Dravet syndrome classically features “febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures, that occur in the first year of life in an otherwise normal infant and are later associated with myoclonus, atypical absences, and partial seizures. All seizure types are resistant to antiepileptic drugs. Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorders.” This description, which is much centered on epilepsy and cognitive impairment, predates the identification of SCN1A as the disease-causing gene and experimental work suggesting that haploinsufficiency causes reduced sodium currents in GABAergic inhibitory interneurons, and that the protein expression clusters predominantly in the axon initial segments of the nodes of Ranvier.

As often happens after a causative gene is identified, the phenotypic spectrum of the syndrome has widened to include a number of additional and unexpected clinical manifestations. This process happens for a combination of factors. First, identifying the causative gene allows mutation analysis, even in patients exhibiting only some of the features of the syndrome. Second, there is a cumulative effect on clinical knowledge derived from the increasing number of patients identified and the additional features that emerge by following them as they age. Third, experimental work produces evidence of pathophysiologic relevance that can be tested in the clinical setting. The study conducted by Gitiaux et al. provides an excellent example of how the above factors can be combined to explain relevant phenotypic features of a syndrome, which were only marginally considered in earlier reports. In fact, although children and adolescents with Dravet syndrome had always been described as exhibiting “ataxic,” “clumsy,” or “awkward” gait, posture, and fine motor skills, it was not until 2012 that the peculiar “crouch” gait was definitely characterized and shown to deteriorate progressively. Normal or nearly normal gait in the first 5 years becomes crouch gait with accompanying skeletal misalignment in the lower limbs in most patients after age 13 years, and can be severe enough to make some require wheelchairs.

Based on previously published work demonstrating that the adult CNS Nav1.1 (the Nav channel isoform for SCN1A) is also expressed in the proximal axon initial segment of nodes of Ranvier in the mouse spinal cord, Gitiaux et al. explored the hypothesis that gait disturbance typical of Dravet syndrome could result from a neuromuscular defect. Using electromyography, they studied 10 patients aged 2 to 17 years (median 7.5 years) and demonstrated, in 7, a chronic neurogenic pattern, consistent with a motor neuropathy/neuronopathy, whose features resemble those observed in spinal muscular atrophy with lower extremity predominance.

According to the authors, these findings could well explain the natural history of the gait impairment, with an initial distal mild motor deficit leading to gait disturbance and orthopedic deformities (e.g., increased femoral neck anteversion, external tibial torsion, pes valgus), followed by a more proximal motor deficit, leading to crouching.

There are open questions remaining, as the neurophysiologic findings, seemingly mild to moderate in degree, do not seem to explain per se the disabling gait impairment and deformities these patients have, or the consequent reduction in autonomous ambulation. Indeed, impaired gait and posture might have a complex origin, which also includes l-dopa–responsive parkinsonism and ataxia, in line with evidence that SCN1A is also expressed in basal ganglia and cerebellar Purkinje neurons. In addition, a possible detrimental effect of a high seizure frequency and multiple anticonvulsants treatment should be also taken into account.

What is certain is that the crouch gait observed in Dravet syndrome differs from that observed in patients with cerebral palsy, because of the absence of spasticity and contractures. Because the causes are probably complex, preventive measures are difficult to prescribe. Longitudinal follow-up studies are warranted in the future, which may also clarify whether

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the instigation of specific orthotic supports, progressive resistance training, or even surgical correction may limit or prevent gait impairment and skeletal deformities.

Clinical observation, flanked by molecular genetics, is building the basis for a personalized treatment approach to patients with Dravet syndrome. The extremely severe epilepsy is certainly the main clinical problem, but is not the only one of medical relevance. Increased awareness of the whole clinical spectrum of manifestations should prompt, from the time of diagnosis, a comprehensive medical assessment and rehabilitation approach addressing the specific multiple manifestations of the syndrome.

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