CASE REPORT

Concomitant amyotrophic lateral sclerosis and paraclinical laboratory features of multiple sclerosis: coincidence or causal relationship?

Nadja Borisow,¹ Thomas Meyer,² Friedemann Paul¹

¹NeuroCure Clinical Research Center and Clinical and Experimental Research Center for Multiple Sclerosis, Charité Universitätsmedizin Berlin, Berlin, Germany

²Charité—Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany

Correspondence to

Dr Nadja Borisow,
nadja.borisow@charite.de

SUMMARY

We report a 55-year-old patient, presenting with paresis, muscle atrophy and dysarthria, all symptoms accordable to definite amyotrophic lateral sclerosis (ALS). However, MRI and cerebrospinal fluid show abnormalities typical of multiple sclerosis (MS). On the basis of this case report, we discuss possible overlaps between both diseases by comparing clinical and paraclinical features including laboratory, radiological and electrophysiological diagnostics. As genetic, as well as environmental, factors are assumed to be involved in the development of both the diseases, literature is reviewed according to similar cases, results of autopsies and possible parallels in pathogenesis. In summary, based on the data currently available, the hypothesis of ALS being a neurodegenerative multisystem disorder, a common pathophysiological pathway or, alternatively, a random comorbidity of ALS and MS in this patient has to be discussed.

BACKGROUND

Multiple sclerosis (MS) is a chronic disease of the central nervous system which, in the majority of patients, begins with relapsing episodes of neurological deficiencies. Only 15–20% of the patients contract a primary progressive (PP) MS with a steadily worsening of symptoms from onset.¹ Frequent symptoms are visual and sensory disturbances, coordination and balance impairment, paresis, spasticity or bladder, bowel and sexual dysfunction. Inflammatory demyelinating as well as neuroaxonal degenerative processes are supposed to be involved in pathogenesis and result in cerebral and spinal tissue damage.¹ MS incidence rates in Europe range between 0.5 and 12/100 000 and rise with increasing distance from the equator.²

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease which preferentially affects the motor part of central nerve system in brain and spinal cord. Typical symptoms are muscle weakness, atrophy or spasticity as well as disturbances of speaking or swallowing. TDP-proteinopathy, glutamate-induced excitotoxic processes, disturbances of axonal transport and dysregulation of RNA-processing are assumed mechanisms playing a role in the pathogenesis of ALS.³ Compared to MS, incidence rates of ALS are considerably lower, ranging between 1.1 and 2.8/100 000.^{4–6}

Occurrence of both ALS and MS in the same patient is until now described only six times in literature.^{7–12} Here we present a case of ALS with

paraclinical signs of MS, compare clinical and paraclinical features of both diseases and discuss possible relationships and overlaps between both entities.

CASE PRESENTATION

In May 2011, the 55-year-old male patient first presented to our outpatient clinic. His wife described impaired walking since 2009, at which time the weakness of elevating the right foot occurred could not be determined. Since March 2011, additionally a slowly progressive weakness and a muscle wasting of the right hand became clinically manifest. No accompanying or relevant previous diseases were described by the patient. In his family, no history of neurological disorders was known.

INVESTIGATIONS

Clinical findings

Neurological examination showed a mild central facial paresis, a high-grade paresis of right foot extensor, mild distal accentuated weakness of right arm and atrophy of right hand and foot muscles. Deep tendon reflexes were brisk and more pronounced on the left side except for the Achilles tendon reflex, which could not be elicited on both sides. No deficit of sensation or coordination was present although weakness interfered with the testing of standing and walking. A subsequent examination 2 months later, revealed new findings including a mild pseudobulbar syndrome with dysarthria, but no dysphagia. No fibrillations or atrophy, but a slowed tongue motility was detectable. Moreover, a minimal weight loss due to reduced appetite was apparent.

Laboratory findings

Blood analysis showed slightly elevated creatine kinase and myoglobine, further parameters as blood count, borrelia antibodies and immuno-electrophoresis were unremarkable.

Autoimmunological diagnostic including ANA, c-ANA and p-ANCA were negative, as were tests for celiac disease (antigliadin antibodies, antitransglutaminase antibodies).

Cerebrospinal fluid (CSF) analysis showed 3 leucocytes/ μ l, protein 52.1 mg/dl and lactat 1.5 mmol/l. IgG level was 64 mg/l, IgG index was 0.86 and oligoclonal bands (OCB) were detectable only in CSF.

Radiological features

Brain MRI performed in February 2011 revealed more than 25 T2-hyperintense lesions located

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Figure 1 Muscle atrophy preferentially affecting small hand muscles of right hand and distal muscles of right leg.

juxtacortically, periventricularly and in the area of the optic radiation. A further lesion was found in the dorsal corpus callosum. Spinal MRI showed various degenerative abnormalities, but no signs of myelopathy or inflammatory lesions.

Electrophysiological diagnostic

The electromyography (EMG) later showed pathological spontaneous activity in muscoli-interosseus dorsalis I and muscoli-abductor pollicis brevis in both hands as well as in right M tibialis anterior.

Sensory-evoked tibial nerve potentials revealed a delay of cortical latency, accordable to a disturbance of sensory afferent pathway of the left lower extremity. Somatosensory evoked potential (SSEP) of the median nerve as well as visual-evoked potentials showed normal findings at both sides.

OUTCOME AND FOLLOW-UP

Recent evaluation was performed on 19 April 2012. The patient described a progression of gait disturbance and right-hand paresis. Time to eat a meal was prolonged to 30 min; compared to May 2011 there was a weight loss of 4 kg. Dyspnoea or orthopnoea were negated, vital capacity was constantly 82%. Investigation of the tongue revealed a bradyglossia and newly developed fibrillations. Figure 1 shows the distinct atrophies of the small hand muscles and the right leg in comparison to the left side. A follow-up MRI performed in March 2012 remained

unchanged with evidence of approximately 25 hyperintense T2-lesions (figure 2).

