments including vitamin supplement, medical diet, medication, organ transplant, and gene-based therapy.[1]

The study by Verity et al. is a landmark publication.[2] It confirms IEM as the largest etiological group and provides real-life information on ethnic distribution as well as age at presentation (80% before the age of 5y) with mitochondrial diseases clustering in infancy, lysosomal storage diseases and X-linked adrenoleukodystrophy often with insidious onset in early childhood, and Huntington disease as well as non-genetic conditions in adolescence.[2]

One must bear in mind, however, that the study spans more than two decades, during which diagnostic technologies advanced from karyotyping in the 1990s to identifying small copy number variants (chromosomal microarray in the 2000s), to single nucleotide variants. Whole genome sequencing unveils mechanisms relevant to PIND such as short tandem repeat expansions, which can cause a variant Creutzveldt-Jacob (vCJD) disease phenotype (ataxia, cognitive decline, neuropsychiatric feature), glutaminase deficiency, and Huntington disease.[3] Additionally, holistic next-generation profiling (e.g. metabolomics, proteomics, and microbiomics) have accelerated the discovery of the genetic as well as non-genetic (e.g. infectious, inflammatory) basis of PIND.[4] Thus, the yield of a diagnostic work-up now differs dramatically from the late 1990s when the PIND study started, as do the treatment options.

The differential diagnosis of PIND in children is a moving target. Not only technological advances, but also public health is of influence as illustrated by the reappearance of subacute sclerosing panencephalitis as cause of PIND likely due to failing vaccination uptake. Surely newborn infant screening policies have also prevented PIND, phenylketonuria being an emblematic example. Expansion of newborn infant screening panels (e.g. stem cell transplant for adrenoleukodystrophy) will hopefully help prevent PIND in the years to come.[5]

Systematic PIND screening and registration should be prioritized across the world. Such programs are game changers not only for prevention of the infectious disease the PIND study was originally designed to target (vCJD), but also for other devastating genetic and non-genetic conditions. I would urge experts in the field to make the most of their valuable data to establish an evidence- and expert-based diagnostic algorithm combining clinical, genetic, and biochemical tests, supported by digital tools (www.treatable-id.org and www.iembase.org) to help clinicians confronted by PIND with an efficient recognition and work-up. Even if diagnostic technologies are not directly accessible, patient material such as DNA, plasma, and fibroblasts should be stored for future use for the individual and collective benefit. Integrated '-omics' profiling of large numbers of patients with PIND will further expand etiological and mechanistic insights, and might also identify (multifactorial) predisposing factors for PIND and neurodegenerative diseases in adulthood. This will enable preconception screening, preimplantation diagnostics, prenatal screening, and therapeutic breakthroughs. Let us join forces and follow the example of the PIND research group for a better future of all children.

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