UNUSUAL PRESENTATION OF ATYPICAL AKINETIC-RIGID SYNDROME AFTER LIVER TRANSPLANTATION: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Introduction*: Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by early postural instability and falls, vertical supranuclear gaze impairment, pseudobulbar palsy, and frontal subcortical dysfunction, with little or no response to L-dopa. We describe a patient with a subacute onset of a PSP-like syndrome after liver transplantation (LT) and review the literature on extrapyramidal complications following organ transplantations. A wide spectrum of neurological manifestations after LT are indeed a significant source of morbidity and mortality, often occurring within 30 days from transplantation. However, the occurrence of an atypical parkinsonism has never been reported before.*

Case presentation*: A 74-year-old man was referred because of a slowly progressive atypical rigid-akinetic syndrome which had started approximately one month after uncomplicated orthotropic LT. Cognitive problems were evident involving memory and frontal executive functions; some signs of apraxia, micrographia and mildly depressed mood were also observed. Additionally, neurogenic bladder dysfunction was detected. Brain magnetic resonance imaging showed midbrain atrophy without significant involvement of the pons, leading to the appearance of the typical "penguin" or "hummingbird" sign. Taken together, clinical and imaging features were consistent with the diagnosis of PSP. Symptoms were not modified by the subsequent anti-parkinsonian drug therapy.*

Conclusion: *We hypothesize that, in this patient, a hypoxic insult of basal ganglia during surgery might have induced the onset of PSP because movement disorders frequently follow brain hypoxia and a particular vulnerability to hypoxia is present in specific brain regions, such as basal ganglia and neocortex. However, alternative hypotheses cannot be ruled out, such as a "trigger effect" of the surgical procedure for a neurodegenerative disease, neurologic consequences of chronic infections (hepatitis C or B), or a cyclosporine-induced parkinsonism. A diagnosis of PSP should be considered when features suggestive of an atypical extrapiramidal disease occur acutely or gradually after an organ transplantation.*

Key words*: atypical parkinsonism, liver transplantation, cerebral hypoxia, neuroimaging.*

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Introduction

Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by early postural instability and falls, vertical supranuclear gaze impairment, pseudobulbar palsy, and frontal subcortical dysfunction, with little or no response to L-dopa. The prevalence of PSP has been reported to range from 1.3 to 4.9[(1)] and its annual incidence in the general population ranges from 0.3 to 1.1/100,000, increasing up to 5.3/100,000 in people over the age of 50 years[(2)]. The median age at onset is 63 years, with both sexes affected, despite a small male predominance[(3)]. The most frequently reported symptoms at onset are impaired balance, movement slowness, subtle personality changes (apathy, disinhibition), bulbar symptoms and impaired eye motion; whereas in the more advanced stages, patients generally have bradykinesia, rigidity and imbalance, with severe gait unsteadiness and frequent falls (usually backward). Some patients may have postural tremor and, less frequently, tremor at rest. They often experience dysphagia and a characteristic growling high-

pitched severe dysarthria, with mixed spastic and parkinsonian features. The diagnostic feature that best characterizes PSP, although not always present, is a vertical gaze limitation, especially downgaze, with preserved ocular-cephalic reflexes[4]. Cognitive and behavioral symptoms can occur early, being sometimes the only presenting features and reaching the severity of dementia[5]. PSP carries a poor prognosis and leads to death within a few years after symptom onset. Mean survival ranges from 5.9 to 9.7 years, according to the different series[4].

Nevertheless, various clinical PSP variants have been described, depending on the different distribution of tau-protein pathology, although they share histopathological, biochemical and genetic features with the classical PSP. The major difference is due to the regional distribution of tau-protein deposition and the resulting clinical phenomenology[6]. Therefore, considerable variability exists in clinical manifestations and some disorders different from PSP may sometimes mimic atypical cases of PSP.

