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NEUROMUSCULAR DISORDERS

Diagnostic NGS for Severe Neuromuscular Disorders

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Related Article: Todd EJ, Yau KS, Ong R, Slee J, McGillivray G, Barnett CP et al. Next generation sequencing in a large cohort of patients presenting with neuromuscular disease before or at birth. Orphanet J Rare Dis 2015;10(1):148.
Keywords: Next-Generation-Sequencing; Novel Genes; Neuromuscular Disorders

Investigators from the University of Western Australia report the diagnostic yield of performing next generation sequencing (NGS; whole exome and targeted capture of 277 neuromuscular genes) in a heterogenous cohort of patients with neuromuscular disorders (NMD) presenting at or before birth. Forty-five patients from 38 unrelated families with fetal akinesia (9 families), arthrogryposis (13 families) and severe congenital myopathies (16 families) underwent whole exome sequencing (23), targeted sequencing (7) and both (8). Ten of these families were consanguineous. A conclusive genetic diagnosis was achieved in 18/38 families (47%). Autosomal recessive was the most common mode of inheritance (15), however dominant (1), de novo (1) and X linked (1) were also identified. Mutations were found in eight previously known neuromuscular disease genes (CHRND, CHNRG, ECEL1, GBE1, MTM1, MYH3, NEB and RYR1) and four novel neuromuscular disease genes (GPR126, KLHL40, KLHL41 and SPEG).

This study highlights the widening spectrum of phenotypes associated with mutations in known neuromuscular genes. For example, null mutations in the *RYR1* are associated with the arthrogryposis and fetal akinesia phenotype while missense mutations in *RYR1* are associated with central core myopathy phenotype (allelic heterogeneity). The study also led to the identification of novel neuromuscular disease genes (*KLHL40*, *KLHL41*, and *LMOD3)* involved in sarcomere assembly and muscle dysfunction. [1]

COMMENTARY. Fetal akinesia deformation sequence (intrauterine growth retardation, contractures, pulmonary hypoplasia and polyhydramnios), arthrogryposis (non-progressive congenital joint contractures in >1 area of the body), and severe congenital myopathies comprise a very heterogeneous group, both phenotypically and genetically, that present at or before birth [1]. The authors used NGS technology to study this diverse group. NGS has enabled sequencing of large numbers of genes in a single reaction and thus has enabled novel disease gene discovery. This technology has been used to sequence large panels of genes, whole exome, or whole genome [2]. Prior to NGS-based panel testing, patients would undergo a battery of invasive and expensive tests, often without obtaining a diagnosis [3].

This study used a combination of whole exome sequencing and targeted exome sequencing of known neuromuscular genes. Functional studies were done in cases of novel genes when feasible [1]. A previous study using comprehensive panel based testing, in patients with a variety of NMD's, reported a yield of 46% (3 fold greater than single gene testing) [3]. For genetically and phenotypically heterogeneous disorders like NMD's, targeted panel based sequencing should be the first step. If negative, it should be followed by exome sequencing to increase the diagnostic yield. This principle has helped find a genetic basis in a variety of undiagnosed neurogenetic disorders in a cost and time effective manner [4]. This approach also helps overcome some unique diagnostic challenges in NMD's such as: genetic heterogeneity (large number of causative genes), phenotypic heterogeneity (multiple genes with overlapping phenotype or a single gene with multiple phenotypes) and allelic heterogeneity (variety of mutations in each gene) [1,3].

Disclosures

The author(s) have declared that no competing interests exist.

