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NEUROCOGNITIVE DEFICITS AND DIFFUSION MR IMAGING ABNORMALITIES IN A CASE OF ADULT-ONSET AUTOSOMAL DOMINANT LEUKODYSTROPHY

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Abstract

Autosomal dominant adult-onset leukodystrophy (ADLD) is a progressive hereditary disease caused by duplication of Lamin B1 on chromosome 5q23.2. It is characterized by autonomic dysregulation, pyramidal signs, and cerebellar dysfunction. Since the first description in 1984, no authors have reported on its neurocognitive sequelae or attempted to quantify the severity of white matter changes. Herein we report a case of ADLD presenting with progressive cognitive changes leading to dementia and its associated white matter damage using diffusion MR imaging.

Keywords

• Adult-onset autosomal dominant leukodystrophy • Diffusion tensor MR imaging • Cognition • White matter disease • Young-onset dementia

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Case report

A 55-year-old man was evaluated for a 10-year history of weakness of the legs (left > right) and gait disturbances. In the last three years, he also complained of significant changes in his cognition. A detailed history revealed changes in attention, memory and organizational skills. He had completed 15 years of education in administration and computer science. His premorbid level of intellectual functioning was estimated in the high average range. He recently quit his occupation largely as a result of progressive cognitive difficulties.

He only took vitamins. Family history was positive for ADLD genotype in his father. One of his two brothers who was deceased carried two alleles for the sacsin-encoding gene and was therefore affected with both ADLD and Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (OMIM 270550).

Neurological examination revealed normal vital signs. He was alert, oriented but bradyphrenic. Cranial nerves were intact. Strength was reduced bilaterally, more pronounced on the left. Pyramidal signs included brisk reflexes throughout, moderate spasticity in the lower limbs (left > right), and bilateral Babinski signs. Cerebellar examination showed dysarthria and mild left dysmetria.

Cognitive examination included a comprehensive 4-hour battery of neuropsychological tests. He performed in the superior range (91st percentile) on tasks of vocabulary and general knowledge. Language and basic visuospatial functions were preserved. However, he showed significant deficits (1st-4th percentiles) in complex attentional skills (working memory, sustained attention), executive functions (abstract thinking, verbal fluency) and learning abilities (poor learning curve, reduced delayed recall, improved with cueing). Visuoconstructional deficits were quite apparent on block design and copy of the Rey Complex Figure (Figure 1A-B) where he juxtaposed details.

He was extensively investigated (TSH, B12, VDRL, autoimmune panel, and CSF analysis) and found positive for a Lamin B1 duplication (R18240), consistent with ADLD. MRI of the brain showed severe and confluent subcortical white matter abnormalities more pronounced in the posterior areas, but no significant cortical atrophy (Figure 2A-B). Cervical spinal cord was severely atrophied (Figure 2I).

High angular resolution diffusion MR imaging (HARDI) was carried out using 64 diffusion directions, a b-value of 1,500 s/mm^2 and parallel imaging to quantify the severity of white matter disease. Apparent diffusion coefficient (ADC) (Figure 2C-D) and fractional anisotropy (FA) (Figure 2E-F) maps showed that compared to our control paired for age and education, FA was 12.5% lower in the patient, while ADC diffusivities (radial and axial) were 5% higher. Preliminary results from HARDI tractography robust to fiber crossing [2] showed chaotic and incoherently organized tracts (e.g., corticospinal tract; see Figure 2G-H).

Discussion

To this date, ADLD had only been known for its progressive onset of autonomic, pyramidal and cerebellar symptoms [3,4]. We report of a 55 year-old ADLD patient with significant deficits in attention, memory, visuoconstruction and executive skills. Deficits particularly affect frontal-subcortical pathways and give rise to

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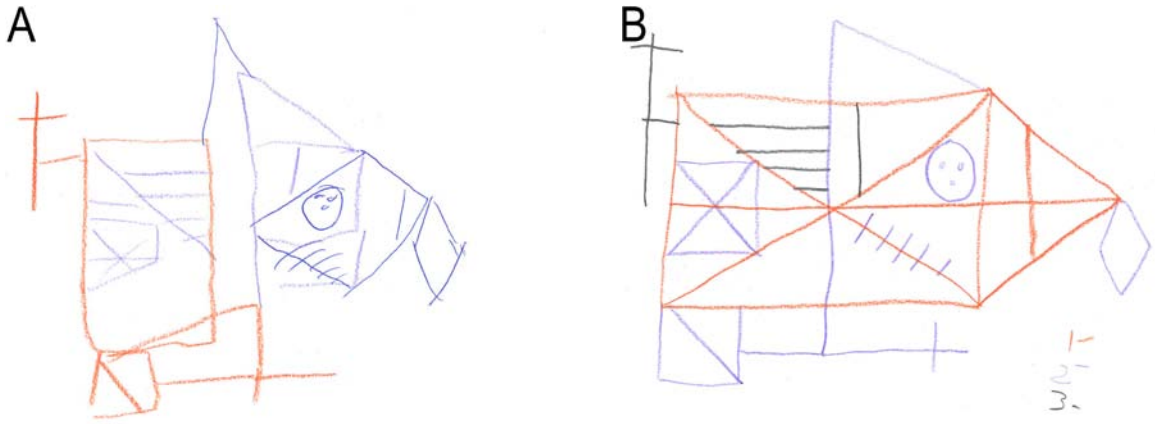

Figure 1. Copy of the Rey Complex Figure (patient, A, and control, B) [1].

