Amyotrophy in Prion Diseases

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Amyotrophic lateral sclerosis was once thought to be caused by persistent viral infection, partly because some patients with transmissible Creutzfeldt-Jakob disease showed prominent amyotrophy. However, in the past 15 years there has been little interest in the amyotrophy in prion diseases, and the possible link to amyotrophic lateral sclerosis has been eschewed. We analyzed case reports of prion disease published after 1968 for evidence of amyotrophy. We defined amyotrophy as clinically evident fasciculation buttressed by electromyographic results in some cases. We sought evidence of motor neuron degeneration at autopsy. Prion disease was proved by transmissibility, immunohistochemistry demonstration of protease-resistant prion protein, or finding a mutation in the prion protein gene. Amyotrophy was noted in 27 patients: 13 with sporadic Creutzfeldt-Jakob disease, 2 with familial Creutzfeldt-Jakob disease, and 12 with Gerstmann-Sträussler-Scheinker disease. Of the 27, 23 showed clinical fasciculation and 10 had electromyographic evidence of denervation. The spinal cord was examined in 8 patients: 6 showed loss of motor neurons, 1 showed vacuolation of motor neurons, and 1 reported no abnormalities. Another 23 patients had typical histopathological characteristics but lacked molecular or biochemical proof of prion disease. The total number of patients with amyotrophy and proven prion disease that we identified was 50. This case review supports the belief that amyotrophy is occasionally a prominent feature of Creutzfeldt-Jakob disease and underscores the importance of documenting lower motor neuron function and the crucial role of examining the spinal cord at autopsy in cases of prion disease.

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We encountered a mother with amyotrophic lateral sclerosis (ALS) and her daughter with growth hormone–induced Creutzfeldt-Jakob disease (CJD) and prominent amyotrophy.1 The dual occurrence of these diseases could have been due to chance or shared genetic susceptibility, and this experience prompted us to review the literature on amyotrophy in prion diseases. Prior to the era of the prion,2 the transmission of CJD to primates was taken as evidence of a possible viral cause of CJD. Also, persistent viral infection was once a favored etiologic theory for ALS. Amyotrophy was so prominent in some cases of CJD that the category of amyotrophic CJD was proposed. This concept has disappeared from the literature.

Nevertheless, there are few clues to the nature of motor neuron degeneration in different diseases. There is no need to invoke a separate category of amyotrophic CJD, only to determine that amyotrophy is seen in prion diseases. For investigators of ALS, it is as important to know that prion disease may cause amyotrophy as it is to recognize the pathological characteristics of the lower motor neuron in poliomyelitis, hexosaminidase deficiency, or human T-lymphotropic virus, type 1, myelopathy.

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BACKGROUND

Amyotrophy in Prion Diseases

In 1968, Kirschbaum, a neuropathologist, reviewed the literature. He noted that “amyotrophies associated with pyramidal tract disease denote the Jakob type of the syndrome and resemble amyotrophic lateral sclerosis but only in part, for the pronounced disturbances of other neurological systems outweigh this diagnosis.” He recognized that amyotrophy occurred in CJD, but the characteristic cerebral manifestations left no doubt about the diagnosis. In 1971, Allen et al introduced the term amyotrophic form of CJD. However, Richardson and Masters, in tracing the history of the disease, concluded that only 1 of Jakob’s 5 cases was likely to have had what today would be recognized as a prion disease. Brown wrote: “As late as 1968, three major overlapping reviews of CJD were still heavily contaminated with diseases other than spongiform encephalopathy.” One of those reviews was by Kirschbaum.

These critics (Brown and Richardson and Masters) noted that neither Creutzfeldt nor Jakob recognized the importance of spongiform degeneration, which has been regarded as diagnostic since 1968 when Gibbs et al demonstrated the transmissibility of CJD. Since then, there has been a consistent correlation between transmissibility and spongiform histopathological changes.

