Juvenile-onset Sporadic Amyotrophic Lateral Sclerosis with a Frameshift FUS Gene Mutation Presenting Unique Neuroradiological Findings and Cognitive Impairment

Kimitoshi Hirayanagi, Masayuki Sato, Natsumi Furuta, Kouki Makioka and Yoshio Ikeda

Abstract

A 24-year-old Japanese woman developed anterocollis, weakness of the proximal arms, and subsequent cognitive impairment. A neurological examination revealed amyotrophic lateral sclerosis (ALS) without a family history. Systemic muscle atrophy progressed rapidly. Cerebral MRI clearly exhibited high signal intensities along the bilateral pyramidal tracts. An analysis of the FUS gene revealed a heterozygous two-base pair deletion, c.1507-1508delAG (p.G504WfsX515). A subset of juvenile-onset familial/sporadic ALS cases with FUS gene mutations reportedly demonstrates mental retardation or learning difficulty. Our study emphasizes the importance of conducting a FUS gene analysis in juvenile-onset ALS cases, even when no family occurrence is confirmed.

Key words: juvenile-onset ALS, sporadic ALS, FUS gene mutation, MRI, cognitive impairment, FTLD

Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by progressive muscle weakness and atrophy (1). Approximately 5% of all ALS cases are familial, and the remaining 95% are sporadic (2). Very rare cases manifest initial symptoms before 25 years of age and are defined as juvenile-onset ALS (3); juvenile-onset ALS is more frequently thought to have a genetic origin compared with adult-onset forms (4). Mutations in several genes responsible for familial ALS (FALS) are known to cause juvenile-onset ALS, and these mutations can also be found in sporadic ALS (SALS) cases (5). In particular, several fused in sarcoma/translated in liposarcoma (FUS) gene mutations have been identified in juvenile-onset SALS cases that exhibited an unusual rapid progression with short disease duration (6). We herein report a case of juvenile-onset SALS with a frameshift FUS gene mutation presenting unique neuroradiological findings and cognitive impairment. A subset of juvenile-onset FALS/SALS cases of FUS gene mutations has been reported to have mental retardation or learning difficulty (6-11). The present case further supports the association between FUS gene mutations and this particular phenotype.

Case Report

A 24-year-old Japanese woman was admitted to our hospital in October 2013. Approximately 5 months before admission, she started to complain of anterocollis and weakness in her proximal arms. She had no family history of neurological diseases, and no consanguinity was found in her parents’ history. On admission, her neurological examination revealed severe weakness in her neck and proximal arm muscles. Tongue atrophy and fasciculation were not obvious at this point. Tendon reflexes were generally hyperactive in all limbs. Needle electromyography (EMG) did not show denervation potentials or other neurogenic findings. Cerebral MRI showed high signal intensities along the bilateral pyramidal tracts on both T2-weighted (T2WI) and fluid attenuated inversion recovery (FLAIR) images. The Mini-Mental State Examination score was 25, the Montreal Cognitive Assessment score was 22, and the Frontal Assessment...
Battery score was 14. The Wechsler Adult Intelligence Scale (third edition) demonstrated a verbal intelligence quotient (IQ) of 55, performance IQ of 57, and full scale IQ of 52 (Table). Although she dropped out of high school, she was socialized and had a part-time job. After the onset of muscle weakness, she became apathetic and showed obvious signs of cognitive decline.

After the first admission, her motor impairment and systemic muscle atrophy rapidly worsened. In December 2013, dysarthria and dysphagia became apparent, and she was confined to a wheelchair because of lower limb weakness. At the time of her second admission in January 2014, she showed obvious tongue atrophy and fasciculation and was almost unable to wiggle and protrude her tongue beyond the front teeth. She also showed progressive muscle atrophy with occasional fasciculation in all limbs. Her second needle EMG showed denervation potentials and neurogenic motor unit potentials in all limbs. In cerebral MRI, high signal intensities along the bilateral pyramidal tracts on T2WI/FLAIR images had increased compared with the first MRI analysis (Fig. 1A, B, F). Furthermore, high signal intensities along the pyramidal tracts on diffusion-weighted imaging (DWI) became more evident (Fig. 1D, E). Cerebral MRI also revealed mild frontal lobe atrophy (Fig. 1C). Single photon emission computed tomography (SPECT) with the easy Z-score Imaging System using 99mTc-ethyl cysteinate dimer (ECD) showed hypoperfusion in the bilateral frontal lobe areas (Fig. 1G) (12). Skeletal muscle CTs performed in the 4-month interval revealed rapid progression of systemic muscle atrophy (Fig. 1H, I). According to the patient’s progressive clinical course and results of the second needle EMG, we diagnosed her with clinically defined ALS. Although she had no family history of ALS (Fig. 1J), we suspected that her disease might be caused by an FUS gene mutation because the age of onset was uncharacteristically young and she showed very rapid progression after onset.

