LETTER TO THE EDITORS

Sensory neuropathy due to RFC1 in a patient with ALS: more than a coincidence?

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Dear Sirs,

In 2019, non-parametric linkage analyses and genome sequencing revealed that biallelic AAGGG expansions in the replication factor C subunit 1 (RFC1) gene are a frequent cause of late-onset ataxia [1]. Subsequent studies described the phenotypic spectrum of patients with pathological RFC1 expansion: they mainly presented in their fifth decade of life with a triad of cerebellar dysfunction (i.e., gait ataxia, dysarthria, ocular motor disorders), sensory neuropathy with concomitant sensory ataxia, and vestibular areflexia bilaterally, denoted by the acronym CANVAS [1]. Quite recently, a multicentre observational study has shown that RFC1 expansion comprises a multisystemic disease with a chronic dry cough, dysautonomia, and bradykinesia as additional clinical features of variable degree [2].

It is still an outstanding issue, whether biallelic AAGGG expansion in RFC1 are not associated with an even broader phenotypic spectrum of neurodegenerative diseases.

A 64-year-old male presented with a 1-year history of progressive and painless weakness of both hands. Neurological examination revealed generalized polytopic muscle fasciculations in 4/4 levels, muscle paresis for finger adduction/abduction (r: MRC 4–5, l: MRC 4), finger extension (r: MRC 4–5, l: MRC 4), thumb opposition (r: MRC 4–5, l: MRC 4), wrist extension/flexion (r: MRC 4–5, l: MRC 4) and hip flexion (r/l: MRC 4–5). A split hand sign was conspicuous on both sides. Muscle reflexes were brisk on the left upper limb with decreased ankle jerks bilaterally. There were neither relevant sensory/proprionicp e deficits nor clinical signs of ataxia/vestibulopathy. Clinical suspicion of a degenerative motor neuron disease was confirmed by electromyography, muscle ultrasound and transcranial magnetic stimulation (for details see Table 1). Sural and superficial peroneal nerve potentials and sensory evoked potentials of the tibial nerves (P40) were absent bilaterally.

Finally, amyotrophic lateral sclerosis (ALS) was diagnosed according to the current diagnostic criteria (see Table 1). Additionally, regarding sensory nerve conduction studies and evoked potentials subclinical sensory neuropathy/neuronopathy was diagnosed.

Acquired conditions for sensory neuropathies/neuronopathies were excluded (see Table 1). The patient did not consent to a recommended additional CSF analysis.

Genetic analysis by CRISPR/Cas9 target enrichment and Oxford Nanopore long-read sequencing [3], revealed biallelic AAGGG repeat expansions (~400) of the RFC1 locus. Negative results of all genetic testing are listed in Table 1.

Due to the detected biallelic RFC1 repeat expansions we post-hoc performed vestibular testing by inner ear calorics and video-assisted head-impulse-test, which revealed isolated bilateral presbyvestibulopathy in the low-frequency range (see Table 1).

This case with a diagnosis of ALS, additional subclinical sensory neuro(no)pathy and bilateral presbyvestibulopathy in the low-frequency range in association with a biallelic RFC1 expansion raises the following noteworthy future question: is ALS/motor neuron disease within the phenotypic spectrum of biallelic RFC1 repeat expansions?

Florian Schoeberl and Angela Abicht have contributed equally to this work.

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Table 1 An overview of the diagnostic procedures and findings in our patient