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NEUROMUSCULAR DISORDERS

Hereditary Neuropathy with Liability to Pressure Palsies

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Related Article: Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 1993 Jan;72(1):143–151.
Keywords: Mononeuropathies; HNPP; Childhood; PMP22 Protein

Investigators from 4 pediatric hospitals in Canada analyzed the clinical presentation and electrophysiological data of 12 children with hereditary neuropathy with liability to pressure palsies (HNPP), caused by PMP22 gene deletion. Peroneal palsy was the most common presentation (42 %) followed by brachial plexus palsy in 25 % of their cases. Complete nerve conduction studies were available in 10/12 cases and it demonstrated 3 major patterns: multifocal demyelination at areas of nerve entrapment without generalized demyelinating polyneuropathy (20 %), isolated generalized sensorimotor polyneuropathy (20 %), combined focal demyelination at the area of entrapment and demyelinating polyneuropathy (60%). All patients had electrophysiological evidence of unilateral or bilateral carpal tunnel syndrome, although it was not always symptomatic. Electrophysiological findings are useful in diagnosis of HNPP, especially in children with heterogeneous clinical presentation. [1]

COMMENTARY. HNPP is the third most common type of hereditary motor and sensory neuropathy [1]. The typical clinical presentation is usually reported as a recurrent, painless monoparesis, with its first attack being in second or third decades [2]. The diagnosis is usually made in early adulthood unless there is a family history. A smaller case series published by Potulska-Chromik et al. about 7 children with genetically confirmed HNPP provides similar observations [3]. Their clinical presentation varied from mononeuropathy to brachial plexopathy, with recurrent episodes in 4 out of 7 patients. An earlier study that included 48 children with HNPP documented > 50 % of children with HNPP has delayed onset of walking (after 15 months of age) [4]. Based on the results of the study, the authors advocate testing PMP22 gene deletion for any children with unexplained mononeuropathy or multifocal neuropathy to facilitate appropriate care and genetic counseling for these patients. The paper alerts child neurologists to consider the possibility of HNPP even in young children with a negative family history when they present with the typical compressive nerve palsy.

Disclosures

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SEIZURE DISORDERS

A Timely Review of the Genetics of Epileptic Encephalopathies

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Related Article: McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol 2015 Nov. S1474-4422(15)00250-1.
Keywords: Epileptic Encephalopathy; Childhood; Genetics; Phenotype

Investigators from UCL Institute of Child Health, London and The University of Melbourne reviewed current knowledge of the genetics of epileptic encephalopathies of infancy and childhood. [1]

COMMENTARY. In an era of expanding availability of clinical genetic testing and a choice of technologies with which to perform this testing, child neurologists need to have a good understanding of the diagnostic methods used and the capacity to make good clinical sense of the results.

This review of the genetic 'lansdcape' of epileptic encephalopathy starts with discussion of the concept of epileptic encephalopathy and an acknowledgement that the relative contribution of developmental and epileptic mechanisms to encephalopathy are difficult to tease out. The authors then discuss the different technologies including chromosomal microarray, next generation parallel sequencing of multiple genes and whole exome sequencing, providing information about their relative strengths and weaknesses and the current yield of these investigations.

The authors describe considerations of heredity and genetic mosaicism that are critical to genetic counselling of families and explain common clinical and research scenarios.

Phenotypic heterogeneity or pleiotropy, whereby mutation in one gene can result in a number of different phenotypes (including no disease) is discussed, as too is genetic heterogeneity, whereby one electroclinical syndrome can result from mutation in any of a number of genes. Insights into the neurobiology of severe epilepsies and translation of these insights into patient care are discussed in terms of future diagnostic approaches and future treatment approaches.

The figures and tables provide more detail about each of the electroclinical syndromes that comprise the epileptic encephalopathies, the proportion of children with specific gene mutations, the ages of onset of the syndromes and the neurobiology summarized in a neuron-synapse cartoon. The supplementary appendix contains some pearls in relation to clinical features, imaging findings and treatments for patients with certain gene mutations. Overall, a nicely written and illustrated summary of a difficult topic.

Another resource that may be of interest to child neurologists and epileptologists is 'The Epilepsiome'. Part of the ILAE Genetic Commission blog, this website is an epilepsy genetics "wiki" that has useful summaries of important epilepsy genes [2].

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The author(s) have declared that no competing interests exist.

