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CASE REPORT

Association of PSEN1 Mutation with Dementia with Lewy Bodies without Features of Alzheimer's Disease

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ABSTRACT

Dementia with Lewy bodies affects 0.4% of people over the age of 65 each year, making it the second most common neurodegenerative form of dementia following Alzheimer's disease. It is more commonly diagnosed over the age of 50, and in men more than in women. As a synucleinopathy, in which alpha-synuclein inclusions accumulate in neurons, dementia with Lewy bodies shares many clinical features with idiopathic Parkinson's disease, including bradykinesia, visual hallucinations, and cognitive decline. Neuroimaging in dementia with Lewy bodies reveals occipital and parietal atrophy and hypometabolism. Some cases of dementia with Lewy bodies and idiopathic Parkinson's disease have been shown to be associated with genetic mutations, such as in the GBA gene. In this case report, we present a unique case of a young man who started showing clinical features of dementia with Lewy bodies at the age of 43, with further confirmation of the diagnosis in neuroimaging studies. However, his genetic test results revealed the presence of a PSEN1 mutation, which has been described with Alzheimer's disease, even though he did not show typical clinical or neuroimaging findings that matched with Alzheimer's disease. This report reveals a potential unique association of the PSEN1 mutation with early-onset dementia with Lewy bodies, indicating that we may have an incomplete understanding of the function of such genes in cognitive development, as well as the phenotypic presentations of dementia with Lewy bodies, idiopathic Parkinson's disease, and Alzheimer's disease.

Introduction

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder characterized by progressive cognitive decline interfering with activities of daily living. At least three of the following clinical features must also be identified as of the most recent criteria established in 2017: fluctuating cognition, recurrent visual hallucinations, rapid eye movement (REM) sleep behavior disorder, and at least one feature of parkinsonism[6]. Features of parkinsonism include bradykinesia, resting tremor, and rigidity[6]. In DLB, cognitive impairments affecting attention, executive function, and visuospatial function can occur early in the course, in contrast to idiopathic Parkinson's disease (PD)[6]. Furthermore, REM sleep behavior disorder can also occur early and can often precede impairments in short-term memory, in contrast to Alzheimer's disease (AD)[6].

The annual incidence of DLB is 4% of new dementia cases, and the typical age of diagnosis for DLB is between 51 and 90 years, with an average age of diagnosis at 75 years[1]. Diagnosis of DLB occurs more often in males than in females[1]. There is also a higher risk of DLB in patients with a family history of dementia of any type. Diagnosis may be delayed in young patients due to overlapping features with psychiatric disorders[1]. In this report, we present a case of a young man who started showing signs and symptoms consistent with DLB at age 40, although they were initially attributed to a coexisting psychiatric disorder. The prognosis for survival in patients with DLB can range from 2 to 20 years from diagnosis, although most often ranges between 5 to 7 years from diagnosis[9]. Treatments are focused on managing the cognitive, psychiatric, and motor symptoms of the disease. Acetylcholinesterase inhibitors have shown some effectiveness in slowing down cognitive decline, most notably with rivastigmine and donepezil, although rivastigmine carries a greater risk of adverse effects[9].

CASE REPORT

History of Present Illness

The patient is a right-handed man with a history of paranoid schizophrenia who presented at 43 years of age with a three-year history of declining short-term memory, concentration, and worsening paranoia. He is married and was previously employed as a door attendant, but reported increasing difficulty with following verbal commands, articulating speech, comprehending reading, and writing clearly. This was associated with difficulty in balance and reduction in left arm swing while walking. His sleep duration increased to ten hours per day, but became disturbed by increased limb movements, causing him to elbow his wife while asleep. He also became increasingly preoccupied with thoughts that people were watching him and that his wife was having an affair. He also reported decreased energy, motivation, and interest in activities. On examination, he was only oriented to person and had reduced concentration, but he retained visual attention. On language assessment, he initially had intact fluency, but reduced comprehension with difficulty naming common objects and repeating phrases. He achieved a score of 3/30 on the Montreal Cognitive Assessment. On assessment of

coordination, he initially had a normal narrow-based gait with no loss of balance, past-pointing, or dysmetria. Initial examinations of reflexes and cranial, motor, and sensory nerves were normal. He subsequently experienced rapidly progressive cognitive impairment, paranoid delusions, and difficulty ambulating, necessitating admission to a skilled nursing facility within two years of presentation. He also developed seizures which were controlled on two antiepileptic medications.