We describe here a patient with a subacute onset of a PSP-like syndrome emerging after liver transplantation (LT) and review the literature on extrapyramidal complications following organ transplantations. Post-operative complications after LT are indeed a significant source of morbidity and mortality, with neurological manifestations such as encephalopathy, akinetic mutism, seizures, stroke, peripheral neuropathy, tremor, and hallucinations occurring in up to 75% of cases[7], often within 30 days from transplantation[8]. Neurological complications occur more commonly after LT than after other solid organ transplantation, such as heart and kidney[9], and it has been suggested that the higher rate is related to the presence of preoperative hepatic encephalopathy, the unfavorable clinical condition of patients awaiting transplantation (e.g., malnutrition, renal insufficiency, hyponatremia, coagulopathy), and the complexity of the operation[10].

To our knowledge, however, the occurrence of an atypical parkinsonism following LT has not been reported before.

Case presentation

A 74-year-old right-handed man was admitted to our research Institute in September 2013 because of an atypical akinetic-rigid syndrome. Written informed consent for the use of the clinical data for scientific purposes was obtained at admission. The past medical history included atrial fibrillation, mild renal failure, benign prostatic hyperplasia, and chronic obstructive pulmonary disease; the patient was treated with oral anticoagulant therapy, diuretics, allopurinol and alpha-blockers. He had undergone orthotropic LT because of chronic hepatitis B and C. No sign of any neurological disorder was present before the intervention and both immediate pre- and post-surgical serum sodium levels were normal. Both surgery and post-operative course were uncomplicated. Cyclosporine and mycophenolate mofetil were prescribed as immunosuppressive therapy, which remained unchanged over time. Approximately one month after surgery, the patient started to complain a gradually progressive gait unsteadiness, with backward falls, hand writing disturbances and slurred speech. When these symptoms first appeared, blood concentration of cyclosporine was within the therapeutic range. He therefore underwent magnetic resonance imaging (MRI) of the brain, revealing a single old lacunar infarct of the pons white matter, together with mild diffuse cortical atrophy. Because of the progressive worsening of the clinical condition, the patient was admitted to a Neurology Department. At that time, clinical examination showed hypophonic and hyperkinetic dysarthric speech, diffusely brisk reflexes, bilateral Hoffman and Babinski signs and a mild cognitive impairment. Nerve electrophysiological evaluation was consistent with a nerve root pathology at the C5-C6 level, on the right side, and L3-L4 and L5-S1, bilaterally. Brain MRI was slightly changed because of a more pronounced bilateral atrophy in the frontal and parietal lobes. At discharge, no specific drug was prescribed and he performed physical therapy only, without improvement. At the last examination, in addition to the signs reported above, the patient had dysphagia and supranuclear upgaze limitation. Increased muscular tone of the extrapiramidal type was noticed in both arms, more evident on the left side, whereas spastic hypertonia was present in the lower limbs, where mild weakness was also appreciated; frontal release signs were visible. The posture was flexed with impaired postural reflexes; gait was slow with small steps and tendency to backward falls. Cognitive problems were evident, characterized by memory and frontal executive functions involvement; some signs of apraxia, micrographia and slightly depressed mood were also observed.

The patient had also a neurogenic bladder dysfunction. Laboratory tests showed a mild impairment of the liver and kidney function tests and a moderate pancytopenia. Electroencephalography revealed diffusely slow background activity. The nerve neurophysiological study was comparable to the previous evaluation. Brain MRI (Figure 1) revealed atrophy of the midbrain tegmentum with a relative sparing of the pons, frontal-parietal cortical atrophy and callosal thinning; the ischemic lesion of the pons was unchanged. Spine MRI was unrevealing except for cervical and lumbo-sacral disk protrusions. Symptoms did not change significantly during six months of anti-parkinsonian drug therapy (levodopa 100 mg + benserazide 25 mg, three times daily).

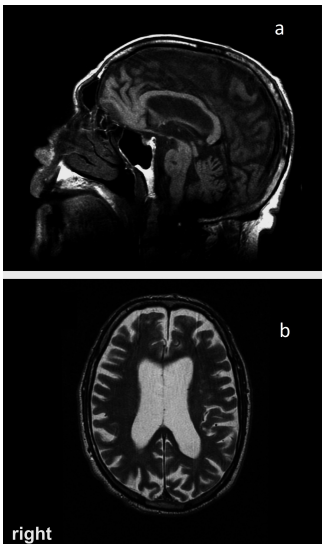

Figure 1: Brain magnetic resonance imaging of the patient. (**A**) Midsagittal T1-weighted magnetic resonance imaging demonstrating midbrain atrophy without significant pontine involvement, forming the silhouette of the "penguin" or "hummingbird" sign. A pontine white matter change due to a single old lacunar infarct is visible. Diffuse thinning of the corpus callosum. (**B**) Axial T2-weighted MRI showing frontal and parietal cortical atrophy and very mild evidence of deep white matter changes due to chronic ischemic lesions.

