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A longitudinal study of a family with adult-onset autosomal dominant leukodystrophy: Clinical, autonomic and neuropsychological findings

Rossana Terlizzi [a,b], Giovanna Calandra-Buonaura [a,b], Stefano Zanigni [b,c], Giorgio Barletta [a,b], Sabina Capellari [a,b], Pietro Guaraldi [d], Vincenzo Donadio [a,b], Ernesto Cason [e], Manuela Contin [a,b], Roberto Poda [a], Caterina Tonon [b,c], Luisa Sambati [a,b], Roberto Gallassi [a], Rocco Liguori [a,b], Raffaele Lodi [b,c], Pietro Cortelli [a,b,*]

[a] IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy
[b] Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Bologna, Italy
[c] Functional MR Unit, Policlinico S. Orsola-Malpighi, Italy
[d] Neurology outpatient Clinic, Department of Primary Care, Local Health Authority of Modena, Modena, Italy
[e] Unit of Nuclear Medicine, Maggiore Hospital of Bologna, Italy

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ABSTRACT

Background and purpose: Adult-onset autosomal dominant leukodystrophy (ADLD) is a rare progressive neurological disorder caused by Lamin B1 duplication (LMNB1). Our aim was to investigate longitudinally the pattern of the autonomic dysfunction and the degree of neuropsychological involvement.
Methods: Three related ADLD patients and one asymptomatic carrier of LMNB1 duplication underwent a standardized evaluation of autonomic nervous system, including cardiovascular reflexes, pharmacological testing, microneurography, skin biopsy, Metaiodobenzylguanidine scintigraphy and a complete neuropsychological battery.
Results: An early neurogenic orthostatic hypotension was detected in all patients and confirmed by a low rise in noradrenaline levels on Tilt Test. However infusion of noradrenaline resulted in normal blood pressure rise as well as the infusion of clonidine. At the insulin tolerance test the increase in adrenaline resulted pathological in two out three patients. Microneurography failed to detect muscle sympathetic nerve activity bursts. Skin biopsy revealed a poor adrenergic innervation, while cardiac sympathetic nerves were normal. None of ADLD patients showed a global cognitive deficit but a selective impairment in the executive functions.
Conclusion: Autonomic disorder in ADLD involves selectively the postganglionic sympathetic system including the sympatho-adrenal response. Cognitive involvement consisting in an early impairment of executive tasks that might precede brain MR abnormalities.

1. Introduction

Adult-onset autosomal dominant leukodystrophy (ADLD) is a fatal inherited progressive disorder affecting the white matter of the central nervous system caused by a duplication of the lLamin B1 gene (LMNB1) on chromosome 5q32 (Padiath et al., 2006). Lamin B1 is one of the major protein components of the nuclear lamina (Cortelli et al., 2012), and its duplication results in an increased expression of lamin B1 mRNA and protein in patient's brain tissue (Padiath and Fu, 2010). The molecular basis of ADLD is still unknown, but some mechanisms have been hypothesized to explain its occurrence (Lin et al., 2011; Ferrera et al., 2014; Giorgio et al., 2013; Bartoletti-Stella et al., 2015).

Demyelination is characterized by preservation of axons and oligodendrocytes with decreased number of abnormal astrocytes (Padiath et al., 2006). Characteristically, magnetic resonance imaging (MRI) shows signal alterations in cerebral, cerebellar and spinal white matter with relative sparing of periventricular areas and U-fibres associated with different degrees of brain and spine atrophy. These neuropathological and neuroradiological findings represent distinguishing features of the disease (Padiath et al., 2006; Sundblom et al., 2009; Melberg et al., 2006). A recent follow-up study demonstrated that these MRI abnormalities can be considered an early hallmark in subjects with pertinent family history (Finnsson et al., 2015).

Since 1984, several families with LMNB1 duplications have been described (Eldridge et al., 1984; Schuster et al., 2011; Marklund et al., 2006; Brussino et al., 2009; Brussino et al., 2010; Potic et al., 2013). Clinically, ADLD is characterized by early autonomic dysfunction followed by pyramidal and cerebellar dysfunction. Onset is usually in the fourth

Abbreviations: 123I-MIBG, iodine-123 metaiodobenzylguanidine scintigraphy; A, Adrenaline; ADLD, adult-onset autosomal dominant leukodystrophy; ANS, autonomic nervous system; DB, deep breathing; EDSS, Expanded Disability Status Scale score; HG, isometric handgrip; HUTT, head-up tilt test; LMNB1, Lamin B1; MRI, magnetic resonance imaging; NA, Noradrenaline; VM, Valsalva manoeuvre.

* Corresponding author at: IRCCS Institute of Neurological Sciences, Bellaria Hospital, via Altura 3, 40139 Bologna, Italy.
E-mail address: pietro.cortelli@unibo.it (P. Cortelli).

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or fifth decade of life and life expectancy is approximately 20 years (Padiath and Fu, 2010; Finnsson et al., 2015).

The site and the pathogenic mechanism of the autonomic dysfunction are still debated. A previous study hypothesized a failure of the sympathetic branch of the autonomic nervous system (ANS) resulting from a distal sympathetic neuronal dysfunction not, however, associated with morphological changes in peripheral nerves, sympathetic ganglia and adrenal medulla (Brown et al., 1987). Recently, preliminary data of an ADLD patient with a selective sympathetic post-ganglionic impairment with sparing of the parasympathetic cardio-vagal function was described by this group (Guaraldi et al., 2011).

