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Article

The Biochemical Changes in Parkinsonism-Dementia-Exploring Theamyotrophic Lateral Sclerosis Complex: A Clinical Case Study and Implications for Diagnosis and Treatment

Ahmed Kareem Thamer[1], Bahaulddin Jafar Seger[2], Gufran Abbas Isewid[3], Nahid Sabah Aldin Saber[4]

1. Assistant Lecturer Pharmacy College, University of Al-Qadisiyah, Al-Diwaniya, Iraq
Correspondence: ahmed.kareem@qu.edu.iq
2. Assistant Lecturer Pharmacy College, University of Al-Qadisiyah, Al-Diwaniya, Iraq
Correspondence: bahaulddin.jafar@qu.edu.iq
3. Assistant Lecturer Pharmacy College, University of Al-Qadisiyah, Al-Diwaniya, Iraq
Correspondence: Gufran.abbas@qu.edu.iq
4. Assistant Lecturer Pharmacy College, University of Al-Qadisiyah, Al-Diwaniya, Iraq
Correspondence: Nahid.Sabahaldin@qu.edu.iq

Abstract: The Parkinsonism-Dementia-Amyotrophic Lateral Sclerosis (PD-ALS) complex, initially identified in Guam, poses diagnostic challenges due to its rarity. This study presents a clinical case to elucidate the nosological and pathogenetic implications of this neurodegenerative disease, particularly in populations where this association is unexpected. A patient of Iraqi origin manifested systemic symptoms evolving over 5 years, followed by cognitive alterations and subsequently developing gait disturbances and motor symptoms suggestive of parkinsonism with atypical features. Motor neuron disease signs were also observed, confirmed by extension studies revealing the involvement of both upper and lower motor neurons. A mutation in the POLG gene associated with mitochondrial depletion syndrome was identified. Diagnosing the PD-ALS complex remains clinically challenging, with molecular mechanisms yet to be fully understood. Common genes associated with parkinsonism and amyotrophic lateral sclerosis have been ruled out, and attempts to localize the locus have yielded inconclusive results. Unfortunately, the prognosis remains fatal, and there are no disease-modifying treatments available. This case underscores the importance of further research into this complex neurodegenerative disease and the need for improved diagnostic and therapeutic strategies. The association between parkinsonism-dementia and ALS is an infrequent entity and difficult to diagnose clinically for inexperienced doctors, for whom it represents a diagnostic challenge. Due to the unfavorable prognosis of the disease and the functional limitation it confers, many times, it is not possible to conclude the diagnosis or provide adequate follow-up. The importance of knowing the clinical data of motor neuron disease and the warning of Parkinsonism has made it possible to standardize the diagnostic conduct from the first evaluation.

Keywords: Parkinsonism, Dementia, Amyotrophic Lateral Sclerosis, Neurodegenerative Disease

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1. Introduction

Parkinson's disease is the best-characterized hypokinetic movement disorder. It is essential to differentiate it from atypical parkinsonism, which is a clinical form with a more progressive and degenerative course. Similarly, amyotrophic lateral sclerosis (ALS) is a motor neuron disease that can be accompanied by parkinsonism in 5-17%. The association between the two diseases is well documented and was first described in the islands of Guam, where it was found; it is known as Lytico-Bodig disease [1].

This is consistent with its translation into the English language: lytic due to paralysis attributable to ALS, bodega attributable to "laziness" within the Parkinsonian spectrum. This pathology had its peak incidence in the 1950s. We currently find most cases reported in Guam, New Guinea, and, we found few reported cases. His age at presentation ranges from 54 to 74 years. The disease remains degenerative and fatal without disease-modifying treatments [2].

2. Materials and Methods

A 73-year-old man of Iraqi origin with a history of a mother diagnosed with Alzheimer's dementia with a negative genetic panel, a brother diagnosed with ALS, and a sister diagnosed with Parkinson's disease. Progressive symptoms began in 2016 and were characterized by progressive symptoms of hyposmia, hearing loss, constipation, and insomnia, which warranted evaluation by an otolaryngologist and an audiologist without a diagnostic conclusion. In 2020, family members noticed that the patient had problems with episodic memory, forgetting objects of daily life, and problems with profit in business (trade) [3].

