Amyotrophic Lateral Sclerosis with Atrophy of the Amygdala

Early and pronounced involvement of the amygdala is known to be characteristic for the behavioral variant of frontotemporal dementia, but it may also occur in ALS.

By Felix Geser, MD, PhD, Leo Hermle, MD, Patrick J. Egan, MD, Johannes Brettschneider, MD, and Tibor C. G. Mitrovics, MD

We report a case of a 76-year-old woman with a prior history of hypertension, hyperlipidemia, bilateral gonarthrosis (with a cartilage transplantation done in 2002 on the right side and a knee prosthesis implanted in 2013 on the left side), hypothyreosis, and coronary artery disease (with two stents implanted in 2009). Additionally, the patient had a cornea transplantation done in 1999 (left side). She reported to be severely hearing impaired on the left side since childhood. Starting in late 2013, the patient developed progressive difficulties with speaking and swallowing as well as depressed mood. She also developed a medium-severe episode of depression that was treated with escitalopram. At the time we first saw her at our hospital, a diagnosis of probable ALS was made.

The patient’s motor disorder was dominated by lower motor neuron signs in bulbar nuclei with pronounced dysarthria and medium-severe dysphagia. In fact, a video-fluoroscopic examination showed evidence of a dysphagia with weak tongue movements, and weak, slowed, and dis-coordinated swallowing. The patient reported to have more problems with liquid than solid food. Speech was severely dysarthric with an unclear, slurred quality. Her voice was weak (hypophonia) and barely understandable, so that she started to write things down on paper in order to communicate. No unequivocal other symptoms or signs of cranial nerve involvement (such as an impairment in oculomotor motility) were seen. Electromyographic testing revealed neurogenic changes in bulbar and cervical segments, and fasciculations, respectively. She showed signs of upper motor neuron dysfunction including exaggerated reflexes and broadening.

Figure 1. 1.5 Tesla magnetic resonance imaging, T1 turbo inversion recovery sequence, coronal plane, showing atrophic amygdala (right: large arrow, left: short arrow) and adjacent parts of the cortex (periamygdaloid cortex) more pronounced on the right as compared to the left side. The temporal horn of the right lateral ventricle (large circle) is larger than the left one (small circle). There also is a rounding/widening of the body of the lateral ventricles right (large asterisk) greater than left (small asterisk).
of reflex zones in the cervical and lumbar segments, respectively. Slight bilateral spasticity was found with the upper limbs. There was no Babinski sign and no clonus of the feet.

A significant decrease in amplitude in somatosensory evoked potentials studies was seen in cervical segments. Motor evoked potential response latencies and the central motor conduction times to the lower, but not upper, limb were delayed. The patient did not report difficulties with sensation. Pallesthesia was tested by using a vibrating mechanical tuning fork placed on the styloid process (7/8 bilaterally) and lateral malleolus (7/8 on the left and 6/8 on the right side, respectively). Auditory evoked potentials showed evidence of a lesion of the retro-cochlear auditory pathway on the left side, and visual evoked potentials and the orbicularis oculi reflex were normal. There was no tremor and no involuntary movements. She complained about an overall
weakness, and there was instability with (tests of) stance or walking.

The patient showed pathological crying (and laughing) and psychomotor slowness. She did not complain about difficulties with memory. Furthermore, no chances in here social activities or behavior were reported. However, her husband noted that she was listening to music or watching the television using headphones for “extended periods of time.” The patient did not complain about bladder difficulty or permanent bowel difficulties. However, for roughly the past 10 years she has experienced fatigue, and for about the same time she complained about slight problems with maintaining, but not initiating, sleep. Her family history was negative for neurological or psychiatric diseases. Analysis of the cerebrospinal fluid did not reveal any significant results. Structural MRI studies showed significant atrophy of the amygdala and adjacent parts of the mediotemporal lobe cortex (such as the periamygdaloid cortex) bilaterally (right greater than left) (Figure 1, Supplemental Figure 1), a rounding and enlargement, respectively, of the supratentorial ventricular system (especially the tips of the temporal horns) (Figure 1, Supplemental Figures 1, 2a, 2b, 3a, 4) and a widening of the subarachnoid space temporo-polar with atrophy of (especially) the tip of the temporal lobe (Supplemental Figures 3a, 3b). The right hippocampus and adjacent parts of the temporal lobe appeared to be somewhat smaller than the left ones (Supplemental Figure 1, 2a, 2b). There were widespread gliotic lesions in the deep white matter of the cerebral hemispheres with patchy subcortical (vascular leukoencephalopathy) and subependymal lesions (Supplemental Figure 4). In addition, a small lacunar defect was detected in the upper part of the right hemisphere of the cerebellum (data not shown).

Neuropsychological testing at our hospital was done at a time when she was treated with two anti-depressants (i.e., venlafaxine and mirtazapin). It showed elevated anxiety values as measured by the State-Trait Anxiety Inventory (trait-anxiety score 59, corresponding to the 95 percentile; state anxiety score 67), mild depression according to the Beck Depression inventory (score: 14), and—a part from impairment in the learning of word lists—average scores for verbal and visual cognitive functions. The Consortium to Establish a Registry for Alzheimer’s Disease neuropsychological battery showed averages scores for verbal and visual cognitive functions except for word learning, which was below average; the Mini-Mental State Examination scored 30. Global cognitive function was unremarkable (score in the clock drawing test: 2), but concentration was far below average.