Owing to MRI and laboratory findings our patient was initially diagnosed with PPMS. Taking into consideration the further course and presentation of symptoms, diagnosis was changed to ALS. With evidence of bulbar and pseudobulbar syndrome, peripheral paresis and myotrophies of extremities, as well as decreased deep tendon reflexes, an affection of first and second motor neuron in the bulbar region in combination with a deterioration of lower motor neuron in cervical and lumbar region has to be considered. EMG showed acute denervation in more than two extremities. Thus, by using the El-Escorial-criteria, the diagnosis of clinically probable, laboratory-supported ALS can be made. A medication with riluzole was initiated in June 2011.

On the other hand, with more than 1 year of disease progression, evidence of dissemination in space by MRI and positive CSF, 2010 McDonald criteria¹³ for diagnosing a primary progressive MS are also fulfilled.

DISCUSSION

MRI abnormalities found in our patient exceed substantially the signal alterations usually described in ALS. The most frequently reported MRI findings in ALS are T2-hyperintensity in the internal capsule, T2-hypointense rim in precentral cortex and signal alterations of anterolateral columns of cervical spinal

Figure 2 Brain MRI with evidence of multiple T2 hyperintense lesions and one lesion in dorsal corpus callosum.

cord.^{14 15} However, as sensitivity as well as specificity is low, the European Federation of Neurological Societies (EFNS) does not recommend conventional MRI to verify the diagnosis of motor neuron disease.¹⁵

Detection of OCB in ALS is uncommon. One survey from 1990 showed positive OCB in 14 of 115 ALS patients.¹⁶ In other studies, only sporadically positive OCB were found in ALS patients.^{17 18}

Our patient did not describe any sensory deficits, although SSEP revealed pathological findings. Sensory deficits are no typical feature in ALS, whereas in MS it is one of the most common symptoms. However, in ALS patients, up to 22% report sensory disturbances, especially numbness and neuropathic pain.¹⁹ Furthermore, abnormalities in sensory nerve conduction studies and in biopsies of sensory nerves as well as delayed SSEP were described in ALS patients.^{19–22} Besides sensory disturbances, other extramotor symptoms, for example, cognitive impairment, contribute to the discussion of ALS being a multisystem disorder with focus or first manifestation in motor neurons.

High-grade peripheral paresis and amyotrophy are not supposed to be relevant in MS, as MS is considered to be limited to central nerve system. However, in 6–7% of MS patients, focal muscular atrophy is reported.^{23 24} As electrophysiological diagnostic revealed no signs of peripheral nerve system involvement, atrophies were ascribed to inactivity resulting from diminished use of the affected hand. In contrast, other studies detected satellite potentials²⁵ and signs of denervation on EMG in MS patients.²⁶ Lesions affecting spinal cord in the area of anterior horn cells or ventral root area were considered to be responsible for the observed peripheral paresis and atrophies, although only in some patients MRI signal alterations in lower cervical spinal cord were evident. This hypothesis is supported by an autopsy study which detected significant loss of anterior horn cells in the upper cervical and thoracic spinal cord in MS patients²⁷ and experimental autoimmune encephalomyelitis, the animal model of the disease.²⁸ Further reasons that are discussed in that context are nerve compression syndromes, especially in wheelchair-dependent patients.

Coexistence of ALS and MS is described extremely rarely in literature; its likelihood is estimated to be 3 : 10 billion.⁹ Since 1986, six cases of comorbidity of MS and ALS,^{7–12} four of them with autopsic evidence of as well ALS, as MS-typical features^{7–9 12} have been reported. The evidence of coexistent PPMS and ALS by clinical parameters is sophisticated, as both take a progressive course and symptoms as dysarthria or spastic gait disorders may occur in both contexts. In that case, MS diagnosis relies on pathological findings in MRI and CSF. In the same manner, diagnosis of PPMS in our patient was made, as clinical picture with amyotrophy and peripheral pareses rather indicates an underlying ALS.

An inherited susceptibility to neurodegeneration and axonal degeneration is supposed to underlie both diseases, although in MS, neurodegeneration is mediated by inflammation, whereas in ALS disturbances in RNA processing and axonal transport are assumed. An Iranian study revealed a significantly higher risk for ALS in first degree relatives of MS patients compared to the general population.²⁹ Vice versa, also first degree relatives of ALS patients were at higher risk of developing an MS, so the same genes were assumed to be involved in the pathogenesis of MS as well as ALS.

Our observations may support the idea that most cases of ALS represent a complex disorder in which the phenotype

arises from multiple genes and yet unknown exogenous factors. It is conceivable, though, that inflammatory and degenerative mechanisms related to MS may contribute to a common pathway in MS and motor neuron disease with an initial immune attack and a secondary progressive axonal damage. On the other hand, until now the pathogenesis of PPMS is unclear and prospective studies of similar cases would be needed.

Learning points

- MRI and cerebrospinal fluid with typical features of multiple sclerosis (MS) do not rule out another disease, in this case an amyotrophic lateral sclerosis (ALS).
- Comorbidity of ALS and MS may be due to random coincidence, common pathway in both diseases or genetic and exogenous factors, leading to an increased predisposition for neurodegeneration.
- Attentive physical examination, besides consideration of MRI and laboratory findings, is necessary to exhaust all therapeutic options and permit a realistic prognosis.

Competing interests None.

Patient consent Obtained.

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