

LMNB1-Related Autosomal-Dominant Leukodystrophy: Clinical and Radiological Course

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Objective: Duplication of the *LMNB1* gene encoding lamin B1 causes adult-onset autosomal-dominant leukodystrophy (ADLD) starting with autonomic symptoms, which are followed by pyramidal signs and ataxia. Magnetic resonance imaging (MRI) of the brain reveals characteristic findings. This is the first longitudinal study on this disease. Our objective is to describe the natural clinical and radiological course of *LMNB1*-related ADLD.

Methods: Twenty-three subjects in two families with *LMNB1* duplications were studied over two decades with clinical assessment and MRI of the brain and spinal cord. They were 29 to 70 years old at their first MRI. Repeated MRIs were performed in 14 subjects over a time period of up to 17 years.

Results: Pathological MRI findings were found in the brain and spinal cord in all examinations (i.e., even preceding clinical symptoms). MRI changes and clinical symptoms progressed in a definite order. Autonomic dysfunction appeared in the fifth to sixth decade, preceding or together with gait and coordination difficulties. Motor signs developed ascending from spastic paraplegia to tetraplegia and pseudobulbar palsy in the seventh decade. There were clinical, radiological, and neurophysiological signs of myelopathy. Survival lasted more than two decades after clinical onset.

Interpretation: *LMNB1*-related ADLD is a slowly progressive neurological disease. MRI abnormalities of the brain and spinal cord can precede clinical symptoms by more than a decade and are extensive in all symptomatic patients. Spinal cord involvement is a likely contributing factor to early autonomic symptoms and spastic paraplegia.

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Leukodystrophies comprise a heterogeneous group of genetic disorders that affect myelin formation and maintenance. The more prevalent subtypes manifest typically in childhood after a period of normal development. Most leukodystrophies are inherited as autosomal-recessive or X-linked traits,¹ and adult-onset autosomal-dominant leukodystrophy (ADLD) represents a relatively rare form.

Eldridge et al² described adult-onset ADLD in an Irish-American family in 1984 and named it “a hereditary leukodystrophy mimicking chronic progressive multiple sclerosis.” Patients present in the fourth to sixth decade with autonomic symptoms involving the bladder or bowel and/or orthostatic hypotension. They develop pyramidal

sign and ataxia. A detailed description of the histopathological and magnetic resonance imaging (MRI) findings of the brain was published in 2006,³ and the designation “adult-onset ADLD with autonomic symptoms” was suggested. In that material, patients exhibited extensive T2 hyperintensities in cerebellar peduncles and the cerebral white matter. It was characteristic of the disease that there was a less-affected periventricular rim around the lateral ventricles.³ Histology revealed vacuolation of myelin and preservation of oligodendrocytes, but only minimal reactive gliosis.^{3,4} The spinal cord white matter was affected as well.⁵

This type of ADLD is caused by a duplication of the lamin B1 gene (*LMNB1*) and increased expression of

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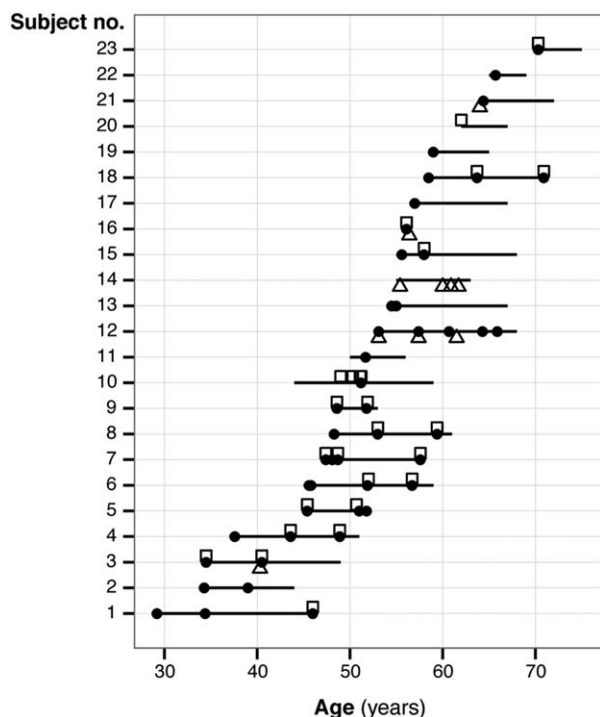


FIGURE 1: Age distribution of subjects at radiological examinations and neurological controls at our hospital. Lines = time span for clinical follow-up at our hospital. Filled circles = magnetic resonance imaging (MRI) of the brain. Empty squares = MRI of the spinal cord. Empty triangles = computed tomography of the brain.

lamin B1,^{6,7} which, in turn, seems to affect maturation of oligodendrocytes.⁸ Cases have been reported from Brazil, Canada, France, Germany, Ireland, Israel, Italy, Japan, Serbia, Sweden, and the United States, among other countries.^{6,7,9–16} Because the molecular background of the disease has already been identified, we propose the name “*LMNB1*-related ADLD” for this entity.

No longitudinal study that describes the long-term course of the disease in a group of subjects has yet been published. The aim of this study is to describe the natural clinical and radiological development of *LMNB1*-related ADLD based on a follow-up study over a two-decade period. These observations may serve as a reference for diagnosis, future interventions, and treatments as well as for assessment of their efficacy in *LMNB1*-related ADLD.

Subjects and Methods

Subjects

Twenty-five subjects from two nonrelated Swedish families segregating ADLD were initially recruited and underwent clinical assessment and radiological studies. The genetic basis of the disease became known after initiating this study,^{6,17} and two asymptomatic subjects without MRI pathology were found to be noncarriers of the *LMNB1* duplication. These two individuals were excluded from the study. The final study material consisted of 23 subjects (12 women, 11 men) with a duplication of

different sizes in the two families⁷; 203,432bp in Family I and 189,731bp in Family II.¹⁵ Twenty subjects derived from Family I and 3 from Family II. Median age was 53 years (range, 29–70) upon the first radiological examination (Fig 1), and clinical data were collected over a period of two decades.

Subjects were studied assessing history, clinical neurological and physical examinations, and followed up by one and the same experienced neurologist. Blood pressure was recorded in the supine and standing upright position within 3 minutes. The Kurtzke Expanded Disability Status Scale (EDSS) was applied in retrospect based on medical records for clinical scoring of pyramidal, cerebellar, brain stem, sensory, bladder and bowel, visual, and mental functions. Symptoms of orthostatic hypotension were included in the autonomic bowel and bladder functional system. The EDSS is commonly used to rate multiple sclerosis (MS) disability. Our rationale for applying the EDSS is that *LMNB1*-related ADLD also affects the white substance in the brain and spinal cord. Clinical examinations were accompanied by radiological investigations. The brain was examined with computed tomography (CT) in 5 subjects. Twenty-one subjects underwent brain MRI, 4 of whom had also undergone CT. In sagittal series, the upper spinal cord was visualized and appeared thin. Therefore, MRI of the spinal cord was added in the study protocol and was performed in 14 subjects. CT of the brain was performed four times during 6 years in 1 subject. MRI of the brain was repeated at least once in 13 subjects with a median follow-up time of 10 years (range, 0.5–17) and MRI of the spinal cord in 9 subjects with a median follow-up time of 5 years (range, 2–10). Age distribution of subjects at the time of examinations is displayed in Figure 1. Data from the first MRI investigation of the brain in 18 of the subjects and from the first MRI of the spinal cord in 12 subjects have been reported previously.^{3,5}

Radiological Techniques

Brain CT was performed using a standard technique. Intravenous contrast medium was used in one examination.

