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Neurogenetics in Child Neurology: Redefining a Discipline in the Twenty-first Century

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Abstract Increasing knowledge on genetic etiology of pediatric neurologic disorders is affecting the practice of the specialty. I reviewed here the history of pediatric neurologic disorder classification and the role of genetics in the process. I also discussed the concept of clinical neurogenetics, with its role in clinical practice, education, and research. Finally, I propose a flexible model for clinical neurogenetics in child neurology in the twenty-first century. In combination with disorder-specific clinical programs, clinical neurogenetics can become a home for complex clinical issues, repository of genetic diagnostic advances, educational resource, and research engine in child neurology.

Keywords Neurogenetics · Genetic diagnosis · Disorder-specific clinic · Undiagnosed disease · Pediatric neurology

Introduction

Classification of disorders is an essential endeavor in clinical medicine. Grouping disorders has implications for delivery of clinical services, research, education, and public health. The field of child neurology is not an exception; since its early stages as an independent specialty, child neurology has classified disorders according to the traditional etiologic, organ/system target, and symptomatology categories. For instance, the third textbook of child neurology (following Bernard Sachs' Nervous Diseases of Children and Bronson Crother's Disorders of the Nervous System in Childhood) [1•], Ford's Disorders of the nervous system in infancy, childhood, and adolescence, included in its third edition (1952) is a chapter on heredofamilial and degenerative disorders along others on other etiologic categories such as infectious disorders and neoplasias [2]. Characteristic of this period, metabolic disorders were grouped under heredofamilial or toxic/metabolic conditions.

Fast-forwarding to the last two decades of the twentieth century, at a time when subspecialties began to emerge in child neurology, textbooks acknowledged the increasing knowledge on genetics by including chapters or sections on genetic mechanisms or disorders (e.g., chromosomal aberrations) [3]. However, most of genetic disorders remained under their syndromic or system categories (e.g., epilepsy, neuromuscular disorders). This reflected prevailing educational strategies and, to some extent, clinical practice. Simultaneously, the concept of clinical neurogenetics developed mainly in adult neurology. A publication by Bird and Hall (1977) [4••] illustrated well the place of clinical neurogenetics in the pre-genomics era. These authors recognized the high proportion of neurological patients with demonstrated or suspected genetic disorders at an academic medical center, both as reported by medical genetics (~50%) and adult and child neurology (8.5 and 20%, respectively). This perspective considers clinical neurogenetics the intersection of medical genetics and neurology practices, with an emphasis on diagnostic issues. Another viewpoint, more focused on management, led to the establishment of neurogenetics clinics for providing care for patients with a multitude of genetic disorders ranging from X-linked lissencephaly to Huntington

Topical Collection on *Pediatric Neurology*

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disease. Publications on the subject reflect the inclusion of a wide variety of neurologic disorders [5•].

Neurogenetics in Child Neurology

Although advances in genetics have transformed our knowledge on the etiology of many pediatric neurological disorders, beyond metabolic disorders, the areas with the greatest impact have been neurodevelopmental disorders, neuromuscular disorders, and epilepsy. In these fields, genetic testing is a major component of the diagnostic procedure and guidelines integrate input from stakeholders such as the Committee on Genetics of the American Academy of Pediatrics (www.aap.org/en-us/about-the-aap/Committees-Councils-Sections) and the American College of Genetics and Genomics (www.acmg.net) with those from the Child Neurology Society (www.childneurologysociety.org) and American Academy of Neurology (www.aan.com). Some of these genetics entities have also developed care coordination and management guidelines for relatively common genetic conditions (e.g., neurofibromatosis, Down syndrome) reviewed in [6]. Because these developments have been mainly focused on specific disorders or the aforementioned categories, neurogenetics as a clinical subdiscipline has had limited growth in child neurology. Few pediatric institutions, usually large ones, have established neurogenetics clinics or programs. Some of the available ones have a strong component of metabolic disorders and a few other rare genetic disorders. In other words, the application of the increasing genetic knowledge to diagnosis and management has remained in the traditional subspecialty clinics (e.g., neuromuscular disorder). Another factor that has prevented the emergence of neurogenetics as a clinical discipline is the increasing number of disorder-focused clinics, most of them serving genetic disorders (e.g., tuberous sclerosis, fragile X syndrome).

