Case Report

Primary Progressive Aphasia With Motor Neuron Disease: A Case Report
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Summary
Primary progressive aphasia is a sub-group of frontotemporal dementia and a degenerative, rarely observed disease that only causes progressive deterioration in language functions for two years. Amyotrophic Lateral Sclerosis (ALS) is a progressive neuro-degenerative disease, clinically characterized with upper and lower motor neuron findings, accompanied by distinctive degeneration in upper and lower motor neurons of the spinal cord. Frontotemporal dementia together with ALS is a case stated in the literature. However, a faster progressing primary progressive aphasia, initiating with motor aphasia and with addition of motor neuron disease to the clinical situation, together with ALS was reported in recent years. Therefore, it was proposed to be assessed as a separate clinical entity. Both these diseases do not have an effective treatment yet. Our case is clinically initiating with primary progressive aphasia and two years later motor neuron disease started. The case is presented with a positron emission tomography (PET) data.

Key words: Primary progressive aphasia, motor neuron disease

INTRODUCTION
Primary progressive aphasia (PPA) is a neurodegenerative syndrome. In this disease, the linguistic multifunctions are slowly progressing and they are the only factor disrupting daily functions. The disease is also characterized by isolated linguistic malfunctioning. As an initiation symptom, abnormalities in word syntax, spelling, using and understanding...
words are observed. Most frequently occurring PPA variants are; 1. progressive non-fluent aphasia (PNFA), 2. semantic dementia (SD), 3. logopenic progressive aphasia (LPA). PNFA is characterized by difficulty in speaking and aggrammatism. In some patients, the syndrome solely starts with deficits in speaking. In SD, the meaning loss in words and objects, and a superficial dyslexia is typically observed. LPA patients can have difficulty in finding words, using a syntactically simple yet correct language and sentence apprehending can get affected. Other cognitive processes such as memory, spatio-visual abilities, judgment and social behavior are preserved at the beginning of the disease.

Progressive loss of linguistic functions in an isolated fashion related with atrophy in left temporo-polar area and two thirds back portion of frontal lobe are first reported by Pick in 1892. Mesulam reported 6 cases with isolated linguistic function disorder without dementia findings; he named them as primary progressive aphasia.

Amyotrophic Lateral Sclerosis (ALS) is a progressive neuro-degenerative disease, clinically characterized with upper and lower motor neuron findings and accompanied by distinctive degeneration in upper and lower motor neurons of the brain and spinal cord.

ALS and frontal lobe dementia cooccurrence is known for a long time, however the prevalence of FTLD-ALS is not known yet. It is still a matter of discussion whether the cooccurrence of FTLD-ALS is a variant of ALS or it is a sub-group of FTLD. In recent times, it is stated that it is a separate pathological entity. The relation between rapid progressive aphasic dementia and motor neuron disease is defined as a separate clinical syndrome among the group of frontotemporal dementias. Although the clinical and neuropsychological symptoms of the syndrome have been defined, the neuropathological findings are published in a small number of post-mortem studies.

Some authors have shown that without ALS and dementia, PPA is related with ubiquitin inclusions in left temporal lobe atrophy, motor and extra-motor areas and overlapping clinical situations.

CASE PRESENTATION

A right handed woman born in 1942, had been in excellent health until 2006 when she noticed difficulty in speaking and swallowing. She has consulted to our outpatient clinic. It was found out that 2.5 years before she had complaints as decline in speech fluency, difficulty in finding words. These complaints increased over time. Approximately 6 months ago she had complaints of difficulty in fluid nutrition intake and articulation disorder. Other than disorder in linguistic functions for 2 years, there was not any additional symptoms for us to consider frontal affection.

Other than hypertension, there was not any specialities in her medical history. It was found out that as anti-hypertension medication, she was using irbesartan 300 mg + hydrochlorothiazide 12.5 mg. In her family history, it was learned that her mother had a stroke.

In her neurological examination, she had decline in spontaneous speech, verbal paraphasia and difficulty in finding words when speaking. Her answers to questions were short and superficial. There were no pathological findings other than naming and severe articulation disorders. Neurological examinations revealed not so discernible muscle wasting in interossei of hands, triceps muscles of arms and tongue. There were fasciculations in the tongue and arms. Deep tendon reflexes were found normal in upper and lower extremities and any pathological reflexes were not obtained. In routine biochemical examinations, there were not any pathological findings except for hyperlipidemia. Hematological and...
serological examinations were found normal. EEG was normal.