Some subjects had undergone their first MR examination at other hospitals, causing some variation in the sequences. All examinations were performed with 1.5T clinical MR systems. Brain MRI contained at least a sagittal T1-weighted and an axial T2-weighted spin-echo (SE) sequence. Follow-up examinations were all performed at our department. Brain images were obtained using a standard imaging protocol, including T1-weighted sagittal and axial SE images, T2-weighted axial and coronal fast spin-echo (FSE) images, and T2-weighted axial fluid attenuation inversion recovery (FLAIR) images. Contrast medium was used in five examinations. Diffusion-weighted images (DWI) were obtained in 10 subjects. Four of them had a DWI follow-up of 4 to 7 years. The spinal cord was examined with sagittal T1-weighted SE and T2-weighted FSE sequences through the entire spinal cord. Axial T2-weighted images were obtained by using a three dimensional SE sequence at the levels of C2, C7, T5 to T6, and conus medullaris in 9 subjects. In 5 subjects, examined in other hospitals, transverse

images were obtained with different T2-weighted SE or gradient-echo sequences at varying levels.

All images were reviewed by an experienced neuroradiologist. Distribution of signal-intensity changes and substance loss as well as progress between examinations were assessed and a five-grade scale was devised (Fig 2). When sizes of intracranial cerebrospinal fluid (CSF) spaces were graded, the effect of the patient's age was eliminated by comparing the images to the copies of a standard image series used in a study of a neurologically healthy population.¹⁸ Maximal width of the third ventricle was measured. Measurements of the brain stem were compared to those in a healthy population in different age groups.¹⁹ Anteroposterior and transverse diameters as well as cross-sectional area of the spinal cord were measured at levels C2, T6, and the conus by two readers. These results were compared to the normal values.²⁰

Statistical Analysis

The free software R was used to perform statistical calculations and for graphical illustrations.²¹ Bland-Altman plots were used to assess variability of repeated measurements and Pearson linear correlation to look for relationships between age and measurements obtained from the spinal cord.

The study was approved by the local ethics committee and performed in accord with the ethical standards of the Declaration of Helsinki. Subjects gave informed consent before participating in the study.

Results

Figure 3 indicates asymptomatic subjects ($n = 4$), onset of symptoms, and EDSS scores at various ages, ages at which neurophysiological examinations were performed, and ages at death. Clinical characteristics of the subjects are summarized in Tables 1, 2, and 3 and Figure 4A.

Autonomic Symptoms

Autonomic symptoms were reported with onset between ages 40 and 58 years (median, 48). Subject 2, who had MRI pathology at age 34, had no symptoms at follow-up at age 43. He died after an accident at age 44. Subjects 1, 3, and 4, who were asymptomatic at the first evaluations, developed symptoms at ages 45 (constipation), 47 (bladder symptoms, erectile dysfunction, and constipation), and 47 years (bladder symptoms, erectile dysfunction, constipation, and gait problems), respectively. Their symptoms occurred 16, 13, and 9 years, respectively, after MR pathology was first documented. Ages of onset and types of the symptoms in the whole material are shown in Table 1. The type of symptoms at onset varied: Autonomic symptoms, usually bladder dysfunction, preceded other symptoms ($n = 14$); onset of autonomic symptoms and motor symptoms were simultaneous ($n = 6$); and in subjects 10 and 16, gait difficulties preceded autonomic symptoms by 3 and 1.5 years, respectively. In subject 10,

gait problems first occurred during a long walk in the mountains and he needed support to walk. Autonomic symptoms included urinary urgency, incontinence, nocturia, and difficulty in emptying the bladder. Four men had erectile dysfunction as an early symptom. Constipation was a common complaint from most study subjects. None of the patients reported inability to sweat as an early feature. All 3 patients from Family II had an early onset of symptomatic orthostatic hypotension. In Family I, orthostatic hypotension was found early in the course ($n = 9$) or later during follow-up, in some cases after several years ($n = 5$). Dry skin was noted in 6 patients. Recurrent urinary tract infections (UTIs) were common.

Motor Symptoms

In 14 patients, autonomic symptoms preceded motor symptoms by several months to years. Motor symptoms had a slow progressive course without acute exacerbations, with initial involvement of the legs, thereafter the arms, and, finally, pseudobulbar palsy. Signs in the legs included spastic paraplegia that progressed slowly with weakness, brisk tendon reflexes, and extensor plantar signs. Maximum walking distance decreased with disease progression and patients used sticks, walkers, and, finally, a wheel chair. Mean age for EDSS 6 was 59 years and 61 years for EDSS 8. However, mean time lapse between EDSS 6 and 8 was 5 years (Table 2). As spasticity and weakness developed, the patients adopted a stooped posture, bending forward in the hips and semiflexing the knees when standing and when supporting the stride, resulting in low back pain. Weak legs frequently resulted in falls. Weakness was also present in the arms, but to a lesser extent than in the legs. Patients eventually developed tetraparesis, flaccid paralysis of the legs with weak or abolished tendon reflexes (subjects 6 and 20), and pseudobulbar palsy, with difficulties in articulation and swallowing in the seventh and eighth decade, corresponding to EDSS 9.5. Gastrostomy was required for appropriate nutrition in 4 patients (subjects 15, 17, 19, and 22).

Disease Duration

Disease duration from onset of symptoms to death ($n = 11$) was between 3 and 24 years (Table 2), with a median survival of 18 years. Four patients survived more than two decades. Eight patients died with EDSS ≥ 8.5 . Median age at death of symptomatic subjects was 68 years. In 3 cases, cause of death was not directly leukodystrophy related: myocardial infarction in subjects 11 and 23 and pulmonary embolism after an operation in subject 16 (EDSS 3.5–6.5).

Pseudoexacerbation

Patients reported heat intolerance and worsening of neurological symptoms during periods of infections or fever

