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Brait-Fahn-Schwartz Disease: A Unique Co-Occurrence of Parkinson's Disease and Amyotrophic Lateral Sclerosis

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Keywords
Case report · Parkinson's disease · Amyotrophic lateral sclerosis · PD-ALS complex

Abstract
The Parkinson's disease-amyotrophic lateral sclerosis (ALS) complex typically manifests as levodopa-responsive parkinsonism, followed by ALS. It is extremely rare for Parkinson's disease and ALS to coexist without other neurological disorders. Named after the scientists who first described this overlap of two neurodegenerative conditions, it is referred to as Brait-Fahn-Schwartz disease. Given its variable presentation, increasing rarity, and lack of any diagnostic test, it poses a diagnostic challenge for physicians. We present a case of a 55-year-old Pakistani male experiencing progressive quadriparesis with spastic lower limbs and flaccid upper limbs, in addition to the cardinal features of idiopathic Parkinson's disease. Since there is currently no cure available for either Parkinson's disease or ALS, all available treatment focuses on improving quality of life, which we achieved in our patient. This case is unique in being the first incidence of Parkinson's disease-ALS complex in a novel geographic region such as Pakistan, where genetic testing and cost constraints limit the diagnosis of rare disorders. The coexistence of extrapyramidal symptoms and pyramidal symptoms is uncommon. In such situations, physicians may overlook one group of symptoms, potentially leading to a misdiagnosis. This case highlights the value of a thorough physical examination and electrodiagnostic studies and suggests the association between Parkinson's disease and ALS. This case demonstrates the significance of understanding when Parkinson's disease symptoms start to appear in patients with ALS and the need to start dopaminergic therapy in those who had Parkinson's disease features before ALS to alleviate the suffering of an individual and enhance quality of life.

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Introduction

Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are two neurodegenerative conditions that can coexist as Brait-Fahn-Schwartz disease and the ALS-parkinsonism-dementia complex of Guam. The most notable features of Brait-Fahn-Schwartz disease that set it apart from the Guam parkinsonism-dementia complex (G-PDC), which is endemic to the Pacific island of Guam, are the positive and persistent response to dopaminergic drug therapy and the order in which progressive parkinsonian features manifest before the onset of ALS [1, 2]. It can be either sporadic or familial. Although the occurrence of Parkinson's disease with ALS is uncommon, 5–17% of ALS patients may have clinical signs of parkinsonism. However, its prevalence has reduced significantly since the late 20th century, raising the possibility of a common pathogenesis [3, 4]. It is believed that mitochondrial dysfunction, microglia-derived neuroinflammation, oxidative stress, and free radical accumulation all contribute to neuronal death in these conditions. In Parkinson's disease, mitochondrial DNA mutations have been identified in the neurons of the substantia nigra, whereas motor neuron disease is linked to mutations in mitochondrial respiratory chain enzymes and proteins regulating cell death [5]. Based on genetic and nuclear medicine data, it was also speculated that patients with ALS and Parkinson's disease may have concurrent TDP-43 and a-synuclein pathology [6].

To date, there is no definitive diagnostic test that can confirm the presence of ALS. Rather, diagnosis is typically made by integrating clinical observations, electrophysiological assessments, and the exclusion of other conditions that may resemble ALS [7]. However, when Parkinson's disease and ALS occur concurrently, the diagnosis becomes considerably more challenging. In this report, we discuss the case of a 55-year-old Pakistani male who presented to us with gradually worsening quadriparesis, marked by spasticity in his lower limbs and flaccidity in his upper limbs, along with the preceding history of the development of features consistent with idiopathic Parkinson's disease. Following a comprehensive diagnostic evaluation, the patient was diagnosed with Brait-Fahn-Schwarz disease. Patient response to dopaminergic therapy reinforced the diagnosis, and symptomatic treatment with rehabilitation enhanced the patient's overall quality of life.

