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Mirror movements and blepharoclonus as novel phenomena in hereditary diffuse leukoencephalopathy with spheroids

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Hereditary diffuse leukoencephalopathy with spheroids (HDLS), caused by dominant mutations in *CSF1R*, presents in adults with executive and memory problems, behavioral changes and atypical parkinsonism, making it difficult to distinguish HDLS clinically from dementia due to frontotemporal lobar degeneration or Lewy body disease [1]. Diagnosis is usually facilitated by MRI, which shows frontal white matter lesions with subcortical atrophy, thinning of the corpus callosum and degeneration of the corticospinal tract. Of note, brainstem lesions should be absent and cerebellar involvement minimal [2]. Here, we present a patient with HDLS, in whom blepharoclonus not only expands the phenotype by a novel hyperkinetic feature, but also revealed infratentorial disease. In addition, mirror movements were present in the more affected hand, differentiating the disorder from Parkinson's disease.

A 61 year old, right-handed woman had progressive deterioration of speech over a course of two years. Apart from a faint voice, halting speech and increasing word-finding difficulties, she reported difficulties in gait and dexterity, urinary urge, multi-tasking problems and labile affect. One year before, she had been diagnosed with severe depression with psychotic symptoms, which was treated with sertraline and quetiapine. Eight months before, lamotrigine was initiated after a generalized tonic-clonic seizure.

On examination, she was fully oriented to place and time and achieved 24/30 in the Montreal Cognitive Assessment, with problems in verbal fluency, working memory and verbal recall. Thinking and speech were slow with word-finding difficulties and semantic as well some phonemic paraphasias. She had asymmetric parkinsonism with hypomimia, right-sided rigidity and reduced arm swing as well as severe bradykinesia and pathological finger tapping with right-sided predominance. There was moderate to severe hypophonia and pseudobulbar dysarthria. Tests of coordination showed no ataxia. Examination of extraocular movements showed vertical upward gaze palsy (up to 20-30°). Smooth-pursuit eye-movements and saccades were otherwise normal without gaze-evoked nystagmus. Repetitive clonic eyelid contractions, consistent with blepharoclonus, were observed upon eyelid closure (see video on line). Glabella and palmomental reflex as well as frontal release signs were negative. Tendon reflexes were brisk, but plantar responses were flexor. Tests of strength and sensation including cortical sensation were normal. There was slight apraxia with left-sided predominance. Movements of the left hand induced mirror movements of the right hand (see video on line), but not vice versa.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2018.07.001.

Brain MRI showed patchy white matter lesions, thinning of the corpus callosum and involvement of the corticospinal tract (Fig. 1). HDLS was diagnosed after genetic testing revealed a known pathogenic c.2381T > C (p.Ile794Thr) mutation in *CSF1R*. Levels of long and very long chain fatty acids as well as CSF analyses including neurodegenerative biomarkers (Aβ42, tau, p-tau and 14-3-3 protein) were unremarkable. Niemann-Pick Type C disease was excluded by sequencing *NPC1* after plasma levels of chitotriosidase and cholestantriol were slightly elevated.

Our observation of blepharoclonus expands the typical hypokinetic "parkinsonian" HDLS phenotype by a novel hyperkinetic feature. Hyperkinetic movement disorders in HDLS previously comprised of finger myoclonus, limb dystonia and palatal tremor, all observed in individual patients [1]. Blepharoclonus is a bilateral and persistent 2-3 Hz clonic contraction of the orbicularis oculi muscle, which is typically triggered by eyelid closure or eccentric gaze. It clearly differs from blepharospasm, which has a fluctuating and lower blink rate of 30–40/minute, and which presents with sustained contraction of the orbicular oculi muscle or as apraxia of eyelid opening, i.e. the inability to open the eyes without visible contraction [3]. Of note, blepharoclonus is observed after lesions of the brainstem, for example by aqueductal stenosis or compression by Arnold-Chiari malformation [4,5]. Given that HDLS is considered a subcortical white matter disease, the presence of blepharoclonus therefore characterizes HDLS as a multisystem disease with both supra- and infratentorial involvement, even early in the disease. Lesions of the brainstem have been shown neuropathologically in selective neuronal subpopulations such as the substantia nigra, but they may be below the limit of detection by MRI [2,6].

The observation of mirror movements in the *more* affected hand represents a clinical cue that may facilitate clinical differentiation of HDLS from Lewy body disease. Specifically, mirror movements occur in up to 89% of patients with early asymmetric Parkinson's disease, where they occur in the *less* affected hand [7,8]. In corticobasal syndrome, mirror movements have also been observed predominantly in the *more*

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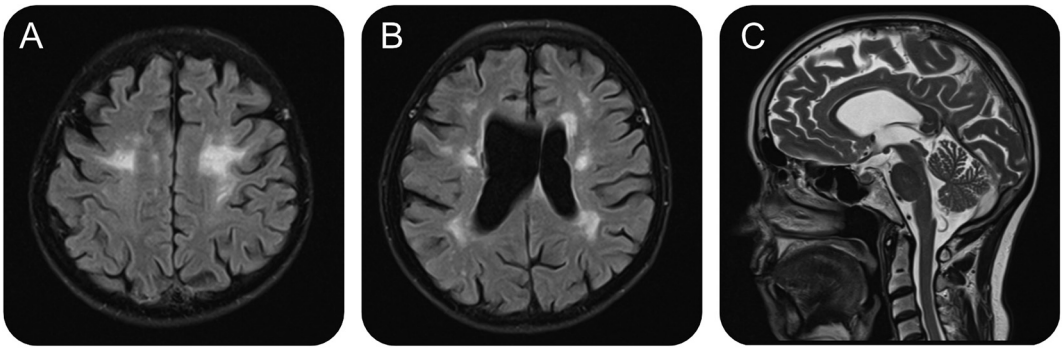

Fig. 1. MRI features suggestive of HDLS. (A, B) FLAIR sequences demonstrating predominantly frontal patchy white matter lesions sparing U-fibers and involving the corticospinal tract. (C) Sagittal T2 sequence shows thinning of corpus callosum.

affected hand, where they may be difficult to distinguish from alien limb phenomena [7]. To our knowledge, however, the relevance of mirror movements in atypical parkinsonism is unclear, and their value for differential diagnosis requires further systematic investigation.

Competing interests

All authors declare no conflicts of interest.

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Andreas Traschütz*
University Hospital of Bonn, Department of Neurology, Germany
E-mail address: andreas.traschuetz@ukb.uni-bonn.de

Elke Hattingen
University Hospital of Bonn, Department of Neuroradiology, Germany
E-mail address: elke.hattingen@ukb.uni-bonn.de

Thomas Klockgether
University Hospital of Bonn, Department of Neurology, Germany
German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
E-mail address: thomas.klockgether@ukb.uni-bonn.de

Sebastian Paus
University Hospital of Bonn, Department of Neurology, Germany
E-mail address: sebastian.paus@ukb.uni-bonn.de

* Corresponding author. University Hospital of Bonn, Department of Neurology, Sigmund-Freud-Straße 25, 53127, Bonn, Germany.