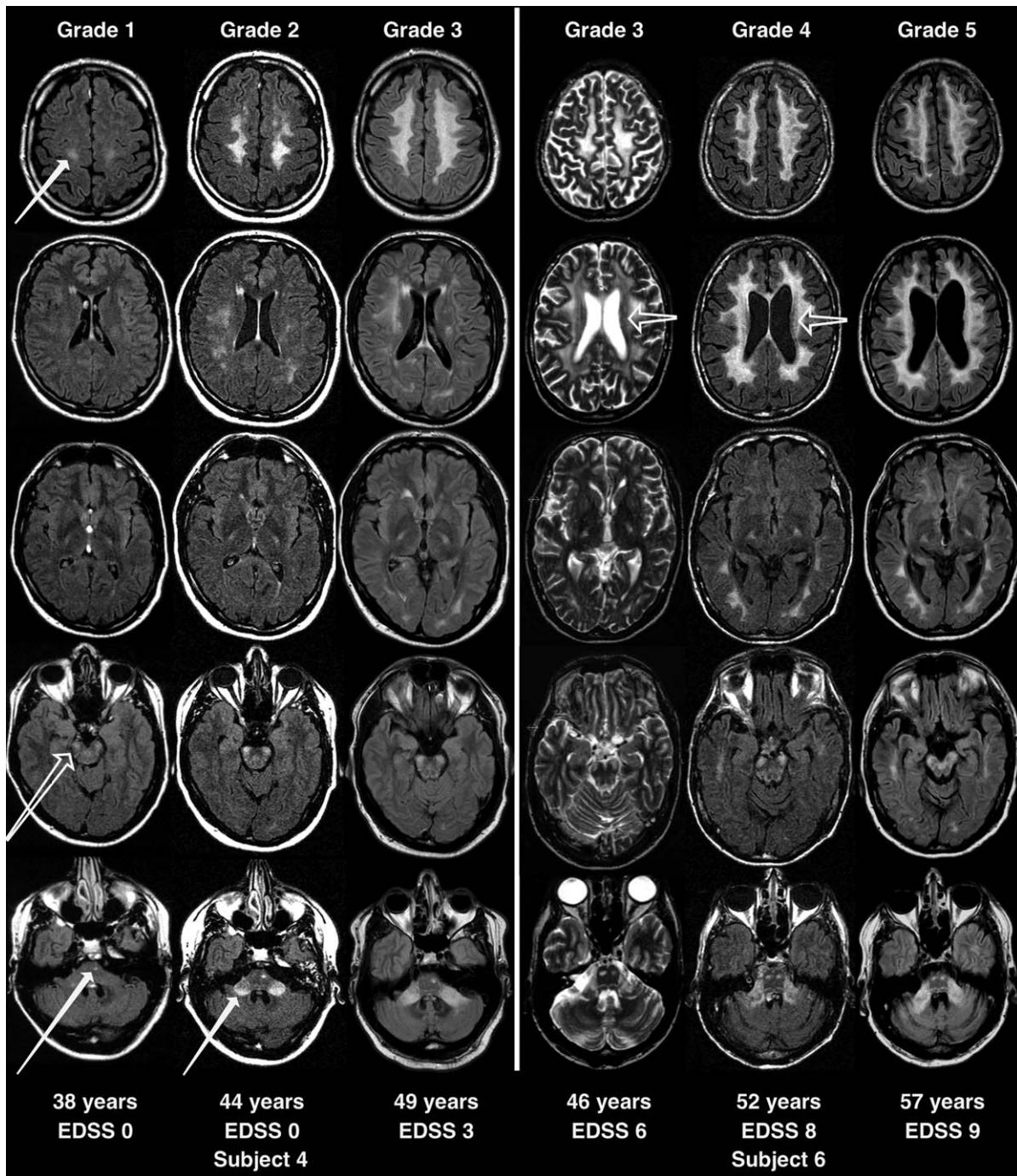


FIGURE 2: Examples of the evolution and grading of signal intensity changes over time in the brains of 2 subjects in T2-weighted images (fluid attenuation inversion recovery sequences except for grade 3 in subject 6 which is a spin-echo sequence). Changes on brain magnetic resonance imaging and EDSS score are not directly comparable, partly because EDSS also reflects changes in the spinal cord. Definitions of the radiological grades: Grade 1: Small T2 hyperintensities under the motor cortex (top arrow) and extending down through the pyramidal tracts, affecting the cerebral peduncles (open arrow) and the pons (bottom arrow). Grade 2: More widespread abnormalities in the cerebellar peduncles (arrow) and cerebral white matter, extending into the frontal and anterior parietal lobes. The periventricular white matter is spared. cerebrospinal fluid (CSF) spaces are minimally larger than in the first examination, but not abnormally wide. Grade 3: Further progress of white matter changes in the cerebrum and the cerebellar peduncles. The changes extend along the occipital horns. Periventricular white matter (open arrow) is less affected than the surrounding pathological white matter. CSF spaces are slightly enlarged. Grade 4: Further enlargement of cerebral white matter changes, which have extended into the temporal lobes. Periventricular less-affected rim marked with an open arrow. CSF spaces larger than in the examination in grade 3 and the lateral ventricles and the third ventricle are pathologically wide. Grade 5: Further progress of white matter changes. The less-affected periventricular rim is still visible, but thinner. CSF spaces are markedly enlarged. EDSS = Kurtzke Expanded Disability Status Scale.

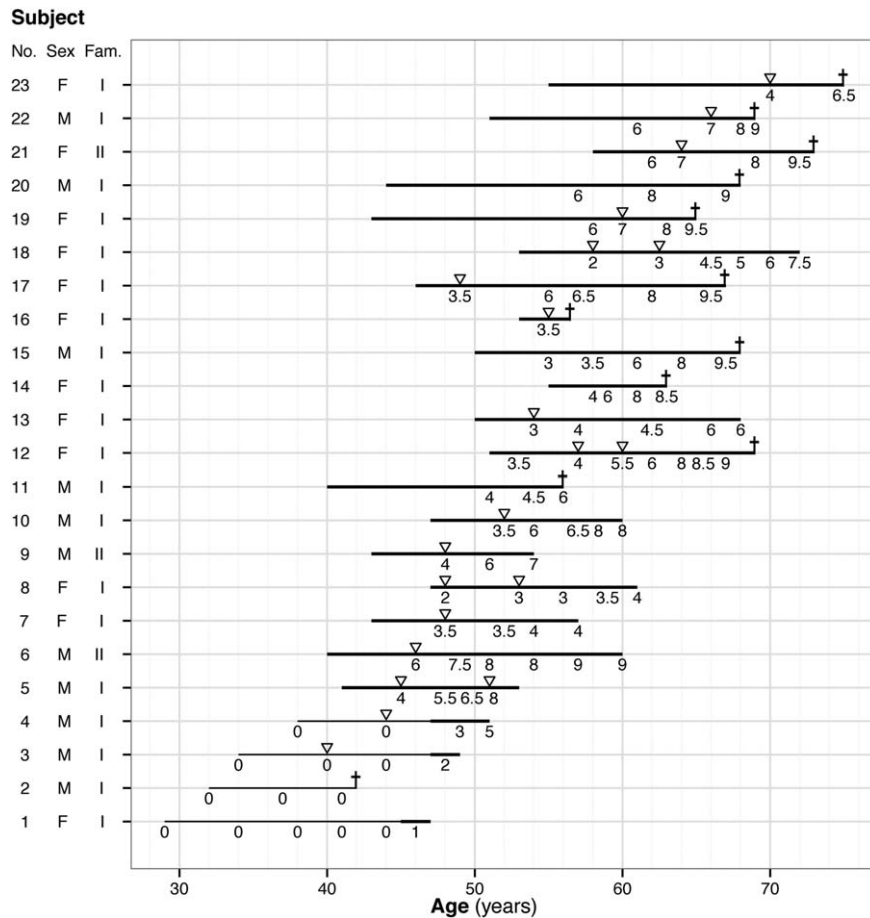


FIGURE 3: Evolution of symptoms and progress of disability. In addition to our own examinations, anamnestic data and information from the patient records in other hospitals have been used. That information was not always sufficient for EDSS scoring. Thin black lines = asymptomatic. Bold black lines = symptomatic. Numbers = EDSS scores. Triangles = neurophysiological examination. Crosses = deceased. M = male; F = female; Fam. = family; EDSS = Kurtzke Expanded Disability Status Scale.

(Table 3). Exacerbations included impaired cognition, motor functions, and consciousness that resulted in repeated hospitalizations. Complications were reversible when patients recovered from infection and when body temperature normalized. Subject 5 developed hypother-

mia during a UTI and pneumonia. Body temperature was 29.5°C upon admission to the hospital, and he required assisted ventilation. The patient had 3 months of hospitalization, including a period of rehabilitation, and EDSS score changed from 6.5 before hypothermia to 8 afterward.

TABLE 1. Symptom Onset of LMNB1-Related ADLD

First Symptom	No. of Subjects	Age at Onset (yr) Mean ± SD [Range]
Autonomic	14	47 ± 5 [40–58]
Autonomic and gait problem	6	48 ± 5.5 [40–55]
Gait problem	2	50 ± 4 [47–53]
Total	22	

ADLD = autosomal-dominant leukodystrophy; SD = standard deviation.

Ataxia

Ataxia (Table 3) was present in patients with pyramidal symptoms. Gait unsteadiness, and subsequently difficulty or inability to stand upright without support, with eyes open and closed was observed. Patients with pyramidal signs and impaired sensation in the legs, including decreased vibration sense, had an atactic heel-knee-shin test with eyes open and closed. There was commonly intention tremor in the arms and, in subsequent stages, dysmetria and dysdiadochokinesis. Only 2 patients had overt nystagmus. Bedside examination showed that smooth pursuit was interspersed by saccadic interruptions in several patients.