Brown rejected the concept of an amyotrophic form of CJD:

First, the manifestations of lower motor neuron involvement can vary from late-appearing minimal muscular atrophy, through significant atrophy and fasciculations during the course of the illness, to prominent lower motor neuron signs at the outset. Thus, there is no clear-cut clinical basis on which to separate an ‘amyotrophic’ form of CJD.

Second, analysis of all cases with lower motor neuron signs referred to the NIH [National Institutes of Health] for attempted transmission, irrespective of etiological diagnosis, has revealed [only 3 such patients] . . . [The third case] had perhaps the most prominent display of lower motor neuron disease of any patient in the series.

Thus, although there is no question that motor neuron manifestations can be a component of transmissible CJD, they are neither sharply enough defined nor common enough to merit a separate category of disease, any more than acute stroke-like onsets, Wernicke-Korsakoff syndrome, parkinsonism, or, for that matter, any other clinical feature, including the so-called amaurotic Heidenhain variant, which has drawn special notice because of its comparative prominence.

Richardson and Masters concurred, stating: “Abundant subsequent experience shows that CJD does not affect the motor neurons of the spinal cord except occasionally as a terminal phenomenon.” Then, in 1983, Salazar et al concluded that the syndrome of ALS-dementia was not transmissible; since then, there has been little interest in amyotrophy associated with prion disease. Creutzfeldt-Jakob disease was not mentioned in a 1991 review of a decade of ALS research.

Epidemiology of Amyotrophy in Prion Disease

About 10% of patients with clinically diagnosed CJD show amyotrophy, and 50% show upper motor neuron signs. In Finland, fasciculation was seen in sporadic but not familial CJD. In Japan, 44% of patients with clinically diagnosed CJD had muscular atrophy and pyramidal signs were registered in 88%. Among patients with pathologically confirmed cases, the frequency of lower motor neuron signs (including fasciculation) was 11%, 12%, 13% or 38% and the frequencies of pyramidal signs were seen in 43% and 44% of cases. However, Masters and Richardson found no clinical or pathological lower motor neuron signs in 21 patients with CJD.

ALS and Prion Diseases

There is no evidence that ALS itself is a prion disease. Brown et al failed to transmit ALS to primates with samples from 59 patients. Fraser et al17 failed to transmit ALS from 1 patient to 4 strains of inbred mice. Mice are generally resistant to human prions, and the authors did not test susceptibility of these mice to CJD, therefore limiting the interpretation of their results. Additionally, postmortem studies of ALS-dementia showed diverse forms of change but not the spongiform degeneration of prion diseases.18 Five cases of frontotemporal dementia with motor neuron disease showed no immunological evidence of protease-resistant prion protein (PrP).

DIAGNOSTIC CRITERIA

Prion Disease

In selecting cases from the literature, we followed strict criteria modified from those proposed by Budka et al. Although transmissibility is adequate proof of prion disease, it is no longer the diagnostic norm because it is too slow and expensive. Instead, a diagnosis is commonly made by demonstrating protease-resistant PrP by immunohistochemistry or Western blot analysis or by finding a mutation in the prion protein gene (PRNP) in patients with clinically appropriate symptoms. Those cases meeting the strict criteria are discussed in detail. We also identified other cases diagnosed solely by a typical clinical picture with characteristic pathological spongiform findings.