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SEIZURE DISORDERS

Vaccinations and Dravet Syndrome

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Related Article: Verbeek NE, van der Maas NA, Sonsma AC, Ippel E, Vermeer-de Bondt PE, Hagebeuk E et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology 2015 Aug;85(7):596–603.
Keywords: Dravet Syndrome; Vaccinations; Prognosis; Seizure Risk; Development

Investigators from various university hospitals, reference medical institutions and epilepsy centers, and the national institute for public health and environment in the Netherlands, studied the effect of vaccinations on seizure risk and disease course in patients with Dravet syndrome (DS). They retrospectively estimated the risk of subsequent seizures after infant whole-cell pertussis (wP), acellular pertussis (aP), and nonpertussis (non-P) combination vaccination, and measles-mumps-rubella (MMR) vaccination in a nationwide cohort of 77 children with DS and pathogenic SCN1A mutations. They analyzed the influence of age at seizure-onset and age at appearance of developmental delay, and compared their results in two subgroups of patients: those with and those without vaccination-associated seizure onset (defined as seizures appearing within 24 hours after administration of an inactivated (pertussis combination) vaccine or within 5 to 12 days after administration of a live attenuated MMR vaccine).

Their results show that children with vaccination-associated seizure onset were significantly younger at first seizure than those without vaccination-associated seizure onset, but age at first seizure unrelated to vaccination, and age at first report of developmental delay or cognitive outcome did not differ between both groups. In addition, the risk of subsequent vaccination-associated seizures was significantly lower for aP and non-P than for wP, and there was an increased incidence rate ratio of seizures of 2.3 following MMR vaccination. [1]

COMMENTARY. This study shows that patients with DS who enter their disease with vaccination-associated seizures do not have a different overall prognosis than those with initial seizures unrelated to vaccinations. In addition, although the absolute risk of seizure after various vaccinations is substantial in DS, the risk of subsequent vaccination-associated seizures is likely to be vaccine-specific, and mainly concerns MMR immunization (although this did not differ from the relative seizure risk in the general pediatric population). These results confirm that a diagnosis of DS is not a contraindication for vaccinations, even in children who presented seizures related to vaccinations at onset. As stated by the authors, it remains nevertheless important to try and select vaccines that carry lower risks of seizures in these children who are particularly prone to develop prolonged seizures, in order to prevent the potential acute encephalopathy described in certain patients with DS after status epilepticus [2].

Disclosures

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CNS MALFORMATIONS

Histopathology of Polymicrogyria

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Related Article: Jansen AC, Robitaille Y, Honavar M, Mullatti N, Leventer RJ, Andermann E et al. The histopathology of polymicrogyria: a series of 71 brain autopsy studies. Dev Med Child Neurol 2015 Jul;(June):9.
Keywords: Polymicrogyria; Cortical Malformation; Histopathology

Investigators from Sainte Justine Hospital (Montreal), Montreal Neurological Hospital and Institute, King's College Hospital (London), and John Radcliffe Hospital (Oxford) retrospectively reviewed medical records, autopsy reports, and genetic studies containing "Polymicrogyria." When available, etiology was assigned and approximately 23 cases had genetic or presumed genetic causes given the presence of multiple congenital anomalies. Five patients had ischemic changes in the CNS localized to the middle cerebral artery. Ten other patients had hypoxic-ischemic changes in the brain. Infection was found in 6. 32% of patients had no attributed etiology.

The brain surface was abnormal overlying the polymicrogyric cortex in 87% of the cases. The leptomeninges were abnormal in 86% of those patients, some showing glial invasion. The majority of cases in which the leptomeninges were abnormal had either a genetic, ischemic, or infectious etiology. In the cases where the leptomeninges were normal, the underlying pia had pathology in a subset of cases (disruption, thickening, subpial gliosis). The grey white matter junction in the majority of cases was blurred, providing further evidence of abnormal cortical geography. Moreover, features of cortical dysplasia were seen in approximately 60% of the cases. In cases where the leptomeninges were abnormal, there was a greater incidence of heterotopic neurons located deep in the white matter. Global brain malformations were also seen which included partial or complete agenesis of the corpus callosum and hippocampal sclerosis. Abnormalities in the brainstem and cerebellum were also present (hypoplastic pyramidal tracts, olivary and dentate nuclei malformations). [1]

COMMENTARY. The post mortem diagnostic threshold for PMG is low, especially in perinatal cases. The astute clinician will often review perinatal imaging prior to or during the prosection for clinical pathological continuity. It was noted that ventriculomegaly was associated with cortical abnormalities including PMG. Other genetic associations with PMG have been reported in the literature (PI3/Akt) which resulted in concomitant PMG and hemimegalencephaly.