These symptoms were progressive until the patient began to have limitations in daily activities, such as driving, changing speeds, and leaving home. At the end of that year, the patient began to present distal muscle weakness, manifested when opening bottles and brushing his teeth, which progressed in an insidious, non-fluctuating manner without a predominance of schedules [4].

In January 2021, the patient began to have gait disorders, which led her to frequent falls, up to more than 6 times a week, due to postural instability. The patient came for evaluation in May. A 16-point MoCA test was performed with alterations in speech fluency and sentence repetition in abstraction, deferred memory, and visuospatial and dysexecutive problems. Luria's test came back positive.

3. Results

The patient presented with a hypomimic facial expression, hypophonic, discontinuous and slow speech and a decreased gag reflex, generalized rigidity predominantly on the left, generalized hypotrophy, bradykinesia predominantly on the left, generalized strength 4/5, muscle stretch reflexes 3/4, abdominocutaneous reflexes abolished, Hoffmann and Trömner signs present bilaterally, bilateral extensor plantar response, lower extremity fasciculations evoked by jumping, gait with short steps, freezing of gait when turning, positive traction test (postural instability). Managed with levodopacarbido for a gradual dose. At follow-up after 3 months, the patient with these results, magnetic resonance imaging (MRI) of the brain was performed (Figure 1) [5].

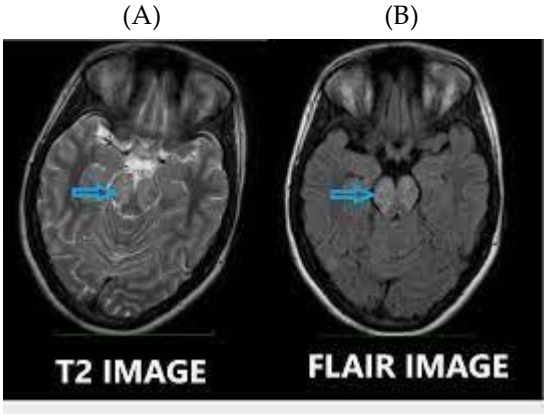

Figure 1. Digital T1-weighted and Axial-weighted FLAIR Magnetic Resonance Imaging, (A) A decrease in volume is observed at the mesencephalic level, with the volume of the pons preserved, and at the cortical level, there is an increase in the diameter of the sulci and fissures. (B) Mesencephalic atrophy is seen, concavity in the mesencephalic tegmentum (blue arrow)

Neuroconduction velocity (NCV) showed thoracic limb motor axonal neuropathy related to atrophy and sensory neuroconduction without alterations. Electromyography (EMG) showed data of active denervation (increased insertion activity, fibrillation potentials, fasciculation) and chronic reinnervation (polyphasic motor unit action). potentials and low recruitment at maximum contraction) in the 5 body segments, which is compatible with motor neuron disease (Figures 2, 3, and 4) [6].

EMG showed increased insertion activity in the bilateral deltoid, biceps, triceps, common digital extensors, and bilateral lingual muscles. Abundant fibrillation potential was observed, and fasciculation predominated in the thoracic limb muscles. Polyphasic, high-amplitude activation of the motor unit action potential (PAUM) was observed during contraction. At maximal contraction, decreased recruitment was observed in most muscles evaluated [7].