The clinical diagnosis of typical CJD is now reasonably accurate, especially if the characteristic periodic activity is seen in the electroencephalogram.22 Clinical diagnosis may be aided by testing for 14-3-3 protein marker in the cerebrospinal fluid. Histopathological findings can be diagnostic. Brown et al noted that spongiform change correlated with at least 1 other test in 95% of cases, whereas transmissibility or protease-resistant PrP correlated with 1 other test in 86%. Among successfully transmitted cases, 33 (100%) showed spongiform change and 29 (88%) had detectable protease-resistant PrP. Spongiform degeneration can be seen in the anterior horn cells (AHCs). However, carriers of a PRNP mutation or individuals with atypical clinical disorder may lack characteristic spongiform changes. Even if there is neither spongiform change nor PRNP mutation, protease-
Amyotrophy in Prion Disease

In reviewing case reports, we deduced the presence of amyotrophy if fasciculations were clinically evident or if there was electromyographic (EMG) evidence of denervation. Visible fasciculations usually imply disease of the perikaryon; exceptionally, fasciculation can also arise in peripheral neuropathies, especially motor neuropathy with conduction block. In those cases, both the perikaryon and peripheral nerves may be affected simultaneously.\textsuperscript{29} Therefore, it is important to note findings in the spinal cord in autopsy reports of prion diseases, a practice that seems to have disappeared. The term spinal cord is not mentioned in descriptions of the neuropathological features of prion diseases.\textsuperscript{3,30-32} Nevertheless, spinal cord samples have transmitted CJD,\textsuperscript{10} and prion-resistant PrP has been demonstrated in the spinal cord using immunohistory in iatrogenic,\textsuperscript{23} sporadic,\textsuperscript{34} and familial\textsuperscript{35} prion disease.

**AMYOTROPY IN PROVEN PRION DISEASE**

**Sporadic CJD**

Salazar et al\textsuperscript{8} attempted transmission experiments in 33 patients with dementia with prominent lower motor neuron signs; transmission was successful in 3 but was dismissed by later authorities. In 2 patients, the clinical features were considered clinically atypical, and in 1, the incubation time for transmission experiments was prolonged. Autopsies were performed in both patients with atypical findings, but the pathological descriptions of the spinal cord were not recorded.

In the first patient, the findings were “atypical” because of a family history of Charcot-Marie-Tooth disease, but the patient was neurologically asymptomatic for almost 66 years and, in the authors’ words, had “a forme fruste.” Unequivocal lower motor neuron signs, including atrophy and fasciculations, appeared only when he developed manifestations of CJD that were fatal 6 months after onset. This case could be considered proven CJD with amyotrophy.

The second patient with atypical disease showed glove-stocking sensory loss attributed to a sensorimotor neuropathy. However, “widespread fasciculation” was prominent in a disease that lasted only 6 months. Nerve conduction study results were normal, with EMG evidence of extensive denervation. It is reasonable to include this case as an example of amyotrophy in proven CJD.

The third patient had typical CJD, as well as clinical and pathological findings of ALS.\textsuperscript{9} In 1983, this case was one of the nontransmitting cases of Salazar et al.\textsuperscript{8} However, in 1988, Connolly et al\textsuperscript{40} wrote that the squirrel monkey that received the transmission died 13 years after inoculation, and the brain showed signs of prion disease. Brown\textsuperscript{40} later confirmed the transmission and included this case in a graph of incubation periods in 300 transmitted cases.\textsuperscript{16}

Roos et al\textsuperscript{37} reported on 2 patients with sporadic CJD with lower motor neuron signs in the body of their article and 3 additional patients in the addendum. Traub et al\textsuperscript{41} published a follow-up series that contained these patients and 5 additional patients. All the patients had characteristic histopathological findings, and homogenates of brain tissue from each patient were transmitted to primates.\textsuperscript{14,37} One patient had prominent fasciculations; she had status spongiosis of the cortex and basal ganglia, but the findings from examination of her spinal cord were histologically normal. The second patient had fasciculations in the legs with pathologically brisk reflexes and spasticity. The autopsy results confirmed prion disease with widespread spongiosis. The AHCs were “shrunk” in the cervical cord. A third patient had amyotrophy, loss of AHCs, and evidence of denervated muscles at autopsy. A fourth patient had diffuse fasciculations and loss of AHCs with astrocytosis. The remaining 6 patients with amyotrophy did not have reported pathological findings from the examination of the spinal cord at autopsy, and some had EMG evidence of denervation. Both articles\textsuperscript{14,37} also mention the man described as patient #7 by Salazar et al,\textsuperscript{8} and Roos et al\textsuperscript{37} also describe patient 1 from Salazar et al.\textsuperscript{8} Including these cases, the total number of reported proven sporadic cases with amyotrophy is 13.