Regardless of the clinic model, the incorporation of new genetic diagnostic methods, mainly targeted gene panels and whole exome sequencing, has changed the practice of child neurologists [7]. Appropriate selection of tests and their interpretation is an evolving endeavor. Involvement of medical genetics specialists in the process is variable, depending to large extent on the level of comfort of the child neurologist although availability of geneticists or genetic counselors is also a factor. Incorporation of genetics to the training of child neurologists needs to be intensified and to include long-term strategies for updates on this evolving field. Unquestionably, "in house" expertise provides better care and education for child neurology practitioners avoiding long waits for appointments in medical genetics. Besides clinical care and training, neurogenetics is a well-established area of research in which child neurologists have made major contributions particularly in translational studies [8–10].

Clinical Neurogenetics: Different Models of Practice

As in every medical field, there is no single model of practice. Variable availability of expertise and resources, as well as funding issues, contribute to the heterogeneity in neurogenetics practice in child neurology. Nevertheless, two main goals are recognized across different settings: diagnosis of complex cases and management of neurologic disorders with genetic bases. Genetic etiology is suspected in cases that present with intellectual disability, epilepsy, and multisystem involvement. Other common factors include autistic features, abnormal muscle tone and its complications (e.g., scoliosis), and feeding/swallowing difficulties. Dysmorphia and other physical abnormalities, as well as CNS malformations and developmental regression/cognitive decline, are less frequently present but highly informative of genetic etiology (Table 1). One way to approach these cases is to identify patterns that resemble specific syndromes (e.g., Rett-Angelman syndromes spectrum [11, 12, 13•]) and to carry out diagnostic work up accordingly, usually in the respective disorder-specific clinic. The alternative, probably the best option for institutions with few disorder-specific clinics, is the neurogenetics clinic proposed several decades ago. Expertise in medical genetics, neurodevelopmental disorders, and epilepsy is essential for the diagnostic success of these specialized neurogenetics clinics.

While diagnosis has been the primary driven force of neurogenetics practice, management of these usually complex patients has become a major issue. The concept of coordination of care or medical home was pioneered by the American Academy of Pediatrics [14] and has led to numerous guidelines on "health supervision" for a variety of disorders that

Table 1 Clinical presentation of genetic disorders in child neurology

Prevalent
Global developmental delay/intellectual disability
Seizures
Multi non-CNS involvement
Relatively frequent
Autistic behavior
Abnormal muscle tone and skeletal complications
Feeding/swallowing difficulties
Uncommon
Dysmorphic features (prominent)
Developmental regression/cognitive decline
CNS malformations

include neurologic genetic conditions [15–17]. Whether a disorder-specific or a general neurogenetics clinic, there is a need for multidisciplinary clinics providing long-term care for individuals with complex neurologic disorders. Although some disorder-specific clinical management guidelines are available, suggesting certain evaluations and therapies at different stages (e.g., consensus documents on clinical practices of the Fragile X Clinical & Research Consortium: https://fragilex.org/treatment-intervention/consensus-on-clinical-practices [17]), there are common features and concerns in a wide variety of neurogenetic syndromes. In addition to the issues listed in the preceding paragraph, need for speech and language therapy, occupational therapy, and management of gastroesophageal reflux and constipation are also prevalent [17–19]. Thus, it is possible to assemble a team with adequate expertise for addressing most issues affecting a variety of neurogenetic disorders affecting children and adolescents. As improved medical care is extending life expectancy and survival [20], clinicians managing individuals with complex neurologic disorders face other challenges such as transition into adulthood and care for adults with chronic neurologic disorders [21]. The last two issues are beyond the scope of this review. However, an increasing number of publications are beginning to address these complex topics, including a recent consensus document on the role of child neurologists in the transition into adult health care [22].