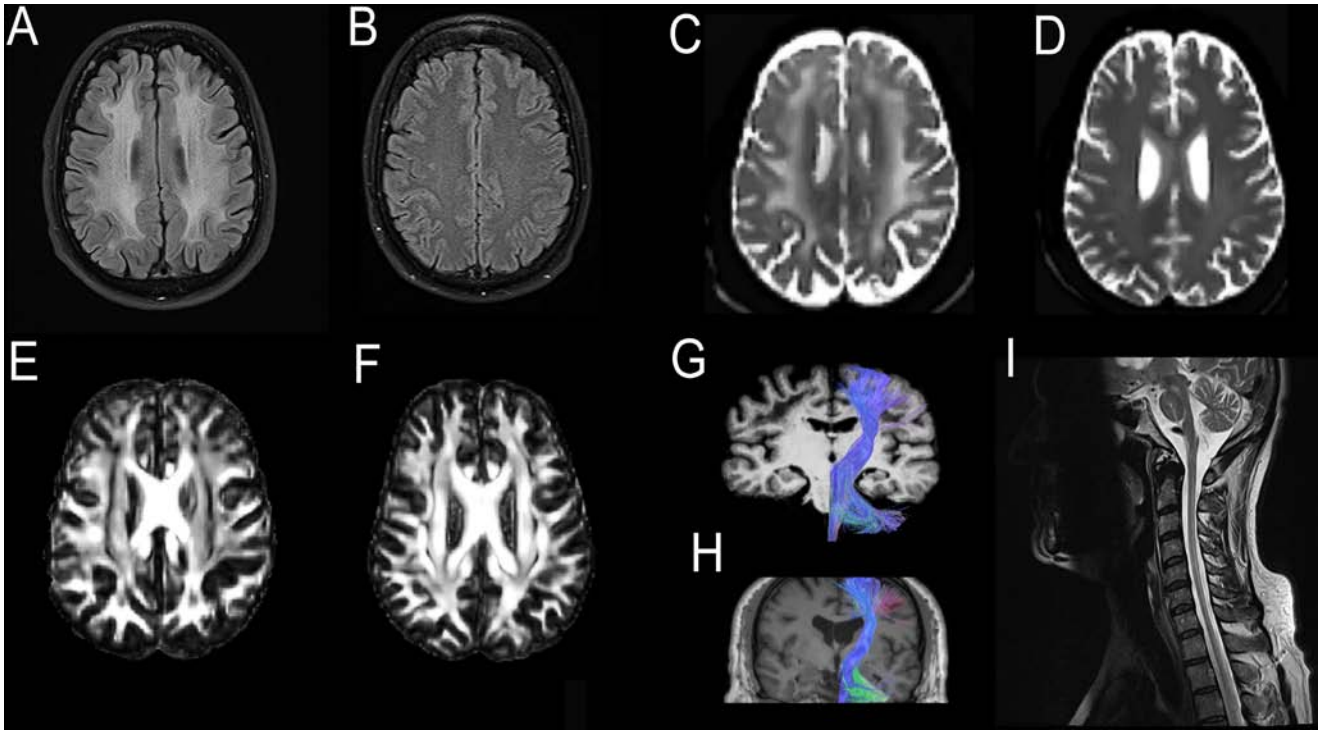

Figure 2. MRI FLAIR (patient, A, and control, B), HARDI ADC (patient, C, and control D), HARDI FA (patient, E and control, F), HARDI fiber tractography of corticospinal tract (patient, G, and control, H), and MRI sagittal T2 of the cervical spine of the patient (I). Abbreviations: Apparent diffusion coefficient (ADC); Fluid Attenuated Inversion Recovery (FLAIR); Fractional anisotropy (FA); High angular resolution diffusion MR imaging (HARDI).

a moderate-severe dysexecutive syndrome. Memory retrieval difficulties are consistent with white matter involvement, and differ from the encoding deficit more typically associated with cortical dysfunction and amnesia. To our knowledge, this is the first detailed report of neuropsychological and HARDI features in ADLD.

These findings have triggered systematic assessment of cognition in our large French Canadian ADLD family, and studies are currently underway to examine their cognitive dysfunctions so that observations from this brief report can be expanded. Furthermore, our case illustrates how little is known about the phenotypical spectrum of ADLD [5]. Lamin B1 duplications sizes vary in different families (suggesting that each are independent mutational events) and some families do not have Lamin B1 duplications (suggesting other Lamin B1 mutations or mutations in other genes are responsible for varying phenotypes) [6-8]. This adds to a difficult differential diagnosis with prior studies in

sporadic leucodystrophy with neuroaxonal spheroids, for instance, revealing a general cognitive decline (sometimes dementia) with frontal subcortical features and/or behavioral/psychiatric disturbances [9].

Finally, this is the first application of HARDI in ADLD. Results indicated significant reduction of FA, increased diffusivities and chaotic fiber tracts with limited organization. Whether HARDI proves valuable in discriminating early white matter changes compatible with ADLD is unknown and further analysis must be conducted with HARDI anisotropy measures in specific fiber bundles. However, our results are currently limited to one single case. Thus, we will pursue further efforts to explore cognition, diffusion MR imaging and fiber tracking in various genotypes-phenotypes of ADLD.

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