Past Medical History

Chronic paranoid schizophrenia

Family History

The patient's twin brother was diagnosed with Lewy body dementia and died at 40 years of age. He initially experienced forgetfulness, then dysphagia, frequent falls, worsening mood disorder, and seizures. The patient also reported having multiple other family members suffering from early onset cognitive impairment, but he could not specify which ones.

Medications

On initial presentation, the patient was taking haloperidol, paroxetine, quetiapine, and clonazepam to manage schizophrenia and behavioral disturbances. Rivastigmine was added within the first three months of follow-up and titrated up to 3 mg taken twice daily to help slow down cognitive decline. Memantine was added within one year of follow-up and titrated up to 10 mg daily to help slow down rapidly progressive cognitive decline. Antiepileptic medications, levetiracetam 1000 mg twice daily and Depakote 500 mg three times daily, were added within two years of follow-up due to the development of seizures.

Complementary Evaluations

The laboratory tests to exclude reversible derangements returned as normal, including complete blood count, comprehensive metabolic panel, vitamin B12, folate, thyroid stimulating hormone, copper, zinc, and urine toxicology.

A brain MRI was performed, and it revealed chronic microvascular changes along with bilateral parietal and occipital atrophy out of proportion for age (Figs. 1-2). The sagittal views of the brain MRI also revealed widening of the parieto-occipital sulcus and calcarine fissure, which are not typical for the patient's age. An axial view of a PET-FDG brain CT revealed a cingulate island sign, with preserved cingulate cortex metabolism surrounded by hypometabolism in both parietal and occipital regions, indicative of advanced DLB (Figs. 3-4).

Due to a similar history of early dementia in his twin brother, and dementia symptoms in multiple second-degree relatives, genetic testing with dementia and PD panels was performed. This panel returned positive for an autosomal dominant PSEN1 gene mutation, c.839A>G (p.Glu280Gly), which is typically associated with AD. There were no point mutations identified in the GBA gene, but whole exome sequencing was not available to identify any GBA gene mutations containing multiple nucleotides.

The patient and family were counseled about the importance of the patient undergoing a lumbar puncture to evaluate for abnormal proteins such as alpha-synuclein, which would assist in determining qualification for newer clinical trials targeting abnormal proteins. They deferred further testing after a multidisciplinary discussion of risks and benefits.