Neuropsychological Assessment
The reading and writing functions of the patient could not be assessed, because she was illiterate. She scored 19 points from the Mini Mental State Test for the illiterate. Neurocognitive battery was applied partially because of her present clinical situation. Her orientation, attention and arithmetic skills were evaluated as normal. The patient could name the objects partially and had paraphasias (such as red instead of cherry). In Boston naming test, she could only name 7 words out of 15. The patient's verbal fluency could not be evaluated. Her low scores in visual instant memory and clock sketches were attributed to her illiteracy.

Neuroradiological Assessment
In her cranial MR examination, a few number of milimetric sized microangiopathic ischemic - gliotic focus in bilateral cerebral hemispheres (15 x 10 mm sized) and an extra axial calcified menengiomata located at the right frontal lob, adjacent to the posterior part were determined. In PET examination with F-18 FDG, in both cingulate cortices, especially in anterior areas, FDG uptake, a sign of glucose metabolism, was less when compared with other parts of the brain (Figure 1 and 2).

Neurophysiological Assessment
Electromyography examination was done for the patient who had complaints of losing strength and especially difficulty in swallowing fluid nutrition in the recent months. In EMG, motor and sensory conduction analyses were normal. In cervical segments and bulbar area, there were normals that are rarefying in innerve muscles, also long term, poly - phased, high amplituted motor unit potentials and denervation potentials in some muscles (genioglossus, trapezius, triceps, first dorsal interosseus), fasciculations in some muscles (genioglossus, triceps, first dorsal interosseus) were seen. Complex repetitive discharges were observed in right rectus abdominis muscle.

Figure 1: .
DISCUSSION

ALS and aphasia can occur together without FTD symptoms. The cooccurrence of progressive non-fluent aphasia and ALS is reported first by Caselli et al. in 1993\(^5\). Although the inception age of PPA is 62 in average, it can begin in any age between 43 and 77. The initial complaints of our case occurred in the age of 65. Generally the cases that start between 65 - 70 are reported in the literature. However, Portera - Cailliau et al. presented cases in which one started with PPA, progressed to mutism, later developed moderate disinhibition with dementia and parkinsonism, and in the further stages also developed ALS, and 2 other cases from the same family with similar complaints. They reported that all 3 cases started in the early ages (4th decade) and resulted in death, displaying a rapid progressive course\(^{21}\).

ALS with PPA usually develops progressive bulbar palsy and shows faster deterioration\(^{4,6,10,24,29}\). Generally, there are also cases reported with the addition of bulbar symptoms and fasciculations 6 - 12 months later, aphasia and motor neuron symptoms started concurrently\(^{3,4,6,14,24,29}\). The disease has a short course between 10 months and 3 years and most of the patients died from respiratory failure due to aspiration pneumonia\(^{3,4,6,14,24,29}\). Da Rocha et al. stated that due to the fast progression ending with death, cognitive symptoms could not be seen\(^{24}\). Matsuda et al. from Japan reported a 67 year old male case, who showed a slow progression of disability in speaking for 2 years and yet died in 3 years\(^{14}\). Neurological symptoms and findings are typically different than ALS. Bulbar deficit starts early, shows fast progression and causes mortality\(^{6,10,24,29}\). Although lower and upper neuron symptoms are seen together, they progress more moderately compared to bulbar symptoms\(^{4,5}\). As the weakness in lower extremities progresses mildly, the patients can be mobile even in the terminal stage\(^{3,5,24,28}\). In our case, the articulation disorder - probably appearing because of bulbar effects - was also reported by Hyodo et al. They proposed that the patients with bulbar ALS and dementia have aphasia more than that could be defined, because bulbar palsy can cover linguistic disorder\(^{10}\).
In 1993, Caselli et al. reported 7 cases that have ALS starting with bulbar and concurrent with progressive aphasic dementia\(^5\). It is proposed that the characteristic features (initiation with bulbar neuron disease and rapid progression) should be taken as a separate clinical entity\(^6,29\). Bak et al. proposed that other than taking it as a separate clinical entity, it should be assessed as a sub-group of ALS\(^4,7\). Lund and Manchester group proposed that cases with ALS and aphasic dementia should be considered as a sub-group of FTD\(^11\). Some authors proposed that ALS related with aphasic dementia represent a heterogeneous syndrome and dysphagia and aphasia are explained with oral apraxia, cognitive symptoms are explained as an atypical range of Alzheimer disease pathology\(^7\). In ALS, the most frequent cognitive affection is frontal lobe type dementia. Rakowicz et al. applied neuropsychologic battery to 18 patients with newly diagnosed sporadic ALS, in order to detect the prevalence of cognitive effects and language deficits in motor neuron disease. It was detected that 3 patients had dementia and effect in language functions, 2 patients had aphasic syndrome of difficulty in finding words without dementia, and 13 patients had normal cognitive abilities, except for decline in verbal fluency. As a result, they proposed that language deficits in ALS patients are more frequent than it is thought and aphasia could be disguised because of dysarthria\(^23\). There are very few cases where ALS and PPA are observed together and neuropathologically verified. In our case, progressive aphasia without initial cognitive and behavioral deterioration, depletion mostly in language fluency and characterization with anomia are typical for primary progressive motor aphasia syndrome. The most obvious deterioration among the language functions was in the speech fluency and it has increased during the four year follow-up. Deterioration in naming things, repetition, reading and writing are correlative for progressive nonfluent motor aphasia. Although slowly progressing, certain deteriorations were observed among them. Because the patient's literacy was totally disrupted and her general condition was getting worse, detailed assessment for dementia could not be made. However, it is possible to say that in time, other cognitive deteriorations were partially added to the deterioration of language functions (such as deterioration of constructive, verbal and non-verbal functions in the MMSE that could be done). In our case, the disease displays a longer course and slower progression, which is different from the literature. Taking into consideration that ALS findings were added 6 months ago and the previous cases, it can be thought that we should expect a shorter life span for our patient. In the cases reported in the literature, motor neuron findings (difficulty in swallowing, dysarthria, weakness, faciculations) are added approximately 6 months after aphasia. In our case complaints in swallowing started 2 years later and in electromyography findings coherent with ALS are observed\(^3,6,24,29\).