While strictly speaking, etiology was only assigned to one category, there is an overlay of histopathologic features amongst all three categories. While most easily identifiable at low power, abnormalities to the leptomeninges and the underlying cortex may only be clinically significant in the appropriate setting. Abnormal elements of the cortical surface without a historical prodrome of epilepsy, developmental delay, motor problems, etc. may not be clinically relevant as it is quite likely that these subtle abnormalities can be present in the unaffected population. Moreover, it is well known that the fetal meninges provide the scaffolding for corticogenesis and neuronal migration.

The set of patients identified by the authors had a large number of perinatal tissue samples. Normal gyration begins at 21 weeks, which essentially includes a well-developed gyrus rectus, insula, and cingulate gyrus. Development of the parahippocampal and superior temporal gyrus are just beginning, and in some instances the brain is relatively lissencephalic at this stage. Examination of the frontal and parietal lobes is paramount in this age group and the majority of landmarks for regional development occur in these two lobes.

While PMG is considered an isolated abnormality, in clinical practice, it is often associated with aforementioned abnormalities. The leptomeninges overlying the pial surface play an important role in cortical development and the authors highlight it is necessary, but not sufficient alone to cause anomalies seen in patients with PMG. [1,2]

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MOVEMENT DISORDERS

Language Impairment in Adolescents with Sydenham Chorea

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Related Article: Harsányi E, Moreira J, Kummer A, Meira ZM, Cardoso F, Teixeira AL. Language impairment in adolescents with Sydenham chorea. Pediatr Neurol 2015 Nov;53(5):412–416.
Keywords: Sydenham Chorea; Rheumatic Fever; Verbal Fluency; Comprehension

Investigators from hospitals in Brazil tested verbal fluency in 20 adolescent patients, ages ranged from 11 to 16 years (mean 13.8 years), with Sydenham chorea compared with 20 patients with rheumatic fever without chorea and 20 healthy controls, matched for age and gender. Performance in verbal fluency and in verbal comprehension tasks differed significantly ($P<0.01$) among the three groups. Patients with Sydenham chorea performed significantly worse than healthy control group in phonemic and semantic verbal fluency tasks as well as verbal comprehension (Token Test). The rheumatic fever group also performed worse than healthy controls in phonemic verbal fluency. Severity of motor signs in Sydenham chorea correlated inversely with performance in phonemic verbal fluency. [1]

COMMENTARY. Nineteenth century reports of clinical manifestations of Sydenham or rheumatic chorea refer to speech but not language problems. Cheadle WB of the Great Ormond Street Hospital, London, UK, describes explosive bursts of inarticulate speech, jerky, or Sydenham's speech [2]. The choreiform movements involving the face, tongue, palate and larynx result in severe dysarthria, stammer and hesitation in talking. The present study using tasks of verbal fluency and verbal comprehension finds an association of rheumatic chorea with receptive and expressive language impairment [1].

The incidence of Sydenham chorea and acute rheumatic fever has declined dramatically in recent years but the disease and neuropsychiatric complications still cause significant morbidity in developing countries. In a follow-up study of 65 Sydenham chorea patients in Turkey, mean age at onset of symptoms was 11.7 +/-2.6 years (range 6-17 yea rs), and 63% were female. History of rheumatic fever was recorded in 30.8% of patients, carditis and EKG valve involvement in 70.5%, normal brain MRI in all of 18 tested, and abnormal slow waves in the EEG of 50% of 18 tested. Recovery following the first attack of chorea occurred in 1 to 6 months in 51.7% of patients, and recurrence in 37.9% [3].

