Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Late Diagnosis of 18p Syndrome with Movement Disorders by Whole Exome Sequencing Read-Depth Based Algorithm

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18p Syndrome is a chromosomal disorder resulting from a deletion of all or part of the short arm of chromosome 18.[1] The incidence is 1:50 000 live-born infants with about 150 cases reported to date.[1,2] Typical clinical presentation predominantly features mild to moderate intellectual disability (ID) and dysmorphia.[2] Moreover, an increasing number of patients with movement disorders (MDs) have been recently reported.[3] We would like to contribute to the description of the phenotype with a patient who suffers from this syndrome and whose story emphasizes the importance of genetical analysis in adult patients with intellectual disability.

Our patient presented with moderate ID and behavioral disorders and received, in childhood, a diagnosis of cerebral palsy caused by neonatal anoxia. Later, as an adult, he was followed by neurologists for nonspecific white matter hyperintensities considered as vascular lesions (Fig. 1A). At 37 years old, he was referred to our Movement Disorders Clinic to manage a cervical dystonia developed a few years earlier. Actually, he presented a more complex hyperkinetic pattern, including generalized dystonia and choreo-athetotic movements. The exact onset of dystonic symptoms was unknown given the absence of available relatives and the anosognosia of the patient. He was able to walk unassisted despite severe dystonic gait troubles with a tendency to trunk retropulsion, retrocolis and choreo-athetotic movements of the upper limbs. His left arm was placed on his hip as a "*geste antagoniste*." The left upper limb was the most affected and presented a typical torsion pattern. His cervical dystonia consisted of the association of a right torticollis, a left laterocolis and a severe retrocolis. He presented no parkinsonian features and cerebellar tests were correctly performed. His spontaneous language was limited with slight dysarthria. Besides a short stature, some dysmorphic features were observed such as hypertelorism, low set protruding ears, a flat nasal bridge and bilateral ptosis (Fig. 1B).

The cause of ID was deemed to be neonatal distress, with no further investigation except a chromosomal karyotyping considered normal according to the standards at the time (1984). The MDs specialist prescribed a Next Generation Sequencing (NGS) gene panel targeted to MDs to deal with this complex hyperkinetic picture. This panel consisted of a Whole Exome Sequencing (WES) from which data for 127 MDs-related genes were extracted for analysis. No pathogenic or likely pathogenic variant had been found. However, a heterozygous deletion of around 12.7 Mb on the short arm of chromosome 18 (ie, sseq [GRCh38] 18p11.32p11.21 (90001_12690000)×1) was identified using the ExomeDepth algorithm. ExomeDepth is a free R package using read-depth data to call Copy Number Variants (CNVs) from exome sequencing experiments.[4] This algorithm compares the number of reads mapping to a chromosome window of the patient with a matched aggregate reference set. Deletion was confirmed by molecular karyotyping performed using shallow Whole Genome Sequencing (WGS) on a NovaSeq 6000 sequencer (Illumina°).

The particularity of this case is the late diagnosis of the chromosomal abnormality. It occurred years after the onset of symptoms and especially MDs. Retrospectively the patient exhibited the typical characteristics of 18p Syndrome (ie, intellectual disability, white matter anomalies, short stature and dysmorphism) associated with a complex hyperkinetic picture.

Several factors may explain the diagnostic delay. Primarily, chromosomal abnormalities are usually diagnosed during childhood because chromosomal analysis is a part of the initial assessment of ID. Indeed, around 14% of children with ID have pathogenic CNVs larger than 400 kb.[5] Secondly, in adult neurology, ID of unknown origin are not sufficiently investigated. Patients frequently have many confounding factors such as parents' unavailability, unconfirmed former diagnosis (eg, cerebral palsy) or genetic results obtained with outdated techniques of lower resolution (eg, former karyotyping).[6]

The diagnosis yield depends on the performance of genetic analysis techniques. Actual NGS panels focus on Single Nucleotide Polymorphisms (SNPs) or small insertions/deletions (indels) because short read DNA sequencing technologies are best suited

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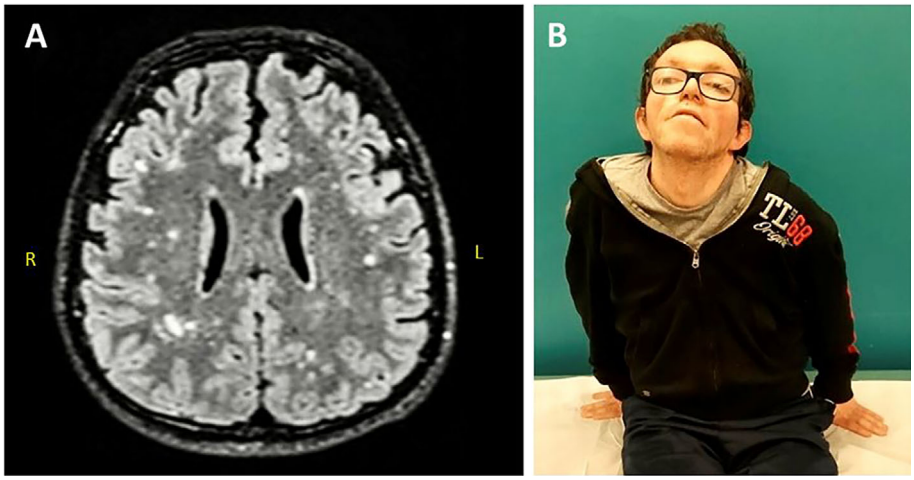

Figure 1. (A) Patient's MRI, T2-FLAIR weighted sequence, axial slice, revealing diffuse white matter lesions. (B) Patient's photograph revealing typical dysmorphic features (ie, hypertelorism, protruding ears, ptosis), cervical dystonia and dystonic posture of the arms.

to call these variants. However, they are less sensitive to the identification of CNVs and may miss large deletion or duplication. To overcome this limitation, strategies exist to call CNVs from exome data (eg, ExomeDepth).[4] These algorithms increase the diagnostic yield by 1–2% when used as a second-line test after Chromosomal Microarray (CMA).[7] This improvement is more significant when they are compared to former techniques, such as molecular karyotyping.[7] CMA is the actual gold standard for clinical CNVs testing. However, the association between a read-depth based algorithm and classical WES may lead to an increase in diagnostic yield by covering all kind of variants (ie, SNPs, CNVs, indels). This eliminates the need of further testing, such as CMA, thereby reducing costs. Here is a significant example of the relevance of this technique.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

C.M.: 1A, 1B, 1C, 3A.

F.D.: 1A, 1B, 1C, 3B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institution review board was not required for this work. The patient has given his written informed consent for the use of his photograph for the purpose of this scientific work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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