Case Description

A 55-year-old Pakistani male was admitted to the neurology department of a tertiary care hospital with complaints of bradykinesia, resting tremors of his right hand, and quadriparesis. Twelve months ago, he noticed slowing of his movements, which was followed 2 months later by resting tremors in his right hand. He developed upper-limb weakness 6 months prior to admission, which progressed to affect the lower limbs, thus impairing ambulation. He also complained of crippling leg stiffness. He could walk and climb stairs without assistance at first, but his condition deteriorated over the course of 5 months. At the presentation, he needed at least one person to help him walk on flat surfaces and could not climb stairs at all. Additionally, his family reported that his voice had become muffled in recent months. Figure. 1 shows a timeline of events illustrating the progression of disease, treatment, and follow-up examinations. There was no history of cognitive impairment, abnormal behaviors, social disinhibition, labile mood, aggression, or hallucinations, either visual or auditory. He reported neither neck or back pain nor any changes in sensations of touch, pain, or temperature. There was no history of vertigo, syncope, lightheadedness, palpitations, increased or decreased sweating, urinary or fecal incontinence or retention, and sexual dysfunction. He did not have a history of drooling, facial weakness, diplopia, drooping of eyelids, or any other visual problems. He also had no difficulty chewing, swallowing, breathing, or olfaction. The patient

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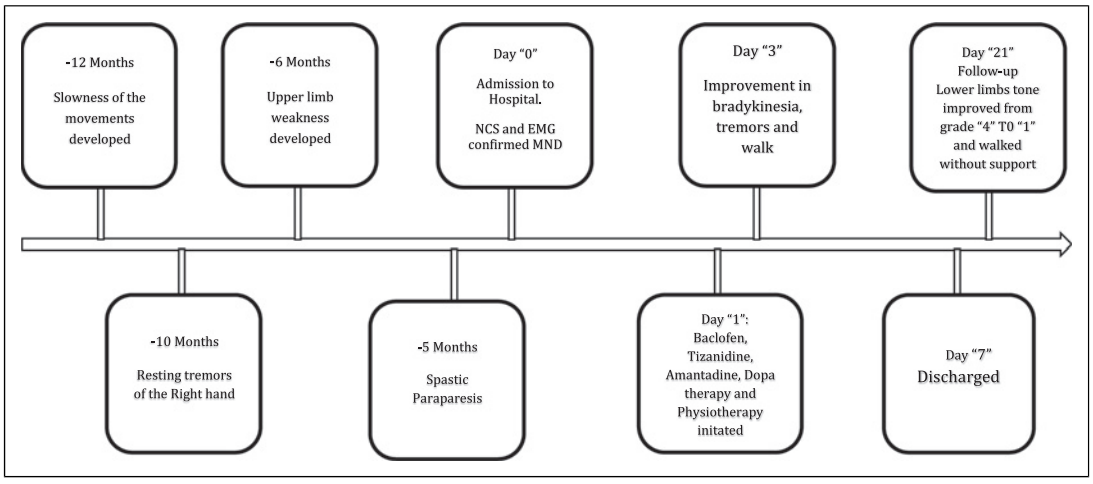

Fig. 1. Timeline of events: sequential depiction of notable clinical events, diagnostic procedures, therapeutic interventions, and follow-up assessments.

was normotensive, non-diabetic, and previously healthy, with no history of related or unrelated hospitalizations. Aside from a two-pack-year smoking history, there was no history of alcohol or substance abuse. He had no dietary restrictions and consumed poultry, vegetables, and red meat on a regular basis. There was no history of similar symptoms in the family.