In MR of the patients who have non-fluent aphasia, left frontal and perisylvian atrophy\(^1,29\), left inferior frontal gyrus, premotor cortex and anterior insular atrophy\(^8\), distinct bilateral fronto-temporal atrophy in left hemisphere\(^4,14,27\), diffuse atrophy\(^28\) can be observed. Atrophy is not seen in cranial MR, but it is reported that in SPECT hypometabolism can be seen in left temporoparietal cortex and right temporal cortex\(^27\). Grossman et al. reported that in PET scanning of a group of patients with PNFA, when compared with controls, they have hypometabolism more specifically in left inferior frontal, superior and middle temporal gyrus, compared to cases with general left hemisphere hypometabolism and possible Alzheimer disease\(^9\). Kempler et al. reported that in PET, when the right hemisphere is normal, generally left temporal hypometabolism can be
mentioned and also reported hypometabolism in left temporal, superior temporal, inferior parietal, insula, beginning of caudate and thalamic areas\(^{(12)}\). In PET scanning of 10 cases with PNFA, hypometabolism was detected in several areas, distinctively in left anterior insula / frontal opercular area. They show that when PET scanning of Alzheimer patients are compared with PNFA cases, the only permanent hypometabolic area is left anterior insula\(^{(20)}\). In SPECT analysis, hypoperfusion in left frontotemporal cortex\(^{(1,4,6)}\), hypoperfusion in left temporal and bilateral parietal areas\(^{(10)}\), irregular defects in bilateral frontotemporal area\(^{(14)}\) are reported. In a study conducted with proton magnetic resonance spectroscopy, it is proposed that in left superior longitudinal fasciculus (the fibrous bundle connecting classical Wernicke and Broca language areas) there is axonal damage and therefore disconnection in language network\(^{(26)}\). In our case, when looked at the PET result, it is observed that cingulate cortex and especially anterior areas were affected and in these areas hypometabolism has occurred. This data does not correspond to the literature. The results did not show any lateralization for brain hemispheres. However, the fact that especially anterior parts of the brain were affected is correlative with the nonfluent motor aphasia findings of our case. The PET conducted on our case coincided with a period when ALS started with cognitive deficits and language functions were severely deteriorated. Therefore, we think that this PET result points out a more prevalent pathology correlated with the clinical situation.

Our case is somewhat different than the similar cases reported in the world with its clinic and its clinical progress. ALS was added to PPA approximately 2 years later. Both this process and the clinical process after the appearance of ALS progresses slowly. Any assessment on its reason would be speculative. In the future, studies with correct methodology on this disease group would enable us to make a more correct assessment and maybe will open new ways for developments that will result in new definitions.

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