Epilepsy of infancy with migrating focal seizures or rigidity and multifocal seizure syndrome, lethal neonatal? Different emphases on a severe phenotype

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Specialists working in neonatal intensive care and paediatric epileptologists know that onset of continual focal seizures in the first weeks or months of life that migrate to multiple independent sites and clinically different body segments, pose diagnostic and therapeutic challenges, with an ominous prognostic outlook. The first detailed descriptions of infants manifesting this electroclinical pattern also highlighted that the co-occurring developmental arrest, motor impairment, and uniformly poor outcome were homogeneous enough to deserve the designation ‘epilepsy of infancy with migrating focal seizures’ (EIMFS) syndrome.1 Twenty-four years after that description, 33 dominant and recessive genetic aetiologies have been associated with this phenotype.2,3

While a few, ‘major’ epilepsy (mainly ‘ion channel’) genes (including KCNT1, SCN2A, SCN1A, KCNQ2, and GABRB3) account for almost half the reported patients, about 25% have been related to a large number of other genes. The remaining 30% of cases of EIMFS are left without a genetic diagnosis and are most likely accounted for by a large number of genes, some not yet related to disease and some, perhaps until now, associated with milder phenotypes. In this scenario, although a physician facing new onset EIMFS has a 70% chance of identifying the specific genetic aetiology, genetic heterogeneity means that only an extended and lengthy molecular diagnostic workout (most probably whole exome sequencing) will comprehensively cover all genes potentially involved. Moreover, whatever the result of testing, the prognostic outlook will be almost uniformly very poor, with profound disability in most and premature mortality reaching 33% in the largest series available.2

The phenotype may also reveal some heterogeneity if clinical attention is not clouded by the overwhelming electroclinical epilepsy syndrome. It is particularly true for rare and complex diseases that some relevant details may take time to emerge, since multiple observers intervene, each emphasizing different angles of observation.

The story of BRAT1-associated phenotypes, which now also include EIMFS, epitomizes this situation. Biallelic pathogenic variants of the BRAT1 gene had initially been associated with recessive rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL; OMIM#614498), a severe condition with intractable multifocal seizures, or at times Ohtahara syndrome (often beginning in the first days of life), microcephaly, severe hypertonia, and premature death.4 After the most severe forms were reported in consanguineous families, less severe, partially overlapping phenotypes emerged in relation to compound heterozygous mutations,5 collectively termed neurodevelopmental disorder with cerebellar atrophy, with or without seizures (OMIM#618056). Children with these less severe phenotypes survive longer, can achieve developmental milestones, and exhibit variable epilepsy phenotypes.

Adopting a paediatric epilepsy syndromic approach to characterize a large cohort with EIMFS, using mainly electroclinical criteria, Burgess et al.1 gathered 135 patients and found five of them (3.7%) carry biallelic BRAT1 mutations. Scheffer et al.3 present the clinical and electroencephalogram findings of these five children illustrating their extreme severity on the EIMFS spectrum. Although the clinical and genetic overlap suggests that BRAT1-related EIMFS and RMFSL are the same thing, Scheffer et al.’s report3 has the merit of bridging the gap of knowledge that at times separates specialists working in neonatal intensive care units from epilepsy specialists. These professionals might not be familiar with each other’s designations and overlook some of the phenotypic elements that may help to finalize and hasten the aetiological diagnostic process and genetic counselling. Paediatric epileptologists are now advised that EIMFS associated with severe rigidity and microcephaly is likely to be caused by BRAT1 mutations and will need to promptly address genetic testing accordingly.

REFERENCES


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