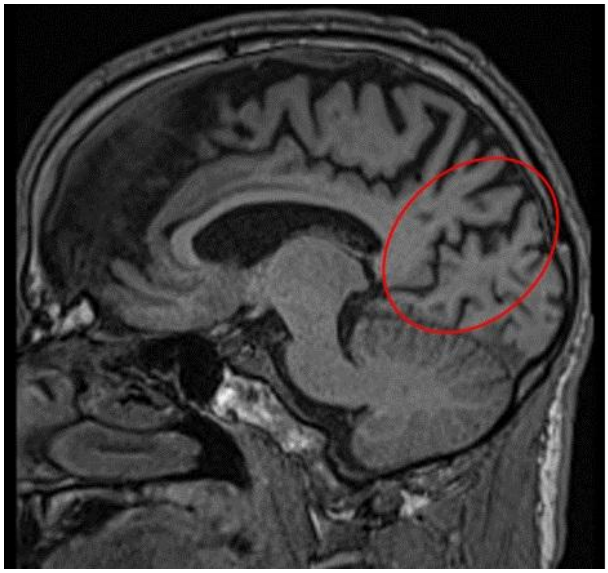

Fig - 1

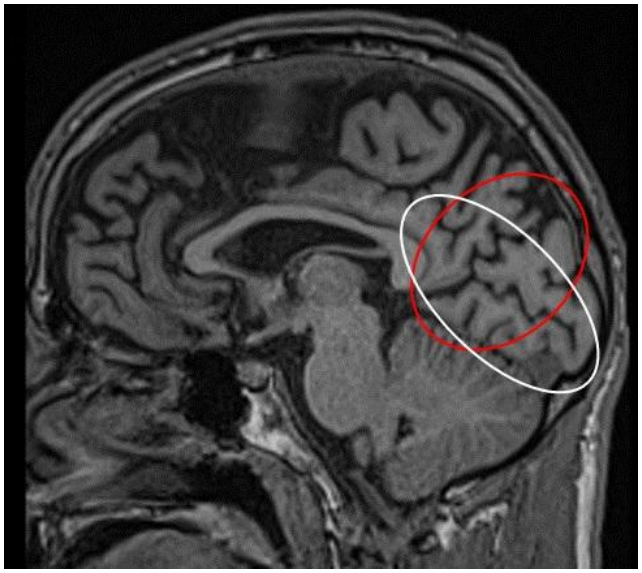

Fig - 2

Figures 1-2. Sagittal views of Brain MRI reveal bilateral parietal and occipital atrophy, with widening of the parieto-occipital sulcus (within red circles) and calcarine fissure (within white circle).

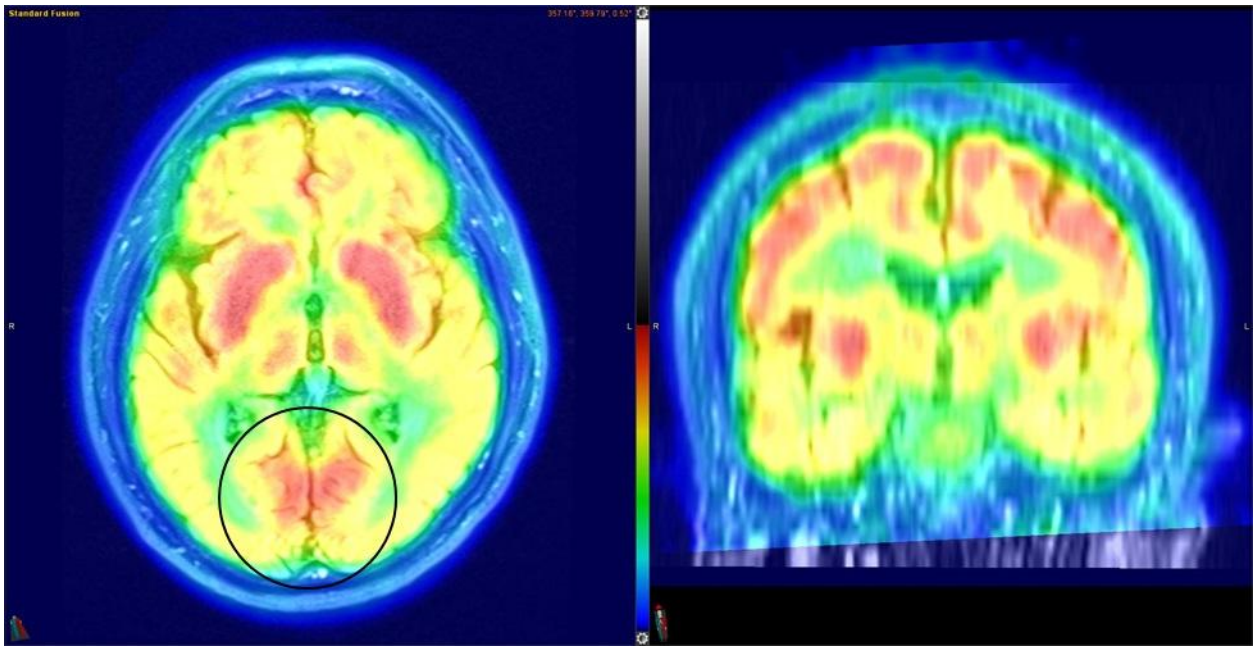

Fig – 3

Fig - 4

Figures 3-4. PET-FDG Brain CT axial and sagittal sections revealing a cingulate island sign (within black circle) showing preserved cingulate cortex metabolism surrounded by bilateral parietal and occipital regions, indicative of advanced dementia with Lewy bodies.