During the general physical examination, the patient had normal vital signs with no evidence of orthostatic hypotension. On neurological evaluation, the patient exhibited several signs of Parkinsonism. He had muffled voice and masked, expressionless face. There were resting tremors in the right hand as well as cogwheel rigidity in the right wrist, which was exacerbated with distraction maneuvers. Bradykinesia was observed on hand and heel tapping maneuvers. A thorough examination of the motor system indicated significant atrophy of the small muscles in both hands. Atrophy of tongue muscles and fasciculations were also noticed. The Modified Ashworth scale indicated grade 4 spasticity in the lower limbs, while power was graded 4 out of 5 (MRC scale) proximally and distally in all limbs. Deep tendon reflexes were reduced (+1) in the upper limbs, with the exception of the right triceps reflex, which was graded +3, whereas exaggerated reflexes (+3) were found in the lower limbs, with flexor plantar responses bilaterally. The clinical findings of LMN and UMN in the upper and lower limbs, as well as in the tongue, were consistent with a definite clinical diagnosis of ALS. The patient was sluggish to initiate walk and took slow, short, shuffling steps with limited arm swing and trouble turning; also, the retropulsive pull test was positive. There were several primitive reflexes present, including palmomental, snout, and glabellar reflexes with an exaggerated jaw jerk. Pursuit and saccadic eye movements, as well as cerebellar function, were all normal. The sensory system examination was also unremarkable. The patient scored 28/30 on cognitive assessment using both MMSE and MoCA, indicating normal cognitive function. The remainder of the systemic examination was unremarkable.

All routine baseline blood tests, including muscle enzymes and inflammatory markers, were within normal limits. HbA1c and thyroid function tests were also within normal limits. Serum electrophoresis, CT-chest, abdomen, pelvis, and bone scans, performed for the paraneoplastic diseases were unremarkable. Radiological investigations included X-rays of the cervical spine, CT brain, and MRI of the brain, craniocervical junction, and cervical spine with contrast. Apart from the incidental finding of a non-compressive central disc bulge at CC5–6 level on the MRI, they were all unremarkable for any pathology. However, electromyography

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Table 1. Summary of electromyography (EMG) results and conclusions

Muscle tested	Response
Right vastus lateralis	No spontaneous activity. Mild reduction of recruitment pattern with motor units of high amplitude up to 3.5 mV, recruited at high firing rate
Left rectus femoris	No spontaneous activity. Moderate reduction of recruitment pattern with motor units of normal amplitude and normal duration, recruited at a high firing rate
Left first dorsal interosseous	Fasciculation, fibrillation and positive sharp waves. Marked reduction of recruitment pattern with motor units of normal amplitude and normal duration, recruited at high firing rate
Right pronator teres	Fasciculation, fibrillation and positive sharp waves. Moderate reduction of recruitment pattern with motor units of high amplitude up to 6.7 mV, recruited at a high firing rate
Right biceps	No spontaneous activity. Marked reduction of recruitment pattern with motor units of high amplitude up to 6.7 mV, recruited at a high firing rate
Right thoracic paraspinal	No spontaneous activity. Moderate-marked reduction of recruitment pattern with motor units of high amplitude up to 4.0 mV, recruited at normal firing rate
Right genioglossus	No spontaneous activity. Mild-moderate reduction of recruitment pattern with motor units of high amplitude up to 3.3 mV, recruited at a high firing rate
Report: Needle examination reveals early neurogenic changes in tested muscles of limbs, tongue, and thoracic paraspinal muscle	
Conclusion: This electrophysiological study is suggestive of anterior horn cell disease	

revealed early neurogenic changes suggestive of anterior horn cell disease. Table 1 summarizes electromyography results and conclusions. Functional imaging and genetic testing were not available in Pakistan and therefore could not be performed.

Given the mix UMN and LMN findings on examination, we considered ALS, cervical spondylitic myelopathy, and syringomyelia as potential differentials. However, the absence of neck or radicular pain and the normal cervical spine on the MRI ruled out cervical spondylitic myelopathy, while the lack of dissociative sensory loss or sphincter involvement, as well as normal neuroimaging, excluded syringomyelia. Normal brain MRI, liver function tests, the absence of drug history or toxin exposure, and no family history of extrapyramidal symptoms ruled out major causes of secondary Parkinsonism. After a thorough review of the patient's medical history, physical examination that revealed symptoms consistent with Parkinson's disease, mixed upper and lower motor neuron features, and the necessary investigations, the final diagnosis of PD-ALS complex was established.