TABLE 2. Disability and Survival Time in LMNB1-Related ADLD

EDSS Score	No. of Subjects	Age at Reaching the Score (yr) Mean ± SD [Range]	Time From Symptom Onset (yr) Mean ± SD [Range]	Time Between the Scores 6 and 8 (yr) Mean ± SD [Range]
6	16	59 ± 8 [45–74]	11 ± 5 [4–19]	
8	11	61 ± 6 [51–69]	14 ± 4 [6–22]	5 ± 2 [2–8]
Death ^a	11	66 ± 6 [56–75]	17 ± 6 [3–24]	

^aOne asymptomatic subject with an accidental death not included.

ADLD = autosomal-dominant leukodystrophy; EDSS = Kurtzke Expanded Disability Status Scale; SD = standard deviation.

Tremor

Postural tremor of the arms was observed in 10 subjects (subjects 5, 6, 8, 9, 12, 13, 15, 16, 19, and 21) accompanied by neck tremor in 4. Subject 13 had tremor involving the jaw as well as having an effect on chewing and speech. Primidone abolished the tremor, but the patient did not tolerate the medication.

Sensory Impairment

Sensory impairment started in the feet (n = 7; subjects 6, 9, 12, 13, 19, 20, and 21) and was found in some of the subjects with long disease duration, weakness, spastic paraplegia, and EDSS ≥6. Subject 6 developed decreased sensation of all modalities that progressed with spinal segments reaching the mid-thoracic level at age 58. This patient had the most severe atrophy of the spinal cord and flaccid paralysis of the legs.

Cognition

Early in the course of the clinical disease, patients had normal or mild deficit on Kokmen’s short test of mental status.²² Detailed neuropsychological testing was not performed. Patients at an advanced disease stage and with pseudobulbar palsy usually had dementia or were unable to perform the test. The severely affected subjects had apraxia, difficulties in speaking, or anarthria (n = 8). Subjects 18 and 23, with EDSS 4 and 6, had a score level above dementia level at >70 years of age.

Neurophysiology

Neurophysiological results are presented in Table 4. Nerve conduction studies and electromyography performed in subjects with EDSS 0 to 7 did not indicate polyneuropathy. Somatosensory evoked potentials with stimulation of the median and tibial nerves showed signs compatible with myelopathy and diffuse involvement of the central nervous system (CNS) in some subjects (EDSS 3–7), but was normal in other subjects with EDSS 0 to 3.5. Magnetic cortical stimulation revealed conduction delay in the motor pathways in 3 subjects, but was normal in 1. Visual evoked

potential, performed in 7 subjects, was normal. Sympathetic skin response measured in the hands and feet disclosed decreased sweat reaction (sympathetic) in the feet in 6 subjects and was normal in 9.

Other Findings

RR interval (parasympathetic) was tested in response to normal and deep breathing (n = 14; subjects 3–10, 12, 13, 18, 19, 21, and 23), during Valsalva maneuver (n = 7; subjects 7, 8, 12, 13, 18, 19, and 23), and during stand-up test (n = 8; subjects 7–10, 12, 13, 18, and 23). The stand-up test implied lying down for 10 minutes, followed by standing up for 1 minute, during which time the RR interval was recorded. Decreased RR

TABLE 3. Prevalence of Some Symptoms and Signs in the 22 Symptomatic Subjects

Symptoms and Signs	No. of Subjects
Autonomic (%)	
Bladder dysfunction and/or obstipation	22 (100)
Orthostatic hypotension	17 (77)
Erectile dysfunction as early symptom	4 (40 [of 10 men])
Pyramidal (%)	20 (91)
Including: lower limbs, lower and upper limbs, pseudobulbar	
Ataxia (%)	20 (91)
Including: spectrum of imbalance of gait, ataxia in upper limbs, truncal ataxia	
Pseudoexacerbations (%)	17 (77)
Tremor (%)	10 (45)
Sensory deficits in lower limbs (%)	7 (32)
Hypothermia (%)	1 (5)

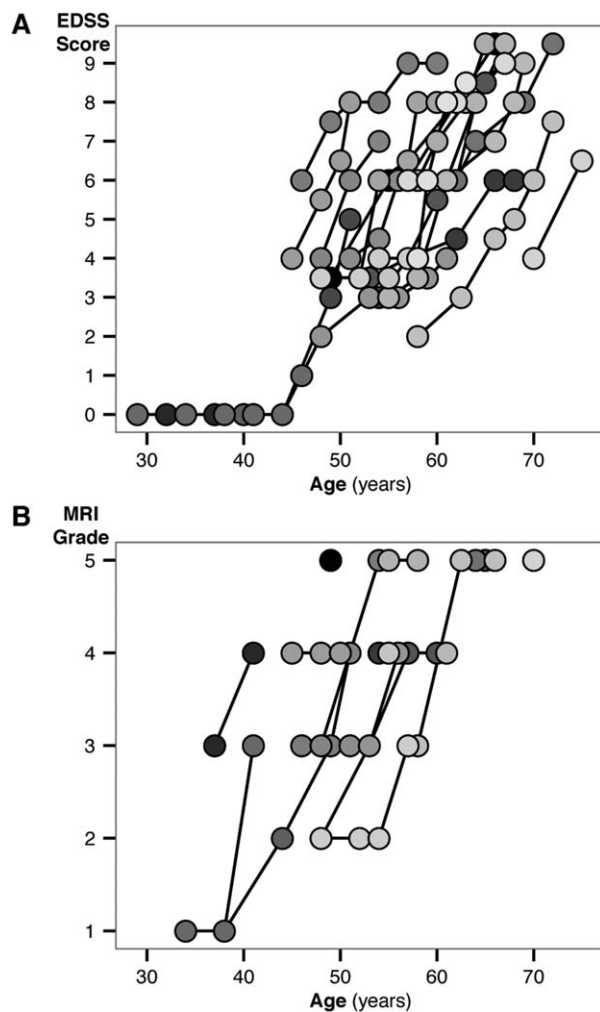


FIGURE 4: Evolution of EDSS scores in all 23 subjects (A) and of radiological grades in the 21 subjects examined with brain MRI (B). Multiple observations of individual subjects maintain the same shade of gray and are connected with lines. Some of the circles and segments of the lines may represent more than 1 subject. For MRI grading, see Figure 2. EDSS = Kurtzke Expanded Disability Status Scale; MRI = magnetic resonance imaging.

interval variability was observed during stand-up test in 3 of 8 subjects (subjects 9, 10, and 13), during Valsalva maneuver in 2 of 7 (subjects 13 and 19), and during deep breathing test in 2 of 14 (subjects 4 and 19). These 14 subjects had autonomic symptoms, except for subjects 3 and 4, who were asymptomatic at the time of the RR interval test.

Radiological Findings

CT was pathologic in all 5 investigated subjects, 4 of whom were symptomatic. The principal CT findings were hypodense areas predominantly in the supraventricular cerebral white matter and in the middle cerebellar peduncles (Fig 5). On follow-up, the extent of the hypodensities increased and there was progressive loss of white matter.

MRI revealed pathology in all examinations of the subjects with genetic linkage to the disease.

BRAIN. T2 signal intensity changes were more prominent than substance loss. Abnormal MRI findings preceded clinical symptoms and signs, with more than a decade in 3 cases. Progress could be observed in MRI in 22 of the 25 repeated examinations, usually, but not always, with a contemporaneous change in EDSS score. The shortest interval at which there was progress in signal intensity changes in the brain was 18 months. Figure 2 exemplifies the evolution of signal intensity changes over time in the brains of 2 subjects. The course of imaging findings over time is summarized in Figure 4B. A certain order in the evolution of the signal intensity changes could be noted. Signal intensity changes started with small T2 hyperintensities under the motor cortex and extended downward through the pyramidal tracts, affecting the cerebral peduncles and the pyramids of the medulla oblongata (Fig 6) and also the cerebellar peduncles, even in subjects who still were asymptomatic (Fig 2). With increasing disease duration, T2 hyperintensities gradually became more widespread and confluent throughout the cerebral white matter, affecting the cerebral lobes usually in the order frontal–parietal–occipital–temporal. Most subjects over the age of 40 years had widespread signal intensity changes in the white matter (grade ≥ 3). All subjects with motor symptoms had extensive areas of T2 hyperintensities in the cerebral white matter (grade ≥ 3).