Nerve	Stimulation site	Recording site	Day 5						Day 12					
			Distal latency (ms)		Amplitude (mV or μV)		Conduction velocity (m/s)		Distal latency (ms)		Amplitude (mV or μV)		Conduction velocity (m/s)	
			RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT
Median (M)	Wrist	APB	3.2	4.1†	6.0	4.5*†			3.4	3.9	2.0†	2.3†		
	Elbow				5.5	2.4*†	48.5†	48.0†			2.0†	2.3†	54.3	49.2
Ulnar (M)	Wrist	ADM	2.7	2.6	3.2*†	3.5†			2.7	2.9	0.3†	1.2†		
	BE				1.7*†	3.2†	58.4	56.5			0.3†	1.2†	58.7	55.0
	AE				0.5†	1.7†	53.3	43.6†			0.3†	1.2†	60.0	50.5
Peroneal (M)	Ankle	EDB	4.7	4.3	7.5	8.1			3.9	3.6	2.5†	2.1†		
	Fibula head				6.8	7.7	39.5	39.2			2.3†	1.8†	45.2	44.5
	PF				3.6	6.7	42.7	39.2			2.1†	2.0†	50.5	48.0
Tibial (M)	Ankle	AH	4.9	5.3	21.9	20.7			3.3	3.5	2.5†	3.6†		
	PF				18.5	12.8	34.0†	37.3†			1.9†	2.4†	43.5	43.9
Median (S)	Digit II	Wrist	2.8	3.0	44.0	48.4	40.9	42.1	2.6	2.9	44.9	16.2	44.2	41.8
	Wrist	Elbow	3.6	3.6	45.2	45.1	50.7	50.7	3.6	3.6	51.1	46.1	52.1	51.5
Ulnar (S)	Digit V	Wrist	2.4	2.6	17.6	22.4	40.9	39.2	2.4	2.8	18.8	11.4	42.9	39.1
	Wrist	BE	3.3	3.5	63.9	70.9	54.0	51.6	3.2	3.2	47.6	78.1	57.3	54.2
	BE	AE	4.8	4.8	18.1	14.1	58.4	58.4	4.7	4.8	22.7	16.1	60.2	57.4
Sural (S)	Lateral malleolus	Lateral calf	3.7	3.8	38.7	22.2	32.5	31.6	2.7	3.1	23.1	19.5	45.2	39.1

Figure 2. Sensory neuron conduction velocity

	n = 154			n = 62	n = 92
Median	**Total***	**15th perc****	**75th perc****	**Men**	**Women**
Latency	3.2 ± 1	2.8	3.4	3.2 ± 0.9	3.2 ± 1
Amplitude	9.7 ± 6.6	6.5	11.8	9.4 ± 6.4	9.8 ± 6.8
Velocity	59 ± 8.2	54	62	59 ± 8.6	58.7 ± 8
Ulnar	**Total**	**15th perc**	**75th perc**	**Men**	**Women**
Latency	3 ± 0.6	2.7	3.2	3 ± 0.6	2.9 ± 0.6
Amplitude	9.2 ± 4.6	6.8	10.9	9.2 ± 4.4	9.2 ± 4.6
Velocity	63.6 ± 14.6	56	68	62 ± 10.8	64 ± 16.4
Tibial	**Total**	**15th perc**	**75th perc**	**Men**	**Women**
Latency	3.4 ± 1	3	3.6	3.5 ± 1.2	3.3 ± 0.8
Amplitude	14 ± 9	9.2	17	13 ± 7.2	15 ± 10
Velocity	49 ± 7.6	45	51	49 ± 8.4	48.8 ± 7
Peroneal	**Total**	**15th perc**	**75th perc**	**Men**	**Women**
Latency	3.4 ± 1.4	2.8	3.7	3.6 ± 1.4	3.3 ± 1.4
Amplitude	7.36 ± 5.8	4.2	9.4	7.5 ± 6	7.3 ± 5.6
Velocity	51 ± 9	47	54	51.6 ± 9.2	51 ± 8.6

Figure 3. Speed from motor neuroconduction. Study of normal sensory neuro conduction in all 4 extremities. Motor neuro conduction with moderately reduced amplitudes in the thoracic extremities, compatible with the axonal pattern

EMG showed increased insertion activity in the bilateral deltoid, biceps, triceps, common digital extensors, and bilateral lingual muscles. Abundant fibrillation potential was observed, and fasciculation predominated in the thoracic limb muscles. Polyphasic, high-amplitude activation of the motor unit action potential (PAUM) was observed during contraction. At maximal contraction, decreased recruitment was observed in most muscles evaluated [8].