This was a challenging case to diagnose due to the coexistence of extrapyramidal and pyramidal symptoms. The extrapyramidal symptoms were more prominent, so the marked lower limb stiffness could have been misinterpreted as rigidity instead of spasticity in this scenario. The exaggerated deep tendon reflexes in the legs could have been attributed to simple anxiety. Moreover, the plantar response was already bilaterally downgoing. Given that the lower motor neuron-type weakness of the upper limbs was subtle, it would have been easy to misdiagnose him as a case of Parkinson's disease. It was the atrophy of small muscles of both hands and tongue fasciculations which raised suspicion on a motor neuron disorder, and prompted us to perform electrodiagnostic tests. The results of these were the key to

reaching a diagnosis of motor neuron disease. Furthermore, there is lack of availability of functional neuroimaging or genetic testing for either ALS or idiopathic Parkinson's disease in Pakistan. Moreover, the lack of functional neuroimaging or genetic testing for ALS or idiopathic Parkinson's disease in Pakistan was our greatest obstacle. However, neurological examination assisted us in determining the presence of parkinsonism features with mixed motor neuron findings, which initially led us to suspect Amyotrophic plus syndrome. Additionally, it was the positive outcome of dopaminergic therapy coupled with unilateral symptoms that prompted us to think about idiopathic Parkinson's disease. In retrospect, the onset of Parkinson's disease symptoms before motor neuron symptoms and the significant response to dopaminergic therapy paved the way for the PD-ALS complex or Brait-Fahn-Schwartz disease.

After diagnosis, the patient was initiated on baclofen 10 mg thrice a day, tizanidine 4 mg once a day, carbidopa/levodopa 25 mg/250 mg one quarter tablet four times a day, and amantadine 100 mg twice a day. Riluzole was not initiated since the patient was in King's clinical stage 3, had an FVC of 88%, and was experiencing financial difficulties. Regular physiotherapy was also commenced. Extrapyramidal symptoms improved with the levodopa trial, but stiffness in the lower limbs persisted. Therefore, doses were modified: baclofen 20 mg thrice a day, tizanidine 4 mg twice a day, and carbidopa/levodopa 25 mg/250 mg half tablet four times a day. Sertraline, 50 mg once nightly, was also added. On these doses, he reported decrease in stiffness. He was discharged on these doses and instructed to return for a follow-up visit after 2 weeks, or earlier if he developed any distressing symptoms. He was also counseled at length regarding the progression and prognosis of his disease.

Two weeks later, he was clinically assessed for both extrapyramidal and pyramidal symptoms. There was significant improvement in bradykinesia and resting tremors. Spasticity in the lower limbs had also improved from grade 4 to grade 1 on the modified Ashworth scale. He was now able to walk without the support of a person or a walking stick on flat ground and could climb stairs with one-person support. He was able to hold objects, comb his hair, and button clothes using his left arm and hand, but weakness and wasting persisted on the right side.

Discussion

This case report presents a rare co-occurrence of idiopathic Parkinson's disease with ALS. The overlap between parkinsonism and motor neuron disease without additional neurological symptoms was first identified by Kenneth Brait and Stanley Fahn. Our patient exhibited signs and symptoms that were consistent with the clinical diagnosis of Parkinson's disease and ALS. Parkinsonian features have also been documented in ALS, with a frequency ranging from 5% to 17% and designated as ALS-plus parkinsonism. There is evidence of reduced striatal dopaminergic function in ALS patients due to neuronal degeneration in the substantia nigra and globus pallidus [8]. When associated with ALS, parkinsonian symptoms develop after the manifestation of ALS and have been referred to as slowness of gait with postural instability, rigidity, and bradykinesia, with an overall poor response to levodopa therapy [9]. Unlike it, the extrapyramidal symptoms in our patient exhibited a distinct clinical progression prior to the onset of motor neuron disease features. Moreover, the response to levodopa therapy suggested that the patient's Parkinsonian features were due to Brait-Fahn-Schwartz disease and not ALS-plus.

