Pediatric Neurology 65 (2016) 1–13

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Treatment of Neurogenetic Developmental Conditions: From 2016 into the Future

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ABSTRACT

BACKGROUND: Neurogenetic developmental conditions represent a heterogeneous group of rare inherited disorders with neurological manifestation during development. Treatments for these conditions have largely been supportive; however, a number of treatments are emerging which target the underlying physiology and offer great potential. Our aim was to present a state-of-the-art overview of the current and potential causal treatments available or under development for neurogenetic developmental conditions. **METHODS:** In this review, we focus on the following neurogenetic developmental conditions: (1) inborn errors of metabolism causing neurogenetic developmental conditions, (2) fragile X syndrome, (3) Rett syndrome, (4) tuberous sclerosis complex, 5) Down syndrome and other neurogenetic developmental conditions. **RESULTS:** A large group of inborn errors of metabolism leads to neurodevelopmental disability, affecting the central nervous system during infancy or childhood and can present with comorbidities such as intellectual developmental disability, epilepsy, atypical cerebral palsy, autism spectrum disorder, behavioral and psychiatric disturbances, for which causal treatments are discussed. **CONCLUSIONS:** The advent of these new disease-modifying therapies has the potential to reverse the underlying neural mechanisms of these debilitating conditions, which may provide prospect to affected individuals.

Keywords: neurogenetic disorders, therapy, genetic diseases, fragile X syndrome, developmental disorders

Pediatr Neurol 2016; 65: 1-13

Introduction

Neurogenetic developmental conditions (NDCs) are a heterogeneous group of heritable conditions with neurological manifestations including intellectual developmental disability (intellectual developmental disorder [IDD], defined as intellectual disability with an IQ less than 70 at greater than five years of age or global developmental delay with deficits in two or more developmental domains, at less than five years), learning disabilities, or autism spectrum disorder (ASD). These may be associated with comorbidities such as epilepsy, cerebral palsy or motor dysfunction, and/or behavioral disturbances or psychiatric diseases. Early identification is critical for specific intervention to improve outcomes and reduce family burden. Given the rarity of these conditions, diagnosis is a challenge. Awareness among clinicians is essential, and several tools are available such as microarrays, genome-wide sequencing, and digital apps that can facilitate diagnosis. Following a systematic approach to the identification of pediatric NDCs that are amenable to treatment shows that collectively these rare diseases may well account for a meaningful proportion of

Article History:
Received March 22, 2016; Accepted in final form July 19, 2016
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http://dx.doi.org/10.1016/j.pediatrneurol.2016.07.010

neurodevelopmental diseases (e.g., fragile X syndrome up to 2% of male IDD, treatable inborn errors of metabolism 5% of all IDD).

Historically, treatments for NDCs have been mostly supportive—designed to treat cooccurring medical, neurological, and behavioral symptoms and support the person to achieve the highest level of adaptive development and function possible. For example, supportive therapies may include pharmacotherapy for control of seizures, sleep management, behavioral modification and/or psychopharmacology for maladaptive behaviors, special education programs, and cognitive-behavioral, occupational, speech, and physical therapy.

The large heterogeneity in genotypes, phenotypes, and response size, combined with small patient population size, poses significant challenges to meeting evidence-based standards for NDC treatments. Specific disease-related Food and Drug Administration–approved treatments that have demonstrated efficacy in controlled trials only exist for a handful of patients. Because of their rarity, it would be impossible to perform the necessary controlled trials for every potential NDC treatment. Therefore, under current medical practice, treatments approved for other disease indications are often used off-label and/or are prescribed based on symptoms for which there are approved treatments. Unfortunately, these interventions do not fully treat the disorder and are not directed at the underlying mechanism of disease. Alternatively, causal treatments that modify the underlying disorders, if used in a timely fashion, offer the potential to slow or prevent undue neurological damage or maldevelopment that leads to disease and disability, thus reducing the need for supportive therapies.