EMG Summary Table											
			Spontaneous				**MUAP**				
Muscle	**Nerve**	**Roots**	**IA**	**Fib**	**PSW**	**Fasc**	**Recruit**	**Effort**	**Dur.**	**Amp**	**PPP**
R. Deltoid	Axillary	C5-C6	Increased	2+	3+	None	Reduced	N	N	Mod Incr	Rare
R. Biceps brachii	Musculocutaneous	C5-C6	Increased	2+	2+	Many	Reduced	N	Mod Incr	Mod Incr	N
R. Abductor pollicis brevis	Median	C8-T1	Increased	2+	3+	Rare	1MUP	N	N	Gr Incr	N
R. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	Increased	1+	3+	Few	N	N	N	N	Few
R. Gastrocnemius (Medial head)	Tibial	S1-S2	Increased	1+	1+	Rare	N	N	N	N	N
R. Vastus medialis	Femoral	L2-L4	N	None	None	Rare	N	N	N	N	N
R. Vastus lateralis	Femoral	L2-L4	N	None	None	None	N	N	N	N	N
R. T10 paraspinal	Spinal	T10-	Increased	None	1+	Rare	N	N	N	N	N
L. Deltoid	Axillary	C5-C6	Increased	2+	2+	Rare	Reduced	N	SI Incr	N	N
L. First dorsal interosseous	Ulnar	C8-T1	Increased	2+	2+	Rare	Reduced	N	SI Incr	Mod Incr	N

Figure 4. Electromyography of the 4 extremities, axial segment, and bulbar region

4. Discussion

The patient was lost to follow-up for one year. Upon returning for evaluation, he was bedridden and aphasic, with increasing signs of parkinsonism and motor neuron syndrome. It was decided to perform a negative genetic panel for C9ORF72 and 143 other

genes involved in neuromuscular and neurodegenerative diseases, including the VCP genes. MAT3, associated with ALS, NOTCH3, associated with frontotemporal dementia, without alterations. A pathogenic variant finding has been reported for the POLG gene: C.2209G>C, p.(Gly737Arg), related to autosomal dominant and recessive mitochondrial depletion syndrome. A genetic counseling session was held, and the patient was informed. In May 2022, the patient presented with dysphagia arrived in a wheelchair, and was then sent to undergo gastrostomy. The table shows a series of reported cases of association between parkinsonism-dementia and ALS [9], [10].

Parkinsonism-dementia association and ALS are degenerative diseases of the central nervous system (CNS) that share similar pathophysiological mechanisms and can develop in the same patient. The relationship between these disorders was first observed in Guam. In this location, it was 100 times higher than in any other population, and many of these patients had an association with the parkinsonism-dementia complex [11].

Extrapyramidal signs and symptoms have been found in ALS due to dysfunction nigrostriatal.55-Hydroxytryptamine, also called serotonin, produced in the raphe nucleus, is involved in the regulation of physiological events such as motor control, the sleep-wake cycle, nociception, cardiorespiratory functions, body temperature, consciousness, learning, and memory [12].

Serotonin receptors 5-HT1A/1B and 5-HT2A-C are crucial in ALS and atypical parkinsonism. The first is located in the hippocampus, amygdala, hypothalamus, and basal ganglia. The 5-HT1B receptor is found primarily in axonal terminals of the basal ganglia and substantia nigra, as well as in presynaptic GABA terminals and the thalamostriate and corticostriate, glutaminergic neurons. In Parkinson's disease, loss of up to 56% of serotonergic neurons occurs, especially in the basal ganglia, hypothalamus, hippocampus, and prefrontal cortex [13], [14].

After 70 years, the etiology remains unclear. There are many hypotheses, including cycad toxin and toxic beta-methylamino-L-alanine. Pathologically, it is a multiple proteinopathies composed of Au, alpha-synuclein, and TDP-43. These findings imply that one or more triggers may induce this disease in patients with genetic predisposition [15].

Our patient's initial symptoms were the apparent prodromal symptoms of Parkinson's disease and subsequently, cognitive impairment; however, due to the lack of histopathological studies, it is difficult to clarify whether the cognitive alterations were due to the Parkinsonism-dementia complex and ALS or part of the ALS association with frontotemporal dementia. In the first case, the association manifests itself. Approximately 5% of cases appear. overlapping neuropathological findings, with neurofibrillary tangles containing proteins in the spinal cord and brain. Although the association between ALS and familial frontotemporal dementia, related to the MAPT gene or without mutations, is currently recognized as closer. Our patient had a hereditary family history of Alzheimer's dementia; However, clinical and genetic phenotypes today vary significantly from those of 15 years ago [16].