| Diagnostic test                          | Result                                                                 | Interpretation |
|------------------------------------------|------------------------------------------------------------------------|----------------|
| Muscle ultrasound                        | Polytropic muscle fasciculations in 4/4 levels                         | Abnormal       |
| EMG                                      | Acute and chronic denervation in 4/4 levels                            | Abnormal       |
| Transcranial magnetic stimulation        | Delayed central motor latency and reduced amplitude to the left abductor pollicis brevis; normal central motor latencies and amplitudes to the right abductor pollicis brevis and both tibial anterior muscles | Abnormal       |
| Neurofilament light chain serum levels (SIMOA) | 82 pg/ml (limit value for ALS: < 45 pg/ml)                          | Increased      |
| Gold Coast criteria (2020)                | Progressive motor impairment, documented by history or repeated clinical assessment, preceded by normal motor function | Fulfilled      |
| Awaji-Shima criteria (2008)               | Upper and lower motor neuron dysfunction in at least one body region or lower motor neuron dysfunction in at least two body regions | Fulfilled      |
| Investigation findings that excluded alternative disease processes | Probable ALS: clinical and electrophysiological signs of lower motor neuron degeneration in at least two regions |              |
| Sensory nerve conduction studies         | Absent potentials of both sural and superficial peroneous nerves; normal potentials of median and ulnar nerves | Abnormal       |
| Motor nerve conduction studies           | Reduced amplitudes of both median and ulnar and left-sided tibial and peroneous nerves; normal potentials of right-sided tibial and peroneous nerves | Abnormal       |
| Sensory evoked potentials                | Absent P40 of both tibial nerves; normal N9 and N20 of both median nerves | Abnormal       |
| Caloric irrigation inner ear (warm/cold water °) | Right: warm − 4.8°, Cold 5.7°  
Left: warm 5.6°, Cold − 7.7°  
Lying in the range of bilateral presbyvestibulopathy (i.e. 6°–25°) | Abnormal       |
| Video-assisted head impulse-test (median gain at 60 ms) | Right: 0.93 ± 0.11  
Left: 0.97 ± 0.06 | Unremarkable  |
| MRI-scan brain (3 T)                     | No pyramidal tract lesion, no brainstem pathology, no cerebellar atrophy, no frontal cortex atrophy | Unremarkable  |
| MRI-scan cervical spine (3 T)            | No spinal cord stenosis, no spinal cord lesions, no nerve root compressions | Unremarkable  |
| MRI-scan brachial plexus (3 T)           | No lesions, no increased contrast-enhancement, no thickened nerve fascicles | Unremarkable  |
| Additional laboratory testings           | Serum glucose, HbA1c-level, liver enzymes, creatinine, vitamin B12 pathway, anti-neuronal antibodies (anti-Hu, -Rh, -Yo, -Ma2, -Tr, Amphiphysin), monoclonal proteins, ganglioside-antibodies (anti-GM1, -GM2, -GD1a, -GD1b, -GQ1b) anti-MAG, antinuclear antibody subtypes (anti-SS-A, -SS-B, -Sm, -RNP, -Scl-70, -PmScl, -Jo1), anti-neutrophilic cytoplasmic antibodies, ganglionic acetylcholine receptor antibodies | Unremarkable  |
To our knowledge, this is the first case of an ALS patient with a concomitant subclinical sensory neuro(no)pathy and bilateral presbyvestibulopathy carrying a biallelic RFC1 repeat expansion. The number of genes associated with monogenic forms or increased risk of ALS is constantly growing including intermediate expansions of the SCA 1,2 genes and huntingtin-trinucleotide expansions [4, 5]. Acknowledging previous reports with abnormal findings in sensory nerve conduction studies in up to 20% of patients with ALS [6] and earlier morphological findings in sensory nerve biopsies suggesting loss of sensory root ganglion neurons [7], an involvement of pathological RFC1 expansions as additional monogenic form or at least genetic risk factor for ALS might be discussed. However, one must admit, that we cannot differentiate an association of pathological RFC1 expansions with a combined phenotype of ALS and sensory neuro(no)pathy in our patient from a bare coincidence of ALS with a beginning CANVAS phenotype due to RFC1 pathology. A recent study revealed that pathogenic SPTLC1 mutations are not only associated with the phenotype of sensory and autonomic neuropathy (i.e. HSAN type 1), but also with juvenile onset ALS [9]. And, for the rare syndrome of “facial onset sensory motor neuronopathy” (FOSMN) typically beginning with sensory symptoms of the trigeminal nerves, underlying TDP-43 pathology in sensory ganglion cells as well as motor neurons was confirmed [10–12], thus classifying FOSMN currently as a rare form of motor neuron disease.

An important limitation of the presented case is, that we cannot assess the influence of rare genetic variants with small effect size or their combinatory effect in terms of polygenic risk modification.

In conclusion, the presented case with a concomitant sensory neuro(no)pathy and proven RFC1 expansion in addition to ALS should prompt a more systematical search for RFC1 expansion in larger patient cohorts with ALS and unexplained sensory involvement in order to disentangle a possible role of RFC1 pathology in ALS.

### Table 1 (continued)

| Diagnostic test | Result |
|-----------------|--------|
| Genetic testings | biallelic AAGGG repeat expansions (~400) of the RFC1 locus |
| NGs-based gene panel testing (ANXA11, CHCHD10, EPHA4, FUS, HRNPA1, KIF5A, NEK1, OPTN, PFN1, SOD1, TARDBP, TBK1, UBQLN2, UNC13A, VAPB, VCP) did not reveal variants of unknown significance, pathogenic or likely pathogenic variants (ACMG class 3, 4 or 5) |
| Testing for repeat expansions in C9orf72 (FTD/ALS), ATXN1 (SCA1), ATXN2 (SCA2), ATXN3 (SCA3), and HTT (Huntington Disease) did not reveal any expansion in the pathological or intermediate range: |
| C9orf72 (repeat units allele 1/2): 8/8 |
| ATXN1 (repeat units allele 1/2): 28/29 |
| ATXN2 (repeat units allele 1/2): 22/22 |
| ATXN3 (repeat units allele 1/2): 14/30 |
| HTT (repeat units allele 1/2): 21/27 |

### Author contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by FS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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### Declarations

#### Conflicts of interest

Dr. Schöberl reports no disclosures; Dr. Abicht reports no disclosures; Dr. Kuepper reports no disclosures; Dr. Voeilk reports no disclosures; Dr. Sonnenfeld reports no disclosures; Dr. Tonon reports no disclosures; Ms Schaub reports no disclosures; Ms Scholz reports no disclosures; Dr. Kleinle reports no disclosures; Dr. Wolf reports no disclosures; Dr. Erdmann reports no disclosures; Dr. Reilich reports no disclosures.

#### Ethical approval

We have obtained the patient’s permission and informed consent for publishing of his information/case.
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