Discussion

Although DLB presents at an average age of 75 years, it has been reported much earlier, as seen in this case. Neuroimaging studies such as brain CT typically do not reveal structural changes, but brain MRI can reveal occipital and parietal lobe atrophy with preserved temporal lobe structure[10]. A brain CT or MRI with FDG-PET can reveal occipital and parietal lobe hypometabolism, often with preserved cingulate cortex metabolism[10]. Additionally, a SPECT scan can reveal decreased dopamine transporter uptake in the basal ganglia, although this can also be seen with PD[10].

Histopathological studies reveal eosinophilic cytoplasmic depositions of alpha-synuclein in clusters in neurons, which are termed Lewy bodies[4]. The studies also reveal loss of dopamine-producing cells in the basal ganglia and cholinergic cells in the basal forebrain[4]. However, since histochemical staining can be difficult and symptoms can overlap with other conditions, such as PD and psychotic disorders, DLB has been underdiagnosed. Although most cases of DLB are sporadic, some familial cases have been diagnosed in the fourth and fifth decades of life, pointing to a genetic basis for these presentations. A multicenter genomic study identified five independent significant loci influencing the risk for developing DLB, including GBA, BIN1, TMEM175, SNCA-AS1, and APOE[3]. Among these, the highest risks of developing DLB are associated with mutations in the GBA gene, which encodes the lysosomal enzyme glucocerebrosidase and is associated with more severe disease; the APOE gene, which encodes apolipoprotein E; and the SNCA gene, which encodes alpha-synuclein[2].

In patients with a family history of dementia, mutations such as PSEN1 and PSEN2 have been described with mixed phenotypes of DLB and AD. In particular, PSEN1 mutations have been discovered in several atypical AD cases, as well as cases of DLB, PD, and frontotemporal dementia (FTD)[7]. Specific PSEN1 mutations, such as Leu170Phe, Leu202Phe, or Ala396Thr, have been found to be associated with Lewy body pathology[7]. A 44-year-old woman with a Glu184Asp mutation of PSEN1 was diagnosed with primary progressive aphasia, but Lewy body pathology was also observed in neuropathological studies[8]. Another 46-year-old female was diagnosed with early-onset levodopa-responsive PD at 35 years of age and was later found to have a PSEN1 mutation without classic AD biomarkers[3].

The current data show that the high incidence of alpha-synuclein aggregates associated with PSEN1 mutations contribute to the predisposition for developing Lewy body pathology in carriers[5]. It is not fully understood how mutations in PSEN1, PSEN2, and APP may influence Lewy body formation in the brains of individuals who are genetically predisposed to develop DLB or AD[5]. Identifying mechanisms leading to the coexistence of tau protein and alpha-synuclein may lead to targets for drugs that can prevent the onset or progression of neurodegenerative disorders.

Conclusion

As information from the patient's neuroimaging and genetic test results were received, they were relayed to the patient and his family. Counseling was provided regarding the patient's diagnosis of DLB, the expected

cognitive decline that would come with this condition, and the prognosis of survival of 5 to 7 years from the date of diagnosis. Since his initial evaluation, the patient has been tapered off clonazepam and haloperidol, and his paroxetine was tapered down to 10 mg daily, due to concern that these medications have had limited benefits. He was started on quetiapine and it has been titrated up to a dosage of 800 mg daily at bedtime to manage behavioral disturbances and insomnia. Levetiracetam was stopped and Depakote was maintained at 250 mg twice daily for seizure prophylaxis and mood stabilization. The patient's progression of cognitive decline and behavioral disturbances has required him to remain in a skilled nursing facility for management.

This case reveals that DLB can develop at an earlier age than conventionally understood and can be associated with genetic mutations that were not previously described to be related. Further research is indicated on the role of PSEN1 mutations in neurodegenerative disorders other than AD, such as in DLB. This case also underlines the importance of early testing for dementia for patients under 50 years of age who show signs of cognitive decline or behavioral disturbances, especially if they have a family history of dementia, since this can help with early diagnosis and treatment.

Conflicts of Interest Statement

All Authors declare no conflict of interest.

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