Table 1. Series of reported cases of parkinsonism-dementia association and ALS in the world

AUTHOR(S) AND YEAR	COUNTRY	POPULATION	AGE	RESULTS
Hiranodal 1961	Guam Islands	47 cases of parkinsonism, cognitive impairment and ALS.	32-66 years Average: fifth and sixth decades of life.	Death occurs within an interval of 3 to 5 years; 7% of deaths among Guam's adult population. Clinical features:

				dementia, parkinsonian syndrome and motor neuron involvement.
Kimurattal 1982	NewWestern Guinea	97 cases of ALS, 19 cases of Parkinson's disease, and 18 of poliomyeloradiculitis.	The mean ages at the start are 33, 43, and 26 years.	Evaluated population of 7000 inhabitants, of which 134 were affected with the disease described. No manufactured products (including metals, ceramics, textiles, petrochemicals, paints, dyes or solvents) were available to them.
Garudottal 1985	Guamy IslandsNewWestern Guinea	Population of Guam Islands of New Guinea, about 3200	people were evaluated.	From the fourth to the seventh decade of life. Decrease in the incidence of patients with parkinsonism, dementia, and ALS born after 1920.
Bokumiya et al., T2001A2012	Papua, Indonesia	cases of parkinsonism	Median fifth to sixth decade of life.	46 cases consisted of 17 definite, probable cases of ALS 3 w, with dementia, 13 overlapping cases of ALS and parkinsonism 5 w, with dementia, 16 cases of parkinsonism, and one with added dementia. Notable decrease compared to 30-35 years ago.
Mannone, 2001	Italy, Palermo	2 cases of ALS with Parkinson's disease.	Man 55 and woman 69 years old.	2 patients who developed Parkinson's disease and ALS. During its

	evolution, superposition was a distinct nosological entity.

Based on the diagnostic strength of the clinical evaluation, patients can be classified as definite ALS, probable ALS, or possible ALS. This patient met the criteria for defined ALS based on clinical evidence and electromyography of upper or lower motor neurons in 3 or more regions. Due to the rarity of the Guam complex, no evidence-based diagnostic criteria exist, but consensus exists. A patient must meet the criteria for ALS, parkinsonism, and cognitive impairment, in addition to genetic alterations [17], [18].

Our patient had a poor response to levodopa. An adequate response to levodopa is a supportive criterion for the diagnosis of Parkinson's disease based on the 2015 MDS. Therefore, it reinforces that this case is a form of atypical parkinsonism. The association between patients with Parkinson's disease and patients who have developed ALS, known as Brait-Fahn-Schwartz disease, in which several standard pathogenetic bases are shared, is well recognized [19].

Hereditary spastic plegia, spinocerebellar atrophies, and frontotemporal lobe degeneration are motor neuron disorders with Parkinsonism. However, in ALS, parkinsonian symptoms are present in a range from 5 to 17%, and the most frequent symptoms are postural instability, rigidity, and bradykinesia [20].

4.1. Neuroimaging And Neurophysiology Studies

Due to the clinical findings, it is necessary to perform MRI studies of the neuraxis to exclude typical findings of atypical parkinsonisms such as the Hot-Cross-Bun sign, bilateral putaminal hyperintensity, colliculus and midbrain atrophy, frontoparietal asymmetric cortical atrophy, etc. At present, no signs suggestive of the Parkinson-dementia association with ALS can be established by MRI, so the findings are often related to the type of parkinsonism each patient presents. In a study conducted on the Kii Peninsula, mild to severe atrophy of the frontal and temporal lobes was the predominant manifestation [21], [22].

In motor neuron disease, MRI helps us rule out an alternative explanation, such as cervical radiculomyelopathy or some other structural cause, which may explain the lower and upper motor neuron results. Single photon emission computed tomography (CT) can be performed in these patients, highlighting the decrease in cerebral blood flow in the frontal and temporal lobes [23].

As a diagnostic complement and having clinical findings of motor neuron disease, it is necessary to perform VCM and EMG studies, which are valuable tools to confirm the absence of sensory involvement and the neurogenic pattern of the disease [24].