In describing the largest series of transmissible CJD, Brown et al\textsuperscript{16} noted: “In 6 patients, significant lower motor neuron signs were present at initial examination; in 2 of them lower motor neuron signs (amyotrophy) were the first abnormalities to occur, and they remained prominent throughout the clinical course.” The transmissible cases with amyotrophy mentioned by Brown et al include many of those in the series by Salazar et al,\textsuperscript{8} Roos et al,\textsuperscript{37} and Traub et al.\textsuperscript{14} Individual clinical data, EMG results, and postmortem descriptions of motor neurons were not reported, so we cannot distinguish any new cases from those described previously. Therefore, these cases are not counted in the Table or in the total number.

**Familial Prion Disease**

Eleven members of 4 families with Gerstmann-Sträussler-Scheinker (GSS) disease demonstrated amyotrophy. In 1 family,\textsuperscript{38} lower motor neuron signs were not emphasized in the body of the first article but were mentioned in case reports in the appendix. Signs of denervation in the results of EMG and muscle biopsy were subsequently documented.\textsuperscript{24,39-42} “Tissue from 3 family members transmitted the disease,”\textsuperscript{14,41,42} and a mutation was found in codon 102 of PRNP.\textsuperscript{39} In a second family with the codon 102 mutation,\textsuperscript{39} 2 members had prominent lower motor neuron signs. In a third family with genetically determined prion disease,\textsuperscript{44} 3 members showed fasciculations and atrophy. The mutation affected codon 117 of PRNP.\textsuperscript{45} The fourth family\textsuperscript{46} also had a mutation of codon 102, and 1 affected person showed prominent amyotrophy.

Three additional familial cases were proved by transmission. Roos et al\textsuperscript{37} reported in the addendum a familial case “with signs of lower motor neuron involvement . . . and status spongiosus” that was transmitted after their ar-
ticle was submitted. Traub et al\textsuperscript{14} described 2 familial cases with evidence of definite amyotrophy and cortical vacuolation at autopsy, although 1 was a member of a family with GSS discussed above.\textsuperscript{38,40} Boudouresques et al\textsuperscript{15} had described a man with GSS who had fasciculations, prominent weakness, EMG-documented denervation, and rarification of the AHCs at autopsy. Homogenates from his brain tissue were injected into primates.\textsuperscript{15} Traub et al\textsuperscript{14} reported the experiments as successful transmission. Including these cases, we found a total of 14 cases of proven familial prion disease with amyotrophy.

Amyotrophy and Prion Disease
Proved Histopathologically

Roos et al\textsuperscript{37} described 3 additional patients with sporadic CJD whose histopathological results were consistent with prion disease and definite amyotrophy. None had transmitted the disease to primates at the time of publication, and no further information about the transmission experiments was mentioned in later series.\textsuperscript{15} Brown et al\textsuperscript{3} gave details of 3 patients with pathologically confirmed sporadic CJD with prominent amyotrophy but without results of transmission experiments. Will and Matthews\textsuperscript{16} described 5 patients with pathologically confirmed sporadic CJD with amyotrophy without individual detail. The diagnoses in these 11 patients lacked support by immunohistochemistry, transmission, or mutation, and they are not included in the Table.