While diagnosis and management of patients with neurogenetic disorders can be provided under different practice models, follow-up of individuals with complex neurologic disorders who are negative for standard genetic testing remains an issue. If the patient presents with features resembling a known genetic disorder, probably the best approach is follow-up in the corresponding clinic. For instance, depending on the clinical presentation, 2–20% of patients with Rett syndrome are negative for pathogenic *MECP2* mutations [23]. Because of this, the diagnosis of Rett syndrome is clinical and presence of *MECP2* mutations is a supportive but not confirmatory feature [13•]. However, how should patients who present with some of the main criteria (i.e., gait abnormalities and hand stereotypies) but no clear history of developmental regression be managed, in particular if they do not have a *MECP2* mutation? Most likely, the best clinical home is still the Rett syndrome clinic. Multiple efforts are narrowing the genetic diagnostic gap and revealing other genes associated with the Rett-Angelman clinical spectrum [24••, 25], which could be periodically re-evaluated in these individuals. Moreover, most of the clinical manifestations of these patients could also be addressed in a Rett syndrome clinic. Inevitably, there will a proportion of individuals who do not resemble any genetic syndrome. For them, their home could still be a general neurogenetics clinic unless certain symptoms (e.g., seizures) take preeminence. Considering the overlap of clinical features, some clinics focus on a spectrum of similar disorders (e.g., Rett and Angelman syndromes, fragile X syndrome, and autism spectrum disorder; labeled as disorder spectrum-specific clinics in Fig. 1).

A strong argument for the existence of general neurogenetics clinics is the need for diagnostic follow-up and expertise. As mentioned above, one of the challenges facing child neurologists these days is to interpret genetic test results, in particular if they are not definitive (variants of unknown significance or likely pathogenicity). When to repeat the test and how likely is a rare genetic abnormality are key questions better answered by a local expert (i.e., a clinician in neurology). The alternative is a referral to medical genetics. It is important to emphasize the role of general neurogenetics clinical programs in education not only for trainees but also for general and specialized child neurologists who cannot keep up with the overwhelming body of new literature in genetics. Finally, as disorder-specific clinics have exemplified, general neurogenetics clinics are by nature sources of research activities.

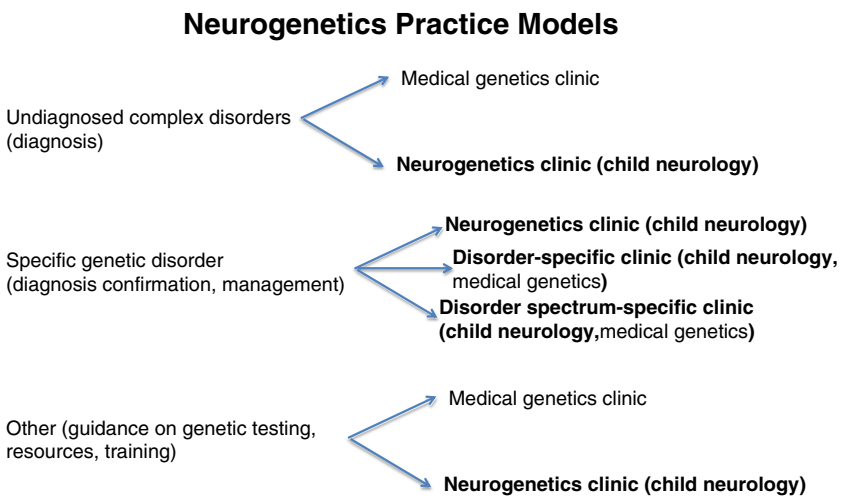

Fig. 1 Issues (*left*) and models (*right*) of practice in pediatric neurogenetics

Conclusion

Increasing knowledge on genetic etiology of pediatric neurologic disorders is affecting the practice of the specialty. The concept of clinical neurogenetics, in particular of clinics evaluating patients with complex neurologic disorders of suspected genetic etiology, remains valid after four decades since its formulation. While disorder-specific clinics have emerged and proliferated in child neurology, there is still a role for a general neurogenetics clinic in child neurology practice. These clinics or programs can adopt and integrate the diagnostic and management experience of disorder-specific clinics and become the home for complex clinical issues, repository of genetic diagnostic advances, educational resource, and research engine (as disorder-specific clinics usually are). As we progress into the twenty-first century, an efficient and patient-centered approach to the evaluation and treatment of children and adolescents with genetic neurologic disorders is needed. No single formula will satisfy these needs; however, expertise in clinical neurogenetics based in child neurology will continue being an essential component to the solutions.

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Compliance with Ethical Standards

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