After obtaining written informed consent, genomic DNA was extracted from the patient’s peripheral blood leukocytes. All exons and their respective flanking intronic regions of the FUS gene were amplified by polymerase chain reaction (PCR), and the PCR fragments were analyzed by direct DNA sequencing. An analysis of the FUS gene revealed a heterozygous two-base pair deletion in exon 14 (c.1507-1508delAG), thus resulting in a frameshift after codon 504 and a truncation by premature termination at codon 515 (p.G504WfsX515) (Fig. 2).

Discussion

To date, more than 20 causative genes have been identified in FALS (5). In the European population, a hexanucleotide GGGGCC repeat expansion in the C9orf72 gene is the most common type of mutation (13). On the other hand, mutation of the FUS gene is relatively common in FALS cases from East Asian countries, including Japan (6, 14). Juvenile-onset ALS is a rare condition with familial or sometimes sporadic occurrence (6), and juvenile-onset SALS is typically caused by incomplete penetrance or a de novo occurrence of FALS gene mutations.

We herein presented a case of juvenile-onset SALS caused by a mutation (p.G504WfsX515) in the FUS gene. This mutation has been previously confirmed in three reports outside of Japan, and two of them were genetically confirmed as the result of a de novo mutation (Table) (6, 15, 16). Although a genetic analysis of the proband’s parents was not performed in the present study, the

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**Table. Comparisons of Clinical Findings among ALS Cases with a p.G504WfsX515 FUS Gene Mutation.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Present case</th>
<th>Ref. (6)</th>
<th>Ref. (15)</th>
<th>Ref. (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>female</td>
<td>female</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td>24 yo</td>
<td>18 yo</td>
<td>33 yo</td>
<td>31 yo</td>
<td></td>
</tr>
<tr>
<td>Site of onset</td>
<td>Neck (anterocollis) and proximal arms</td>
<td>Right arm</td>
<td>Left hand</td>
<td>Right forearm</td>
</tr>
<tr>
<td>Family history</td>
<td>SALS</td>
<td>SALS, de novo</td>
<td>FALS</td>
<td>SALS, de novo</td>
</tr>
<tr>
<td>Fasciculation</td>
<td>Rare</td>
<td>Common</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Hyperactive</td>
<td>Hyperactive</td>
<td>Absent</td>
<td>NA</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>~/-</td>
<td>+/-</td>
<td>~/-</td>
<td>NA</td>
</tr>
<tr>
<td>Others</td>
<td>Cognitive impairment</td>
<td>Learning difficulties</td>
<td>Normal cognitive function</td>
<td>No cognitive and/or behavioral impairment</td>
</tr>
<tr>
<td>Cognitive examinations</td>
<td>MMSE</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>MoCA</td>
<td>22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FAB</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>WAIS-III VIQ</td>
<td>55</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PIQ</td>
<td>57</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FTQ</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Typically, most juvenile-onset SALS cases associated with the FUS gene mutations exhibit a rapid progression, with short disease duration, to death or tracheotomy (6). The present case also showed a rapid progression of systemic muscle atrophy (Fig. 1H, I) and required tracheotomy at 8 months after onset.