As described previously,³ the periventricular white matter was spared or less affected. On T2-weighted SE images, signal intensity of periventricular white matter was consistently lower than that of more peripheral white matter (Figs 2 and 7–9). The same signal pattern was observed on T2-weighted FLAIR images in most cases (Figs 2, 7, and 8). However, the T2 FLAIR signal intensity of the most severely affected white matter was suppressed in later stages in 12 patients (Figs 7 and 9), making the periventricular less affected rims less well seen. This relative increase of the periventricular signal intensity on FLAIR images started in the slices above the ventricles. In 4 patients, periventricular signal intensities looked partially even higher than in more peripheral pathological white matter (Fig 9B).

Apparent diffusion coefficient (ADC) values were increased or simulated normal values in affected areas of the cerebral white matter (Figs 8 and 9), but the abnormal area could sometimes look smaller than in morphological T2-weighted images. Pathological areas in cerebellar peduncles did not show ADC changes in 5 of 10 subjects. Periventricular ADC values were first lower than in more

TABLE 4. Neurophysiological Examinations

Examination	No. of Subjects	Result	EDSS Score	Subject No.
Nerve conduction	16	No polyneuropathy	0–7	3–13, 17–19, 21, 23
Somatosensory evoked potential	16	Normal, N = 6 Delayed conduction compatible with myelopathy and diffuse CNS involvement, N = 10	0–3.5 3–7	3, 4, 7, 8, 10, 17 5, 6, 9, 11, 12, 16–19, 23
Magnetic cortical stimulation	4	Normal, N = 1 Conduction delay in motor pathways, N = 3	3.5 3.5–8.0	10 5, 6, 13
Visual evoked potential	7	Normal	3–6	6–8, 12, 13, 16, 23
Sympathetic skin response	15	Normal, N = 9 Decreased in feet, N = 6	0–5.5 3–5	3, 4, 7, 8, 10–13, 16 5, 6, 9, 18, 19, 23

EDSS = Kurtzke Expanded Disability Status Scale; CNS = central nervous system.

peripheral affected white matter (Fig 8C), but they increased during disease progress, resulting in a reverse ADC pattern (Fig 9C), at least partially, in 5 subjects. ADC values were never lower than in normal brain.

No pathological enhancement was noted after contrast medium administration. Starting in the fifth decade, there was progressive loss of white matter leading to widening of ventricles and peripheral CSF spaces. Cortical thickness was relatively well preserved.

SPINAL CORD. All measurements obtained from the spinal cord were significantly (>2 standard deviations) smaller than in the normal population.²⁰ On follow-up examinations, only 3 subjects exhibited a decrease in cross-sectional area or diameter, defined as >8mm² or >1.5mm difference between two measurements. These cut-off points were estimated based on Bland-Altman plots of the variability between two readings. A 1.5-mm cutoff is also consistent with voxel size. We found a

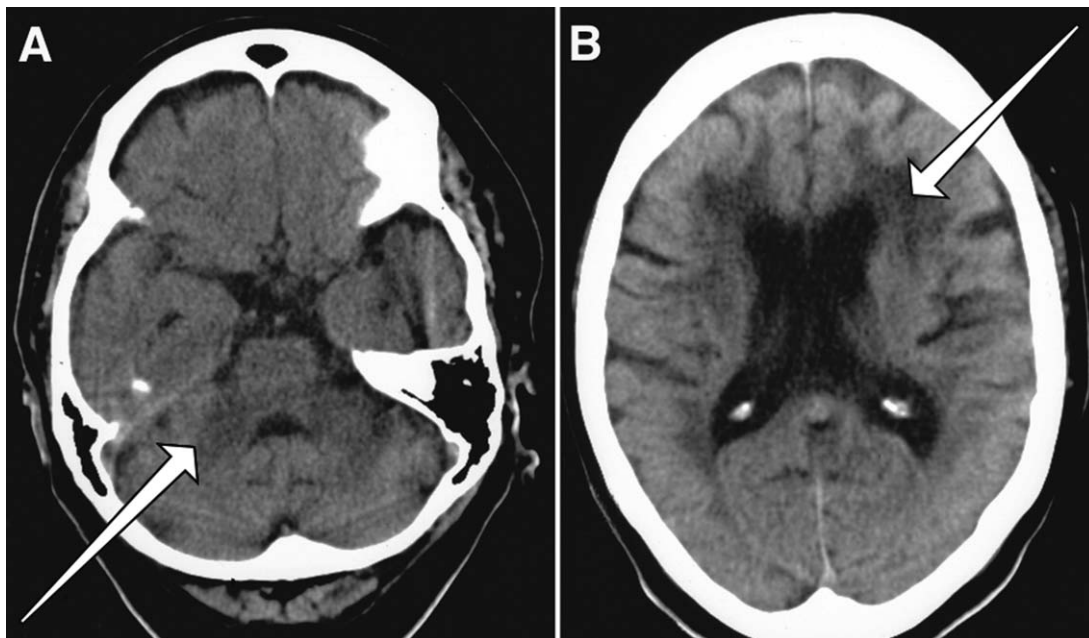


FIGURE 5: Example of computed tomography findings in a 60-year-old patient with hypodense areas in the cerebellar peduncles (A) and cerebral white matter (B). EDSS 7.5. EDSS = Kurtzke Expanded Disability Status Scale.



FIGURE 6: High signal intensity in the pyramids in the medulla oblongata (arrow) is a typical finding, detectable when the entire length of the intracranial pyramidal tract is affected, noted already in grade 1. T2-weighted fluid attenuation inversion recovery image of an asymptomatic 43-year-old man.

strong linear correlation between age and cross-sectional area at the level of the conus ($R^2 = 0.67$) and slight-to-moderate correlations between age and the other measurements obtained from the spinal cord ($R^2 = 0.26$ – 0.40), except for the sagittal diameter at the level of the conus. All subjects, even asymptomatic ones, exhibited abnormal T2 signal in the white matter of the spinal cord. The typical finding, observed even in 1 asymptomatic subject (subject 4), was high white matter signal intensity in the entire spinal cord (Fig 10). Only in 2

subjects was the white matter not totally involved. One of them (subject 3) was asymptomatic when he was examined at ages 34 and 40 years. In the first examination, only lateral parts of the white matter were hyperintense; however, in the second examination, the entire white matter emitted a high T2 signal intensity. The other subject (subject 16 with EDSS 3.5) only underwent one spinal MRI in which anterior and lateral white matter did not appear totally pathological.

Discussion

We present the first clinical and radiological long-term follow-up in subjects with an *LMNBI* gene duplication leading to *LMNBI*-related ADLD. The study comprised 23 individuals, which is extensive considering the rareness of the disease. Importantly, the recruitment of asymptomatic individuals preceding clinical onset made it possible to follow the entire course of the disease.