The motor features of rheumatic chorea are often complicated by neuropsychiatric disorders, most commonly obsessive-compulsive behavior, and less frequently ADHD, anxiety, and depression [4]. The prevalence of ADHD before and after chorea was 30% and 37%, respectively. The prevalence for anxiety before, during, and after Sydenham's chorea was 71, 79, and 79%, and for depression, 19, 69, and 44%. Streptococcal antibody titers and duration of treatment did not correlate with ADHD, depression, or anxiety disorders. Seizures are reported rarely with Sydenham chorea, but reports of the EEG are abnormal in ~50%, returning to normal in one to 4 weeks [5,6].

Disclosures

The author(s) have declared that no competing interests exist.

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INFECTIOUS/AUTOIMMUNE DISORDERS

Epstein-Barr Virus Neurologic Complications

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Related Article: Mazur-Melewska K, Breńska I, Jończyk-Potoczna K, Kemnitz P, Pieczonka-Ruszkowska I, Mania A et al. Neurologic complications caused by Epstein-Barr virus in pediatric patients. J Child Neurol 2015 Oct. [Epub ahead of print]
Keywords: Epstein-Barr Virus; Infectious Mononucleosis; Encephalitis; Cerebellitis; Myeloradiculitis; Children

Investigators at the Karol Marcinkowski University of Medical Sciences, Poznan, Poland, analyzed the records of 194 children diagnosed with Epstein-Barr virus infection and having the viral capsid antigen IgM antibody. The most common symptoms of EB infection were drowsiness, and lymphadenopathy (in 30%) of children with neuroinfections, hepatomegaly (in 47.4%), and splenomegaly (in 41.7%). The incidence of neurologic complications was 5.2%. Patients with severe neurologic complications underwent MRI (6 abnormal) and EEG (generalized slow activity in those with encephalitis or cerebellitis). Age at infection was in two peaks, 1) in children aged 1 to 5 years (62% cases), and 2) in teenagers (24.6%). Febrile seizures occurred in 6 (3.1% of cases) <5 years age, and headaches in 47 (24.2%) patients, mostly teenagers 13-17 years old. Ten children presented with severe, neurologic complications: meningoencephalitis, acute encephalitis (5 cases), acute cerebellitis (2), transverse myelitis, and myeloradiculitis. Epstein-Barr virus is a common pathogen that should be tested for routinely in pediatric patients with a neuroinfection. [1]

COMMENTARY. The diagnosis of neurological complication of Epstein-Barr virus infection may be difficult to differentiate from febrile seizure in young children and from infectious mononucleosis in older children with headaches. The authors suggest that the incidence of neurologic pathology may be underestimated and the pathogenesis of Epstein-Barr virus encephalitis is often undetermined. Two previous reviews of pediatric Epstein-Barr virus associated encephalitis emphasize the difficulty in diagnosis, prognosis and the neuroanatomic localization of the infection. Twenty-one (6%) of 216 children in the Encephalitis Registry at University of Toronto had Epstein-Barr virus serology and/or positive PCR; 81% had CSF pleocytosis, 48% had seizures, 57% an abnormal EEG slow background, and 71% had abnormal MRI. Two patients died, 2 suffered mild deficits, and 16 were neurologically normal at follow-up. Only 1 had symptoms of infectious mononucleosis; all others had nonspecific prodrome including fever and headache [2]. In a review of 100 cases of Epstein-Barr virus encephalitis from University of Lund, Sweden, the neuroanatomic localization of involvement was the cerebral hemispheres, cerebellum and basal ganglia. Patients with isolated hemispheric gray or white matter involvement achieved good recovery while half of the patients with thalamic involvement developed sequelae. The highest mortality rate was among patients with isolated brain stem involvement. Neuroanatomic distribution of radiologic abnormalities in Epstein-Barr virus encephalitis may be a prognostic indicator [3].

Disclosures

The author(s) have declared that no competing interests exist.

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