At the time of initial diagnosis, the patient complained about pain of the right side of the face and tongue and pain when swallowing. She also said she was tired of life, but there was no actual suicidal tendency in the sense of a factual plan to end her life. The patient was put on riluzole while other attempts in her neuropsychiatric medication—in addition to her antidepressant medication—including quetiapine, pregabaline, zolpidem, and melperon. Within a short period of time, which was by mid-2014, she became too weak to stand without assistance, and the disease progression of ALS necessitated the placing of a percutaneous endoscopic gastrostomy for nutrition. She became completely anarthric, and there was a further deterioration in her mood (crying) and writing (not legible). The patient and her husband consented on publication.

DISCUSSION

Motor neuron disease, cognitive impairment as well as speech impairment have been known to co-occur for many years, and (clino-)pathological studies corroborate the multi-system nature, including the limbic system, with overlapping features of this disorders or changes in aging individuals. Atrophy, as measured by in vivo neuroimaging techniques, mirror the structural changes as occurring in “normal aging” and diseases and can thus be used to determine topographical pattern of degeneration and monitor rates of disease progression. Structural neuroimaging studies in ALS have yielded in varying, and in part, conflicting results such as atrophy of the spinal cord and the grey matter in frontal, temporal, occipital lobes as well as limbic regions. Studies on ALS patients have shown that emotional disturbances (depression, anxiety, and “pseudobulbar” affect) do occur to varying degrees in this disorder. The amygdala is known to play a pivotal role in emotion. Indeed, functional MRI has been used to show an activation of the amygdala/periamygdaloid cortex during conditioned fear acquisition and extinction in normal subjects. In patients with ALS, emotional responses has been shown to be altered towards a positive valence, suggesting involvement of the amygdala. An MRI volumetric study found a statistical trend towards lower total amygdala volume in the ALS as compared to control subjects.

This case presentation demonstrates amygdala atrophy bilaterally (right greater than left) in a patient with bulbar predominant ALS and emotional disturbances. There also was a loss of volume of the mediotemporal lobe as a whole and a widespread leukoencephalopathy, which may be—at least partially—due to hypertension and hyperlipidemia. Widening of the subarachnoid space was especially visible at the tips of the temporal lobes of our case. Cognitive dysfunction was not absolutely absent, but much less pronounced as compared to the motor and mood disorder. The latter two started at around the same time. Correspondingly, the morphological signs of atrophy of the cerebral cortex were more pronounced at the tips of the temporal lobes and a widening of the subarachnoid space (especially temporo-
polar) were present, but only to a slight degree. On functional imaging, ALS patients have been found to display an altered left amygdala-prefrontal cortex connectivity. In patients with the “temporal variant” of frontotemporal dementia, emotional comprehension has been shown to correlate with atrophy in the right amygdala and the right orbitofrontal cortex. In a post-mortem study of cases with the behavioral variant frontotemporal dementia, the amygdala has been demonstrated to be among the brain regions affected earliest in the disease, whereas in ALS antemidal temporal lobe structures are affected last.

For depression and anxiety, it is known that activation of the amygdala occurs and there may be both an increase and a decrease in amygdala volumes in these disorders. It has been, in fact, suggested that there is a time course in these volumes with larger amygdala occurring with the first episodes of depression (probably reflecting hyperactivation with higher metabolism and blood flow) than with subsequent, recurrent episodes. As the diseases progresses, excitotoxic processes may result in a neurodegenerative process and finally in atrophy. In this respect, it is of interest that the anti-glutamate agent riluzole has at least a modest effect on survival in ALS. Furthermore, intoxication with hoomic acid, which is structurally related to glutamate and has excitotoxic properties, has been followed by neuronal loss and gliosis predominantly in the hippocampus and amygdala after ingestion of contaminated mussels. White matter changes of vascular origin in aging individuals do occur—this could be one contributing factor in the disease of our patient; in a study on healthy older adults, individuals with mild cognitive impairment and patients with Alzheimer’s disease showed no significant group differences in white matter changes properties. However, there were strong associations between diffusivity of white matter changes and ventricular volume, volume of white matter changes, and total white matter volume. In comparison, group differences in parahippocampal white matter microstructure were found for all diffusion metrics and were largely explained by hippocampal volume. Moreover, it is known that in brains with vascular lesions (such as Binswanger’s disease or subcortical ischemic vascular dementia) atrophy of medial temporal lobe grey matter measures including the amygdala occur, which may be similar to Alzheimer’s disease.

CONCLUSION

Our findings indicate that the bulbar form of ALS in an elderly, aging individual can present as a complex neuropsychiatric syndrome with bilateral amygdala atrophy and a vascular leukoencephalopathy associated with anxiety/emotional disturbances and relatively intact cognition. Primary neurodegenerative and non-neurodegenerative (vascular) pathologies mechanisms may result in similar, but complex, clinical phe-