In line with previous reports, symptoms started in the fifth to sixth decade,^{3,7,9} and in the great majority of patients autonomic symptoms preceded or occurred together with gait problems and dyscoordination.^{2-4,7,9-12,15} In the original family reported by Eldridge et al,² onset was reported from the fourth to fifth decade. Two of our patients reported gait difficulties preceding bladder control problems. To our knowledge, there are only two reports of *LMNBI*-related ADLD that describe motor signs as the first symptoms: in a Serbian family¹⁶ and in a Brazilian patient.¹⁵ In an Italian

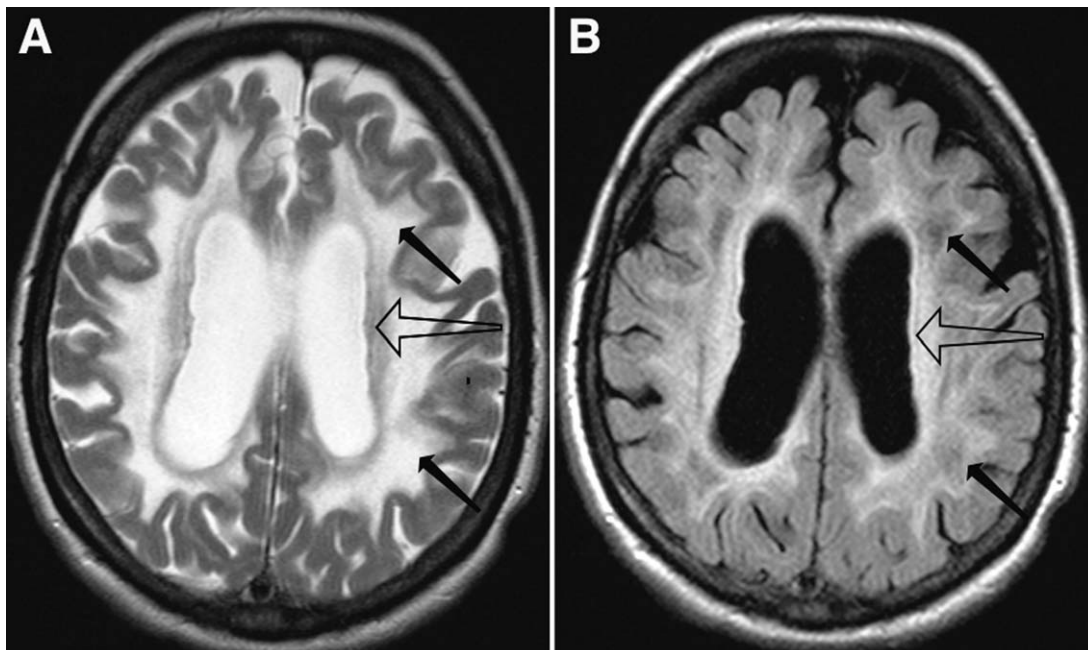


FIGURE 7: Periventricular white matter (open arrows) is typically less hyperintense than more peripheral white matter on T2-weighted spin-echo images (A), but in this severely affected 65-year-old patient (subject 12, EDSS 8.5), this relationship is reversed on T2-weighted fluid attenuation inversion recovery images (B) in which the signal intensity is suppressed in the most severely affected areas (arrows). EDSS = Kurtzke Expanded Disability Status Scale.

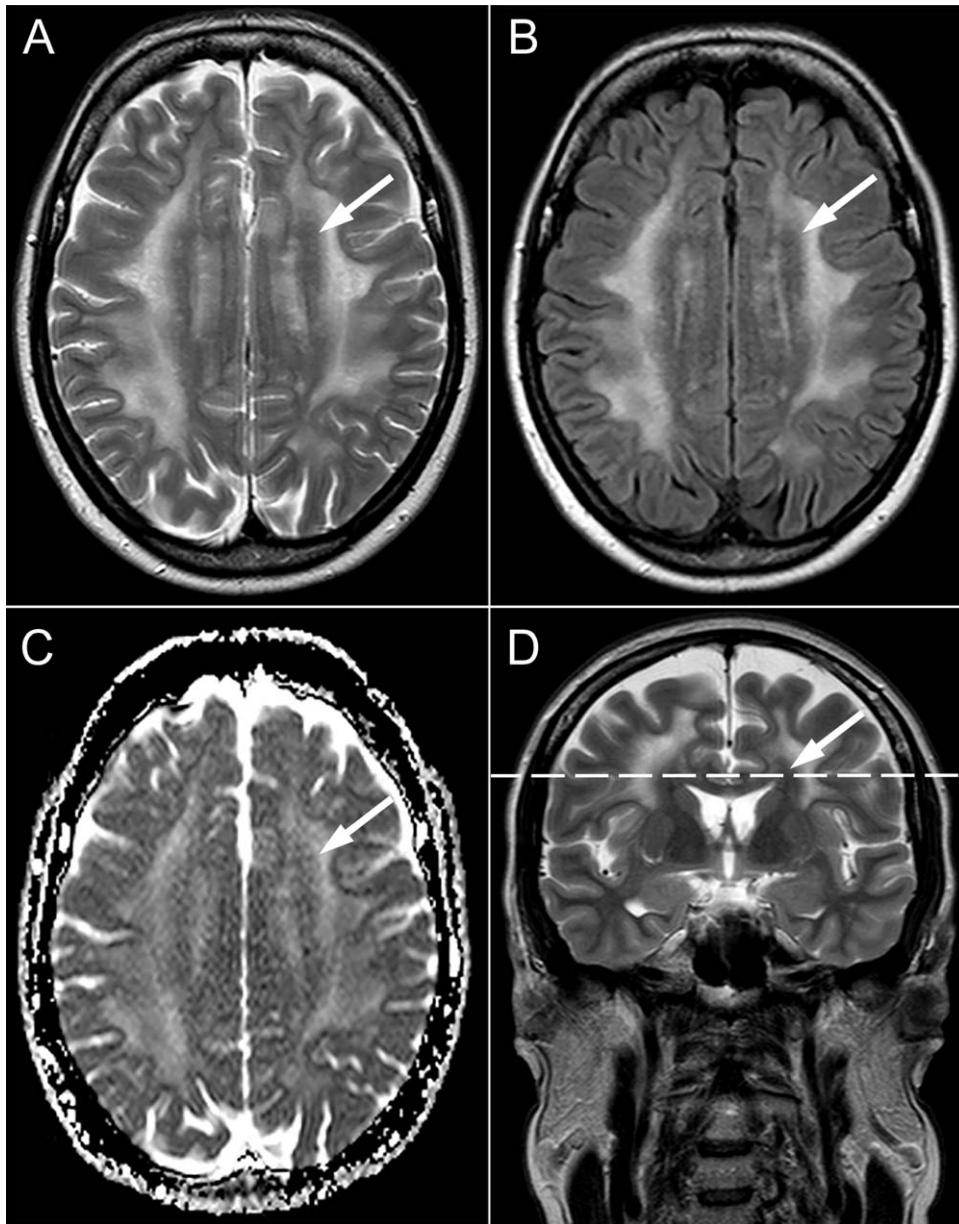


FIGURE 8: Comparison of a T2-weighted spin-echo (SE) image (A), T2-weighted fluid attenuation inversion recovery (FLAIR) image (B), and an (ADC) map (C) in a 46-year-old woman (grade 3, EDSS 1). Slice position just above the lateral ventricles is shown in a coronal T2-weighted SE image (D). Dashed line represents the middle line of the 5-mm-thick slice. Area of pathological signal intensity is the same in the T2-weighted images both with SE and FLAIR sequences. The apparent diffusion coefficient map shows increased diffusion in the same area. Observe nonaffected rims around the lateral ventricles in all images (arrows). EDSS = Kurtzke Expanded Disability Status Scale.

ADLD family, with genetic linkage to chromosome 5q23 and the *LMNB1* locus and increased expression of lamin B1 in lymphoblastoid cells,²³ but without *LMNB1* duplication or point mutation, pyramidal signs were the presenting feature.