The present case initially developed weakness of the proximal muscles in the neck and arms. A similar phenotype was previously reported in some cases (11, 21-24), and Ticozzi et al. suggested that a certain FUS gene mutation may be associated with a specific clinical phenotype (21). The present case also showed a characteristic nonmotor symptom of cognitive impairment. Cases of ALS with a mutation in the FUS gene are rarely associated with cognitive impairment, including frontotemporal lobar degeneration (FTLD) (5). Similarly, a subset of juvenile-onset FALS/ SALS cases with a mutation in the FUS gene reportedly has mental retardation or learning difficulty (6-11). In addition, juvenile-onset ALS with mental retardation or cognitive impairment is frequently associated with frameshift mutations in the FUS gene (6).

The present case also exhibited characteristic MRI find-
cases of juvenile-onset SALS due to an FTLD and ALS phenotypes (30). To date, four autopsy type that typically shows juvenile onset and can present both philic inclusion body disease (BIBD) (29). BIBD is a sub-
disease, atypical FTLD with ubiquitin inclusions and baso-
into three subtypes: neuronal intermediate filament inclusion (28). FTLD-FUS is further classified
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P lobe degeneration.

cognitive impairment may have been derived from frontal
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frontal lobe areas according to the Tc-ECD SPECT analy-
sis. These findings support the hypothesis that the patient’s
cognitive impairment may have been derived from frontal
lobe degeneration.

Neuropathologically, FTLD is classified into four sub-
types: FTLD-tau, FTLD-TDP, FTLD-FUS, and FTLD-UPS, according to the characteristic misfolded proteins within the respective inclusions (28). FTLD-FUS is further classified into three subtypes: neuronal intermediate filament inclusion disease, atypical FTLD with ubiquitin inclusions and baso-
phlic inclusion body disease (BIBD) (29). BIBD is a sub-
type that typically shows juvenile onset and can present both FTLD and ALS phenotypes (30). To date, four autopsy cases of juvenile-onset SALS due to an FUS gene mutation have been reported, and all were confirmed to have the BIBD pathology (10, 11). These four autopsy cases had some clinical similarities to the present case with regard to juvenile onset (13 to 22 years) and rapid progression (died within 6 to 20 months after onset) (10, 11). More interestingly, one of the four BIBD cases with a frameshift FUS gene mutation (c.1554_1557delACAG) had learning difficulty (10). From these clinical and genetic similarities, we speculate that the present case also had the BIBD pathology.

The present case suggests that a FUS gene analysis should be considered in juvenile-onset ALS cases, even if there is no familial occurrence. To clarify the association between FUS gene mutations and cognitive impairment, further studies on the molecular mechanism underlying FUS proteinopathy leading to FTLD are warranted.

The authors state that they have no Conflict of Interest (COI).

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References

5. Chen S, Sayana P, Zhang X, Le W. Genetics of amyotrophic lat-

Figure 2. Genetic analysis. Results of the FUS gene analysis. The forward and reverse DNA sequence chromatograms showed a heterozygous two-base pair deletion in exon 14 (boxed in the wild-type sequence), resulting in a frameshift after codon 504 and a truncation by premature termination at codon 515 (p.G504WfsX515).

ings of bilateral high signal intensities on T2WI/FLAIR/ DWI images, which may correspond to the degeneration of the upper motor neuron (UMN)/corticospinal tracts (Fig. 1A, B, D, E, F). The high signal intensities along the corticospinal tracts on T2WI and FLAIR images were previously reported in ALS cases (25). However, to the best of our knowledge, high signal intensities on DWI images observed in the present case (Fig. 1D, E) have not been reported previously. The high signal intensities of the corticospinal tracts on DWI images were occasionally observed in the early stage of cerebral infarction as an expression of Wallerian degeneration (26). Therefore, we speculate that the high signal intensities of the corticospinal tracts on the DWI image in the present case reflect a rapid degeneration of the UMN and the corticospinal tracts, which is not a common finding in ALS cases with an FUS gene mutation.

No specific findings, including abnormal signal intensities of the corticospinal tracts, have been reported on cerebral MRI of ALS cases with an FUS gene mutation (8, 24, 27). The present case also exhibited mild frontal lobe atrophy on MRI, as well as reduced cerebral blood flow in the bilateral frontal lobe areas according to the Tc-ECD SPECT analysis. These findings support the hypothesis that the patient’s cognitive impairment may have been derived from frontal lobe degeneration.

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