Despite the challenges, there have been many advances in the development and implementation of “targeted” or “causal” treatments for NDCs in recent years. Causal therapy constitutes interventions targeting the pathophysiology at a cellular or molecular level with the goal of treating underlying etiology to prevent or improve neurological manifestations of disease. In this review, we discuss causal treatments for the following NDCs: (1) inborn errors of metabolism (IEMs) causing NDC, (2) fragile X syndrome (FXS), (3) Rett syndrome, (4) tuberous sclerosis complex (TSC), (5) Down syndrome, and (6) other nonmetabolic conditions of genetic origin. These will be outlined in the context of currently available treatments and practices, and some of the latest new and upcoming therapies will be discussed.

IEMs causing NDCs

IEMs constitute a class of single-gene disorders involving impaired biochemical or cellular processes. The majority are due to defects in genes that typically affect the synthesis or breakdown of molecules leading to accumulation of toxic molecules and deficiency of cellular energy and/or required substrates for many important intracellular processes. Many of these IEMs affect the central nervous system during infancy or childhood and thus present as NDCs, in particular, IDD, epilepsy, cerebral palsy, ASD, behavioral and psychiatric disturbances.

A number of affordable, accessible, and safe treatments are available to treat these IEMs including (alone or in combination) dietary restriction/supplement, cofactor/coenzyme, vitamin, substrate inhibition, (small molecule) substrate reduction, enzyme replacement, bone marrow and hematopoietic stem cell transplant (HSCT), and gene therapy[1] and are listed in Table 1. The majority are positively affected by therapy with outcomes including improvement and/or stabilization of psychomotor or cognitive development (about 20% of IEMs), behavioral or psychiatric disturbances, seizures, and neurological and systemic manifestations. The evidence levels for treatments indicated in Table 1 are limited by the small patient cohorts inherent to rare diseases; however, many are considered standard of care.

Intellectual developmental disorder

A total of 89 IEMs presenting with IDD as the predominant phenotypic feature, for which causal therapy is available, were identified via systematic review and published previously[1,2] (Table 1). Although many of these can present with unspecific IDD as sole feature (e.g., creatine transporter deficiency), most of the treatable IEMs list are associated with additional neurological features which may include spasticity, behavioral disturbance, dementia, episodic encephalopathy, epilepsy, hearing loss, hypotonia/myopathy, neuroimaging abnormalities (basal ganglia, cerebellum, cerebrum, cysts/dysgenesis, white matter, mixed), neuropathy, ocular movement abnormality, psychiatric disturbance, sensorineural hearing loss, spasticity, stroke, vision loss, and various types and degrees of movement disorders (e.g., dystonia, dyskinesia, and ataxia). However, it is important to note that non-neurological or systemic features are a prominent phenotype in 57 of the 89 treatable IDDs (64%) listed in Table 1. Other presentations vary from “stable IDD” (i.e., without a history of regression or plateauing) to neurodegenerative with or without multiorgan involvement. The timing and nature of onset also vary; some are characterized by acute decompensations—often in the neonatal or early childhood period, whereas others present with a “late onset” form of nonspecific or chronic nature.

A two-tiered protocol (Fig 1) developed through the Treatable Intellectual Disability Endeavour (TIDE, www.tidebc.org, a five-year funded clinical research project at BC Children’s Hospital, Vancouver) was designed to enhance early diagnosis of treatable IEMs in children presenting with IDD. The first tier involves biochemical testing of blood and urine (costs $528 CAD), which potentially indicate 60% of the currently known treatable conditions and should be applied in all patients with unexplained IDD. The next step is to apply the 2014 diagnostic practice parameters for IDD,[3] which include chromosome microarray as a first-line test and, in selected individuals, fragile X testing, neuroimaging, and other tests, in combination with the second tier of the TIDE algorithm for the identification of the remaining 35 treatable IDs (Fig 1). The latter conditions require a more targeted or selective approach, including single metabolite or primary molecular analysis, based on a clinical differential diagnosis, i.e., the presence of signs and symptoms; these tests often require more invasive sampling procedures and/or extensive funding. A free digital application is available (via www.treatable-id.org and the Apple App Store as the