We observed that motor deficits progressed in the same order in both families. Initial symptoms and signs of the lower spinal segments were spastic paraplegia developing to tetraplegia and eventual pseudobulbar palsy in the seventh to eighth decade. Tremor, previously reported in *LMNB1*-related ADLD,^{2,7} was present in less

than half of the patients and caused major complaint in 1 patient. We found no signs of polyneuropathy, confirming earlier reports.^{2-5,24} A new observation in this follow-up study is that sensory impairment started in the distal part of the legs and ascended over time to the thoracic level, consistent with myelopathy, and development of flaccid paralysis of the lower limbs.

Pseudoexacerbation in association with exposure to heat, fever, and infections was a frequent complication in patients from both families. This is an important aspect associated with this type of leukodystrophy, previously

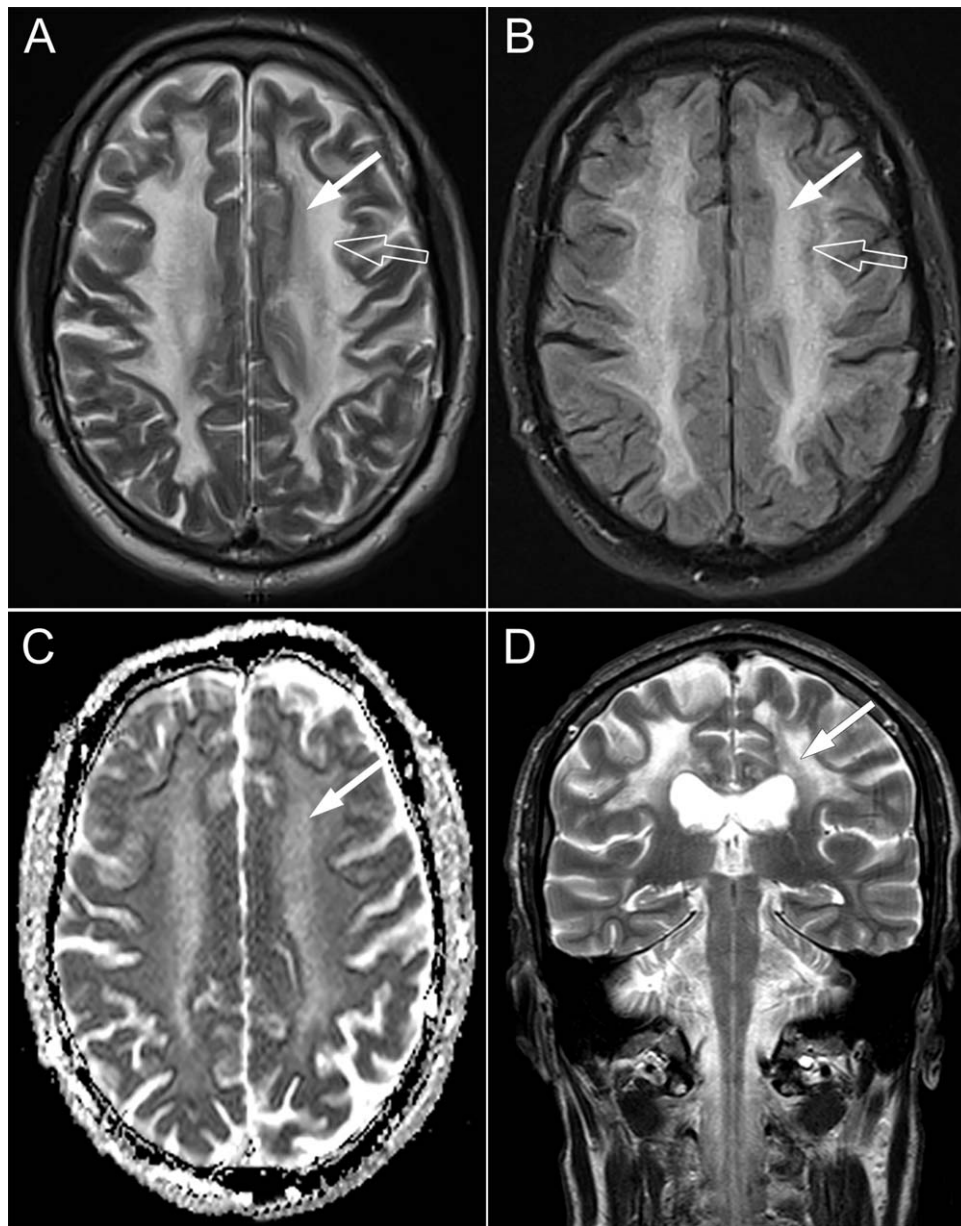


FIGURE 9: Comparison of a T2-weighted spin-echo (SE) image (A), T2-weighted fluid attenuation inversion recovery (FLAIR) image (B), and an apparent diffusion coefficient (ADC) map (C) in a more advanced case: 51-year-old subject 5 (grade 4, EDSS 6.5). Slice position just above the lateral ventricles is shown in a coronal T2-weighted SE image (D). Dashed line represents the middle line of the 5-mm-thick slice. Total area of pathological signal intensity is the same on the T2-weighted images both with SE and FLAIR sequences, but in the areas with the highest signal intensity on the SE image, the signal has been suppressed on the FLAIR image (open arrows). A less-affected periventricular rim is observed on the SE image (white arrow), but on the FLAIR image that rim looks most hyperintense (white arrow). The same area shows high ADC values (white arrow), but in other pathological areas, diffusion is less pathological or even simulates normal: There is a dark line between the affected and normal brain (so called border effect). EDSS = Kurtzke Expanded Disability Status Scale.

mentioned only in 1 German and 1 Swedish patient.⁷ Interestingly, similar pseudoexacerbations are observed in MS, which shares several clinical features with *LMNB1*-related ADLD. Life-threatening hypothermia, previously reported in a Canadian patient having *LMNB1*-related ADLD,⁹ occurred in 1 of our patients.

Detailed neuropsychological testing has not been performed in a larger series of patients with *LMNB1*-

related ADLD. Below-average test results or cognitive deficits have been described in a 47-year-old German patient¹¹ and a 55-year-old Canadian patient,²⁵ respectively. In an Italian family, mild cognitive impairment and dementia were reported.¹⁰ Eldridge's original report concluded that intellectual acuity is often well maintained.² In our study, patients did not complain of cognitive impairment or they only showed mild cognitive

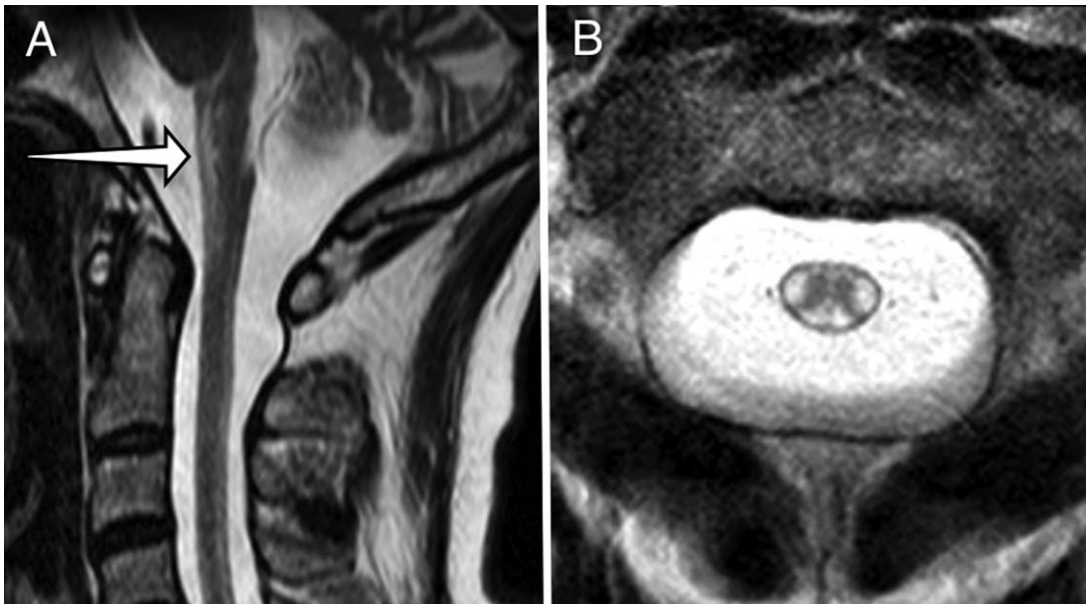


FIGURE 10: T2-weighted spin-echo images of the spinal cord, sagittal (A) and transverse (B) slices of a 63-year-old female (EDSS 3). Pronounced spinal cord atrophy. Increased signal intensity in the whole white matter. In healthy subjects, signal intensity is lower in white matter than in gray matter. Pathological signal intensity in the pyramids in the medulla oblongata is also well observed (arrow). EDSS = Kurtzke Expanded Disability Status Scale.

deficit early in the disease course. However, patients with advanced disease and pseudobulbar palsy usually had dementia.