Traub et al\textsuperscript{14} described a familial case with definite amyotrophy included in the series of Roos et al\textsuperscript{37} as a patient with Alzheimer disease. The review of pathological slides confirmed CJD, but transmission experiments were pending.\textsuperscript{14} In another family with presumed GSS based on pathological results and family history, the index patient had a mix of upper and lower neuron signs and showed AHC pathological findings at autopsy.\textsuperscript{49} Another 10 patients\textsuperscript{40,50-52} had amyotrophy and presumed familial prion disease based on clinical and family history and physical and characteristic histopathological findings; in 3 of the 10, motor neuron pathological findings were reported.\textsuperscript{49-51} These 12 patients are not included in the Table because the diagnoses lacked support by immunohistochemistry, transmission, or mutation.

OTHER CASES REPORTED IN THE LITERATURE

Many reports in the literature suggest the presence of amyotrophy in cases of prion disease without definitive proof of one or the other. Although we did not include them in our total of 50 cases in the tabulation in the Conclusions, several of them are worth noting.

Possible Amyotrophy in Proven Prion Disease

Descendants of Gerstmann's original family with GSS carry a mutation at codon 102 of PRNP. Prominent weakness was described in some patients without mention of amyotrophy.\textsuperscript{53} Several members of the family showed changes at autopsy in the pyramidal tracts and neurogenic changes in muscle, but motor neurons were not mentioned.\textsuperscript{53,54} Two other families\textsuperscript{55,56} had genetically determined prion...
disease and a strong family history of ALS. In one family, the propositus lacked amyotrophy, but 4 other family members had been diagnosed with ALS. Some reports mention motor neuron degeneration in patients with prion disease without mentioning fasciculations.49,57

In other families, lower motor neuron signs were attributed to peripheral neuropathy. Neufeld et al58 described clinical fasciculation in 2 patients with a codon 200 mutation of PRNP: one had slow nerve conduction velocities and a cerebrospinal fluid protein content of 1.6 g/L, the other showed multifocal conduction block, antibodies to Gm1 ganglioside, and demyelination in a teased nerve preparation. Neither patient had postmortem examination of the AHCs. Another patient with peripheral neuropathy with a codon 200 mutation had slow conduction velocities and histological demyelination. Fasciculation was not mentioned, and the motor neurons were histologically normal.59 Peripheral neuropathy without fasciculation occurs in sporadic CJD.60

Amyotrophy in Possible Prion Disease

In one family, the clinical picture was that of ALS; autopsy showed spongy degeneration of white matter of the spinal cord, brain stem, cerebellum, and thalamus but no loss of AHCs. Studies for prion disease were not mentioned. In other cases, the diagnosis of CJD was dubious before or after the era of transmissibility. Some cases with amyotrophy were noted without details.63

CONCLUSIONS

We identified 50 reported cases of prion disease with amyotrophy (see tabulation below). In 27, the proof of prion disease included experimental transmission, biochemical evidence of protease-resistant PrP deposition, or identification of a PRNP mutation. Another 23 had typical histopathological findings but lacked molecular evidence or experimental transmission as confirmation.

<table>
<thead>
<tr>
<th>Prion Disease with Amyotrophy</th>
<th>No. of</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmitted*</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Typical clinical picture with typical histopathological findings without transmission or molecular support†</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation identified*</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Transmitted</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Positive family history and typical histopathological findings without molecular support</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td></td>
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</tbody>
</table>

*Cases are reported in the Table. †Molecular support includes identification of protease-resistant PrP by Western blot analysis or immunohistochemistry and identification of a mutation of PRNP.

The cases reviewed herein support the belief that amyotrophy is occasionally a prominent feature of prion disease. The exact incidence of amyotrophy is unclear and probably differs for different types of prion disease. Future studies of lower motor neuron dysfunction in prion diseases seem warranted, and we need a more rigorous definition of amyotrophy. The paucity of information about spinal motor neurons and the corticospinal tract in prion diseases could be alleviated by explicit statements in future case reports about findings from the neurological examination, EMG, and postmortem examination of the spinal cord. Cases of ALS-dementia warrant testing for protease-resistant PrP in the brain and for PRNP mutation.

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