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ANTECOLLIS AND LEVODOPA-RESPONSIVE PARKINSONISM ARE LATE FEATURES OF DRAVET SYNDROME

Dravet syndrome (DS) is a severe genetic epileptic encephalopathy mainly caused by *SCN1A* mutations.¹ Children usually develop frequent and pharmacoresistant seizures of several types. Besides cognitive delay, some patients later develop gait ataxia. “Crouch gait” has also been described in older patients.^{2,3}

Given the poor knowledge of the clinical features of patients with DS surviving until adulthood, we prospectively investigated the motor abnormalities in a consecutive sample of adults with genetically proven DS.

Methods. Patients were evaluated using a standardized protocol including videotaping. We excluded patients chronically exposed to antipsychotics. Patients who presented with severe bradykinesia, gait disorder, or balance impairment underwent a trial of 300 mg/day of levodopa. Groups were compared by Mann-Whitney *U* test and Spearman test was used for correlation analysis.

Standard protocol approvals, registrations, and patient consents. Written consent was obtained from all patients’ parents. Ethics approval was granted by the University Health Network Research Ethics Board.

Results. Twelve patients entered the study (table e-1 on the *Neurology*[®] Web site at Neurology.org). All but one patient presented with severe cognitive delay; mild spasticity was seen in 12% of patients. All cases presented with mild to severe flexion of the head in the sagittal plane ($42.9 \pm 19.7^\circ$; figure) and 8 (66%) fulfilled the diagnostic criteria for antecollis.⁴ Severity significantly correlated with age ($p = 0.59$, $p = 0.04$). There was no evidence of weakness of cervical muscles, and EMG in the only compliant patient with antecollis (case 5) found no sign of myopathy in the posterior cervical muscles but continuous activation of sternocleidomastoid muscle, suggesting dystonic co-contraction. The 3 oldest patients (cases 7, 10, and 11) presented with camptocormia and one of them also had Pisa syndrome⁴ (figure). Eleven patients (91%) presented with mild parkinsonism, mainly characterized by global bradykinesia and asymmetric rigidity with a cogwheel phenomenon. Unified Parkinson’s Disease Rating Scale significantly

correlated with age ($p = 0.61$, $p = 0.03$) but not with seizure frequency; it was not different in patients receiving valproate ($n = 8$, 10.8 ± 7.9) or not ($n = 4$, 14.5 ± 7.9), or correlated with the daily dose ($p = 0.11$, $p = 0.73$).

Nine patients had gait impairment with small steps, high variability, en bloc turns, crouch gait, and wide base (video 1). Postural reflexes varied from normal (case 12) to inability to stand unassisted (case 11).

Parental consent for levodopa treatment was obtained in 2 of the 4 most affected patients (cases 6 and 7). These patients experienced a sustained (16 weeks) improvement in slowness and rigidity with no side effects; notably, patient 7 was no longer wheelchair-bound for long-distance walks (figure and video 2).

Discussion. We describe for the first time that the majority of adult patients with DS have levodopa-responsive parkinsonism and antecollis. We recognized crouch gait in 5/12 cases, in keeping with previous adult case series.²

In keeping with an involvement of the basal ganglia, a previous adult series reported (1) lingual dyskinesias (unknown whether drug-induced), rigidity, and dystonic gait in 4 of 14 adult patients with DS⁵; (2) “extrapyramidal signs” without additional description in 3 of 24 patients with DS⁶; and (3) “kyphosis” only in patients 13 years old or older.^{3,6} The etiology of these postural abnormalities is difficult to determine and is likely caused by multifactorial processes.⁴ Given the lack of full cooperation, we could not systematically assess the strength of neck extensor muscles. Central mechanisms almost certainly play a role. This is supported by the partial benefit on posture after levodopa treatment and the EMG findings. Structural changes of bone and ligaments may also contribute, although it is not clear whether they only represent secondary changes. As DS is caused by sodium channel gene mutations, a key question is how it could lead to these late features. Ataxic gait is thought to be related to the expression of the protein in the cerebellar Purkinje neurons. It is interesting that the same sodium channel is also extensively expressed in the frontal lobe and basal ganglia but not in the bone or muscle.⁷

Our study has some limitations. First, this is not a longitudinal study, although the significant correlation

Figure Postural abnormalities in patients with Dravet syndrome

The repertoire of postural abnormalities in patients with Dravet syndrome (DS). Head flexion can vary from slight forward bending to severe antecollis with the “chin on the chest” phenomenon. The oldest patients can also display camptocormia. The bottom panel shows patient 7 before and after levodopa administration; a slight improvement of antecollis can be seen (see video 1). Camptocormia and antecollis were diagnosed as a marked (minimum 45°) trunk or neck flexion in the sagittal plane, with almost complete resolution in the supine position.⁴

between age and severity of symptoms supports the possibility of a progressive condition. Second, we could not rule out a role of antiepileptic drugs in the pathogenesis of the motor signs. These drugs more typically cause ataxia, tremor, and dyskinesias rather than parkinsonism or postural disorders. Third, parkinsonism is difficult to diagnose in uncooperative patients with severe cognitive delay; however, asymmetric cogwheel rigidity, small-stepped gait, flexed posture, and the response to levodopa support our diagnosis, although we could not obtain other support such as imaging of the nigrostriatal dopamine system.

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- Depienne C, Trouillard O, Saint-Martin C, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. *J Med Genet* 2009;46:183–191.
- Rilstone JJ, Coelho FM, Minassian BA, Andrade DM. Dravet syndrome: seizure control and gait in adults with different SCN1A mutations. *Epilepsia* 2012;53:1421–1428.
- Rodda JM, Scheffer IE, McMahon JM, Berkovic SF, Graham HK. Progressive gait deterioration in adolescents with Dravet syndrome. *Arch Neurol* 2012;69:873–878.
- Doherty KM, van de Warrenburg BP, Peralta MC, et al. Postural deformities in Parkinson's disease. *Lancet Neurol* 2011;10:538–549.
- Jansen FE, Sadleir LG, Harkin LA, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. *Neurology* 2006;67:2224–2226.
- Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. *Epilepsia* 2011;52(suppl 2):44–49.
- Lukk M, Kapushesky M, Nikkila J, et al. A global map of human gene expression. *Nat Biotechnol* 2010;28:322–324.