Median survival time after onset of symptoms was 18 years, which is comparable to earlier reports.^{2,9}

MRI revealed pathological findings in the brain and spinal cord in all subjects and a regular progression of brain changes, in both symptomatic and asymptomatic subjects. In the brain, subjects first present T2 hyperintensities in the white matter underlying the motor cortex. These were present in even our youngest subject (age 29), so we cannot say for certain at what age they can first be observed. T2 hyperintensities progress down through the pyramidal tracts, and these findings can precede symptoms of the disease by up to 16 years. The extent of the changes in some of the asymptomatic subjects is astonishing. Many patients with very large pathological areas manifested relatively mild symptoms. One explanation may be the lack of inflammation and preservation of neurons.³ Proton MR spectroscopy only demonstrated increased water content, compatible with vacuolization of myelin in the lesions,³ but no pathological relationship between the main metabolites.²⁶ Increased ADC values in the white matter, consistent with increased diffusivity, and the drop in signal intensity in some T2-weighted FLAIR images are also in agreement with an increase in free water content. The spinal cord was thin and displayed pathological white matter signal intensity in all 14 imaged subjects. We only found radiological progress in 4 of 9 subjects examined twice, but progress may be difficult to demonstrate in a

very thin spinal cord because of the limited spatial resolution of the MRI. In addition, the area is technically difficult and artifactual signal intensity changes may hamper morphological evaluation.

The involvement of the corticospinal tracts and cerebellum, observed radiologically and pathologically, explains the clinical pyramidal signs and ataxia.³ The cause of autonomic symptoms and signs, such as urinary bladder dysfunction, has been suggested to be a manifestation of frontal lobe disease.²⁴ A distal lesion of sympathetic noradrenergic neurons has also been suggested,²⁷ as well as isolated noradrenergic failure.²⁸ Spinal cord involvement in *LMNB1*-related ADLD has been reported previously.⁵ This follow-up study gives a strong indication that spinal cord involvement is clinically significant in this type of leukodystrophy and may also, at least partly, explain the autonomic dysfunction. Previous histopathological studies have verified involvement of the spinal cord in a patient already at 3 years after onset of symptoms⁵ and more-severe changes in a patient with longer disease duration.²⁴ In our study, clinical assessment, radiological findings, and neurophysiological examinations indicate myelopathy. The most severe case with the most advanced atrophy of the spinal cord had ascending sensory impairment over time, reaching the mid-thoracic level, clearly indicating clinical myelopathy. Signs from the legs, in this case, included flaccid paralysis and weak-to-abolished tendon reflexes, although there were no signs of spasticity. Early autonomic dysfunction, such as disturbed bladder and bowel control as well as

erectile dysfunction, is likely, in part, a result of myelopathy. A similar conclusion has recently been presented in an autosomal-recessive leukodystrophy, adult polyglucosan body disease, where bladder dysfunction is an initial symptom, likely correlating to spinal cord atrophy.²⁹

Differential Diagnosis

A few disorders may resemble the clinical and/or radiological findings observed in *LMNB1*-related ADLD. Patients with adult polyglucosan body disease and bladder dysfunction, spinal cord atrophy, and axonal neuropathy develop cerebral white matter lesions, but these are different from the changes observed in this study.²⁹ Another type of leukodystrophy that may present with autonomic dysfunction, ataxia, and pyramidal signs is autosomal-dominant adult-onset Alexander disease. However, these patients usually have palatal myoclonus and focal enhancing MRI changes in the cerebellum, brain stem, and cervical cord.^{30–34} A clinical presentation with autonomic symptoms including orthostatic hypotension may resemble Shy-Drager syndrome. Furthermore, spastic paraplegia and autonomic dysfunction may suggest a spinal cord compression/lesion. In fact, MRI of the spinal cord was the first radiological investigation performed in 2 of our patients. T2 hyperintensity in the middle cerebellar peduncles is a relatively rare finding, and besides in *LMNB1*-related ADLD, it is characteristic in symptomatic elderly men with a fragile-X premutation.³⁵ Those patients present cognitive decline and ataxia from approximately 60 years of age and a family history consistent with X-linked inheritance. Further differential diagnosis between *LMNB1*-related ADLD and other leukodystrophies and leukoencephalopathies has been presented in articles by Melberg et al³ and Sundblom et al⁵

The MRI findings of the brain in *LMNB1*-related ADLD are highly specific. Patients exhibiting extensive T2 hyperintense areas in the lobar supratentorial white matter with spared or less severely affected periventricular white matter and T2 hyperintensities in the cerebellar peduncles and along the corticospinal tract can be suspected of having the disease, even without clinical information. Together with the clinical history, the imaging findings presented herein and well demonstrated on T2-weighted SE images can be considered as pathognomonic for *LMNB1*-related ADLD. Early MRI changes can be easier to detect on FLAIR images, but advanced cases are more difficult to interpret on them.

In this longitudinal study, we have found MRI to be the method that first reveals abnormalities in subjects affected by *LMNB1*-related ADLD displaying T2 hyperintensities in the brain and the spinal cord white matter long before onset of symptoms. These findings can thus

be considered as early markers of the disease in subjects with the pertinent family history. Given that the radiological changes precede the clinical symptoms, they could, theoretically, be incidental in individuals imaged for other reasons. T2 hyperintensities along the corticospinal tracts are nonspecific, although not very common in the pyramids in other diseases. In *LMNB1*-related ADLD, they are accompanied by early and typical changes in the cerebellar peduncles. The first MRI changes in *LMNB1*-related ADLD restricted to the upper corticospinal tracts may be identical to those in adult-onset Krabbe disease.³⁶ However, at that stage, patients with adult-onset Krabbe disease present with clinical symptoms such as paraparesis, in contrast to patients with *LMNB1*-related ADLD.

We conclude that *LMNB1*-related ADLD is a slowly progressive disease affecting both the brain and the spinal cord. Radiological findings in the brain and spinal cord may precede the clinical symptoms by more than a decade and subjects having radiological abnormalities develop a clinical disease. The early symptoms, including autonomic dysfunction and pyramidal signs, indicate myelopathy. Clinical symptoms of myelopathy with autonomic dysfunction in combination with characteristic radiological findings enable diagnosis of *LMNB1*-related ADLD.

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Authorship

A.M. and R.R. designed the study and acquired the material, A.M. made clinical examinations, R.R. was responsible for radiological examinations, N.D. was responsible of the genetic studies, and J.F. and J.S. participated in data collection and analysis. All authors participated in interpretation of the data and in writing and revising the article and approved the final version of the text. A.M. and R.R. contributed equally in the study.

Potential Conflicts of Interest

Nothing to report.

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