The aim of the study was to characterize, through a longitudinal analysis, the autonomic dysfunction and the neuropsychological pattern in an ADLD family.

2. Material and methods

2.1. Subjects

This study included three ADLD patients native to southern Italy, segregating LMNB1 duplication and one asymptomatic family member carrier of LMNB1 duplication, identified by performing the genetic analysis on 7 asymptomatic members at risk, i.e. adult children of affected members. They were studied in order to detect any different genetic influences on the clinical phenotype (Bartoletti-Stella et al., 2015). The study was approved by the local ethics committee in agreement with the principles of the Declaration of Helsinki. Patients signed an informed consent before enrolment.

2.2. Method

The three ADLD patients (IV11, IV10 and IV12; Fig. 1) were followed up for 8, 6 and 3 years, respectively, depending on the disease duration. ADLD patients were longitudinally evaluated with a neurological examination and the corresponding Expanded Disability Status Scale score (EDSS). Cardiovascular ANS function was assessed through cardiovascular reflex, neurochemical and neuropharmacological tests. Further microneurography, skin biopsy, and iodine-123 metaiodobenzylguanidine scintigraphy (123I-MIBG) were performed once. Consecutive brain MR studies were obtained to follow up the neuroradiological progression and a neuropsychological battery was used to characterize the cognitive involvement. The asymptomatic carrier of LMNB1 duplication and the non-affected members were studied through a single evaluation based on the same protocol with the exception of pharmacological tests and 123I-MIBG, which were not performed.

2.2.1. Autonomic investigations

Cardiovascular ANS control was investigated through head-up tilt test (HUTT), Valsalva manoeuvre (VM), isometric handgrip (HG), and deep breathing (DB). The patients were tested in the morning between 8 a.m. and 12 a.m. in a clinical investigation room (23 ± 1 °C) with continuous polygraphic recording of systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), and oronasal and abdominal breathing, according to a standardized procedure. [Appendix S1] Plasma noradrenaline (NA) and adrenaline (A) were collected by an indwelling cannula in a forearm after 25 min of supine rest and at the 10th min of HUTT. The biochemical analyses were performed by using high performance liquid chromatography. ANS was further studied with pharmacological testing to localize the lesion site; microneurography to evaluate efferent post-ganglionic sympathetic nerve activity; skin biopsies to visualize somatic and autonomic skin nerve fibres; 123 I-MIBG scintigraphy to evaluate myocardial post-ganglionic sympathetic nerves (Appendix S1).

2.2.2. Neuropsychological investigations

We explored global cognition by Mini Mental State Examination (MMSE) and Brief Mental Deterioration Battery (BMDB). Depression was evaluated by using the Beck Depression Inventory (BDI) (Table S1). All tests results were corrected for age and education according to standardized values referring to the Italian population.

2.2.3. Neuroradiological investigations

Brain MR studies were performed using a 1.5 Tesla system (GE Medical Systems Signa HDx 15, General Electrics Medical Systems Milwaukee, Wisconsin) equipped with a quadrature birdcage head coil. All patients underwent the same MRI protocol including: T1-weighted volumetric FSPGR sequence, axial and coronal FLAIR T2, axial FSE T2-weighted images. Diffusion tensor imaging (DTI) of contiguous 3 mm axial slices were obtained using a single-shot SE-EPI sequence (TR 10 s, TE = 85.4 ms, FOV = 32 × 32 cm, in-plane resolution = 128 × 128, 64 diffusion-weighted directions and 7 unweighted scans, b-value = 900 s/mm^2). Fractional Anisotropy (FA) and Mean Diffusivity (MD) values were calculated within regions of interest (ROIs) placed on supra- and infratentorial white matter as well as on medulla, pons, midbrain, dentate nuclei, thalami and basal ganglia. FA and MD values of the patients were compared to those from 15 sex- and age-matched controls (Zanigni et al., 2015).

3. Results

We collected three cases with familial ADLD (2 males and 1 female; mean age 54 ± 6 years, mean age at disease onset: 46 ± 3 years; mean current disease duration: 8 ± 2 years) and one asymptomatic carrier of the LMNB1 duplication (23 years old). LMNB1 duplication was

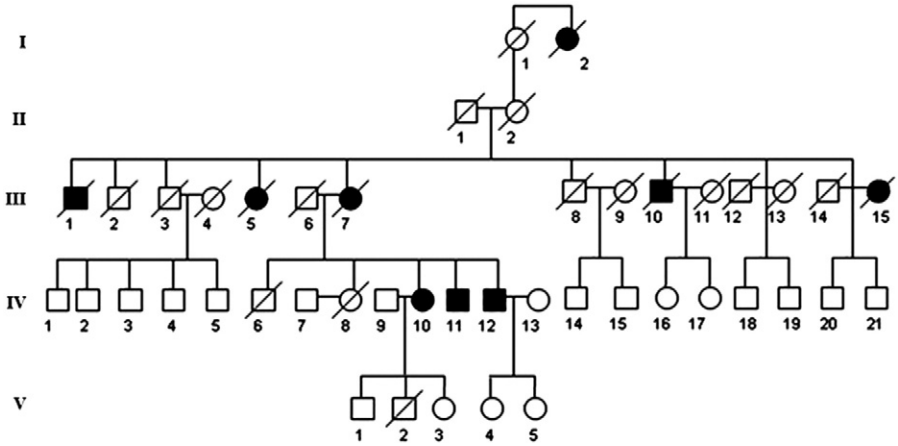

Fig. 1. ADLD family pedigree. Solid: ADLD affected subjects.