4.2. Differential Diagnosis

When you have a patient with isolated findings of diffuse weakness, you should consider myopathy, a defect in neuromuscular junction transmission, polyradiculopathy, or predominantly motor polyneuropathy. Myopathy can be excluded due to failure to increase creatine kinase (<1000 U/L) with pre-involvement. The existence of sensory involvement in nerve conduction studies would indicate an inherited acquired polyneuropathy. If the pattern also had demyelinating features, it would suggest chronic inflammatory demyelinating polyradiculoneuropathy or multifocal motor neuropathy, which often constitute differential diagnoses [25], [26].

Other processes that must be excluded are infectious (varicella-zoster virus, cytomegalovirus, West Nile virus, Lyme disease, HTLV-1/HTLV-2, or HIV) or neoplastic (lymphoma or carcinomatous neoplasm). As regards parkinsonism, generally among the atypical forms that present with dementia, there is supranuclear gaze palsy, which has 7 clinical subtypes. All are accompanied by dementia, in addition to there being a variety that shares symptoms and signs with ALS, corticobasal degeneration, which in this case is accompanied by a behavioral variant of frontotemporal dementia or primary progressive aphasia. Due to the visuospatial alterations, language, and positive Luria test, it seems that our patient mainly had a history of dementia [27].

4.3. Guam Complex Genetics

Finally, the Guam complex is believed to share genetic and environmental components (cycads, mineral deficiency, infectious agents, heavy metal toxicity) due to the decreased incidence of disease in these areas and the agricultural changes that have also occurred in the area. However, it is not yet possible to give a shared pathogenetic explanation. Analysis of several genes in this association was reported primarily on the C9ORF72 hexanucleotide repeat expansion in 89 individuals from the Guam/Mariana Islands population with ALS and frontotemporal dementia, and no correlation was found [28], [29].

Also, expansions and mutations of SOD1 were reported in patients with parkinsonism-dementia and ALS from the Kii Peninsula and in other relatives presenting with ALS, frontotemporal dementia, Parkinson's disease, and ALS-frontotemporal dementia. Mutations in the TDP43 and DJ-1 genes have been identified in multigenerational families of parkinsonism-dementia and ALS. In addition to these association genes, genes associated with atypical parkinsonism and other neuromuscular diseases must be excluded. In the case of our patient, the POLG gene is associated with mitochondrial depletion syndrome. It presents with multiple important clinical phenotypes, such as sensory ataxic neuropathy with gastrointestinal dysmotility and ophthalmoplegia, while slowly progressive dementia and parkinsonism have been found in adults [30], [31].

Although this alteration may be related to clinical manifestations, no cases have been reported. It is recommended to always carry out genetic tests in cases of ALS and complex parkinsonism-dementia due to the high certainty of transmission to other relatives. However, in cases of ALS with associated dementia but without first or second-degree relatives, it is not advisable to perform these tests because the majority of cases are due to sporadic ALS [32].

The disease continues to have a fatal course, without changing treatments and with respiratory and infectious complications that will lead to death. The prognosis is characterized by a progressive disease, with a survival of 3 to 5 years and, in some cases, up to 10 years of life after the onset of symptoms. In this case, the treatment improves the patient's quality of life. May have, in addition to the control of neuropsychiatric manifestations. It is essential always to remember the use of genetic tests in the Guamy complex and other forms of ALS since the possibility of gene therapy is foreseen in the future [33], [34].

5. Conclusion

The association between parkinsonism-dementia and ALS is an infrequent entity and difficult to diagnose clinically for inexperienced doctors, for whom it represents a diagnostic challenge. Due to the unfavorable prognosis of the disease and the functional limitation it confers, many times, it is not possible to conclude the diagnosis or provide adequate follow-up. The importance of knowing the clinical data of motor neuron disease and the warning of Parkinsonism has made it possible to standardize the diagnostic conduct from the first evaluation.

The patient has a high familial genetic load; his mutation is autosomal dominant and recessive, with a high probability of transmission to another family member. Therefore, the importance of genetic diagnosis is evident. Currently, the association between Guam and Kiri is highly disputed, so we cannot establish that any relationship exists with Baghdad city in an Iraqi location. We consider the reporting of this case relevant, given that the association between these diseases has drastically decreased since their appearance. Furthermore, reports of overlapping diseases predominate in Baghdad city of Iraq, but there are no cases currently reported in the literature from the Guam complex. With this review, we hope to encourage clinicians to adopt a rapid diagnostic approach.

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