There have been several reported cases where ALS and Parkinsonism coexist with dementia. Historically, most cases of the ALS-PD-dementia complex have been endemic in Guam and the Kii Peninsula of Japan. This complex is believed to be caused by

environmental factors, such as exposure to toxins produced by cyanobacteria or the consumption of cycad seeds [10]. Whereas genetics plays a role in the case of Brait-Fahn-Schwartz disease, with mutations in SOD1, TAR DNA-binding protein, and altered tau protein metabolism being implicated in its pathogenesis. Unlike the Gaum complex of ALS-PD-dementia, Brait-Fahn-Schwartz disease can occur anywhere in the world, and patients typically have normal cognition. Additionally, patients with Brait-Fahn-Schwartz disease respond persistently to dopaminergic therapy, as was observed in our patient [11].

In Pakistan, Parkinson's disease diagnosis is primarily based on clinical examination and the Movement Disorder Scale since functional imaging is not available. 7-T MRI and SPECT scans can reveal typical Parkinson's disease features, including loss of nigral hyperintensity and reduced striatal uptake [12]. Diagnosing overlap syndromes can be challenging in regions where such cases are uncommon. In our case, the extrapyramidal symptoms overshadowed the less prominent ones, making the diagnosis difficult. It was through meticulous history-taking, detailed physical examination, and appropriate electrodiagnostic studies that we arrived at our final diagnosis of the PD-ALS complex and initiated appropriate treatment. This case highlights the importance of understanding when Parkinson's disease symptoms begin to appear in patients previously diagnosed with ALS-plus, as well as the need to initiate dopaminergic therapy in patients exhibiting PD features prior to developing ALS features. As there is currently no cure for ALS, the primary goal of treatment is to improve the patient's quality of life, which we were able to achieve in this case.

There are several limitations that the authors would also like to acknowledge. The patient being lost to follow-up prevented us from assessing any late complications of motor neuron disease or idiopathic Parkinson's disease. Additionally, the lack of genetic and functional imaging studies is another limitation, which could have provided further insight into the underlying disease mechanisms and helped to confirm the diagnosis of the PD-ALS complex. However, our case is a valuable addition to the existing literature as it represents the first reported instance of levodopa-responsive Parkinson's disease and amyotrophic complex as Brait-Fahn-Schwartz disease in Pakistan. This presents new avenues for research, including functional imaging and genetic studies, in a previously understudied population, ultimately leading to a greater understanding of this disease complex.

Conclusions

This case study highlights the unique co-occurrence of Parkinson's disease and ALS as Brait-Fahn-Schwartz disease and emphasizes the importance of understanding the relationship between these two conditions. Early intervention with dopaminergic therapy can improve disease outcomes in patients who present with Parkinson's disease features before the onset of ALS symptoms. Additionally, the case underscores the value of modest symptomatic therapy in improving the quality of life of patients with motor neuron disease at an early stage. These findings suggest the need for research to better understand the underlying pathophysiology of this complex condition and to identify new and effective treatments to manage its symptoms, including the use of biomarkers for early diagnosis and monitoring ("The CARE-Checklist" completed by the authors for this case report is attached as an online suppl. file; for all online suppl. material, see https://doi.org/10.1159/000532092).

Patient Perspective

Before this treatment I relied on my family for everything, I could not even go to the toilet by myself. I felt like a burden on them. Now I am much more independent, which is a huge relief for me. I have been informed that no cure exists for my condition, but these medicines and exercises have made daily life much easier for which I am very grateful.

Statement of Ethics

The studies involving human participants were reviewed and approved by the Ethical Review Committee, Mayo Hospital Lahore, with letter no. 464/RC/KEMU dated October 27, 2022. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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All authors have declared that they have no financial relationships at present or within the previous 3 years with any organizations that might have an interest in the submitted work.

Author Contributions

Ayesha Aslam contributed significantly to the conception, design, and acquisition of data for this research study. Eisham Sarmad and Ahmad Nawaz were responsible for drafting and editing the manuscript, as well as critically revising it for important intellectual content. Ahsan Numan provided final approval for the version of the article to be published. Azba Ahmad and Muhammad Aarish have made significant contributions to the critical revision of the manuscript. All authors made substantial contributions to the article and approved the submitted version.

Data Availability Statement

The authors will freely share the raw data supporting the article's results. Further inquiries can be directed to the corresponding author.

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