Discussion

Overall, the clinical features and the neuroradiological findings of this patient are concordant with a diagnosis of PSP. To our knowledge, this is the first report of a new-onset PSP occurring after LT; only a report of Parkinson's disease after LT has been published before[11].

Neurological complications may occur in up to 45% of patients after LT, although it is often difficult to identify the cause, because of the non-specific nature of their presentation[11]. A post-operative cerebral syndrome poses the possibility of an ischemic insult resulting from a peri-operative thromboembolic event. However, the latent and progressive course of the symptoms in our patient cannot be explained by a single ischemic event and, additionally, there were insufficient signs of ischemic load, differently from the PSP reported in the multi-infarct state[12]. Nevertheless, a subtle intra-operative hypoxemia, that occurs almost invariably in this type of surgery, cannot be excluded as one of several factors that could have triggered the pathophysiologic process. In this context, our patient possibly developed intra-operative hypoxic microlesions of the basal ganglia followed by a slowly progressive course. A review of the literature reveals that the predominant clinical residuals after a hypoxic brain injury are movement disorders, which may manifest after a significantly long latency[13]. Moreover, delayed onset and progressive extrapyramidal features are well recognized after basal ganglia damage, and subsequent collateral sprouting, ephaptic transmission, inflammatory changes, transynaptic neuronal degeneration, and central synaptic reorganization have all been suggested as possible mechanisms[13].

A selective vulnerability of different brain areas, such as the neocortex and the basal ganglia, to a diffuse insult may be related to a distinct neuronal injury, resulting in variations of the related clinical manifestations. The hypothesis that hypoxemic perioperative stress affecting specific metabolic paths might share a common vulnerability trait has also been reported in a case series in which patients developed PSP a few weeks after uncomplicated surgery of the ascending aorta aneurysm/dissection[14]. Another possibility might be that a very mild, pre-existing, and unrecognized PSP becomes more manifest after the trauma of surgery, although our patient did not have any history of neurological disorder.

An intriguing alternative hypothesis may consider the possibility of a neurological damage related to a hepatitis C virus (HCV) chronic infection which, as already known, is associated with a wide spectrum of extrahepatic manifestations. In particular, neurological complications occur in a large number of patients and range from peripheral neuropathy to cognitive impairment. Pathogenetic mechanisms responsible for this nervous system dysfunction are especially related to the up regula-

tion of the host immune response, with production of autoantibodies, immune complexes, and cryoglobulins, as well as possible extrahepatic replication of the HCV in neural tissues or the effects of circulating inflammatory cytokines and chemokines[15]. Chronic hepatitis B virus (HBV) infection is less frequently complicated by neurological disorders, including Guillam-Barre syndrome, mononeuritis multiplex, auditory neuritis, and seizures, probably due to a direct cytotoxicity of the virus, an immune-mediated damage or, at least in some cases, a vasculitis of the vasa nervorum[16]. However, although we cannot exclude a possible contribution of a chronic hepatitis viral infection, the clinical features, the electrophysiological data (such as peripheral neuropathies or myopathies) and the neuroradiological findings (such as cerebral vasculitis, acute cerebrovascular disease, leukoencephalopathy or encephalomyelitis) that are frequently associated with CNS complications of hepatitis C and B were not present in the patient described here.

Finally, it is worth noticing that the occurrence of cyclosporine-induced parkinsonism has also been reported[17]; although this is an extremely rare event, it cannot be excluded that cyclosporine might trigger the onset or worsen the course of a neurodegenerative disorder in predisposed individuals.

In conclusion, a PSP syndrome should be considered when features suggestive of atypical extrapiramidal disease occur acutely or gradually after an organ transplantation. The occurrence of an atypical parkinsonism after LT has never been reported before and might contribute to the definition of the clinical spectrum of neurological complications following organ transplantation.

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