

Amyotrophic Lateral Sclerosis and Idiopathic Normal Pressure Hydrocephalus: A Random Combination or a Genetic Explanation?

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Abstract

We present a 56-year-old female who was presenting with dysarthria and slow speech 4 - 8 months prior to her hospitalization with rapid deterioration. The patient initially experienced slow and slurred speech 4 - 8 months prior to her admission, following by dysarthria and hypernasal voice speech, which was gradually deteriorating. She also reported a difficulty in swallowing liquids, accompanied by cough. Based on the significant enlargement of the ventricles and the cerebral atrophy, which were detected by a brain MRI scan, we thought the possibility of a diagnosis of idiopathic Normal-Pressure Hydrocephalus (iNPH) with bulbar symptoms. The patient did not appear the triad of gait apraxia/ataxia, urinary incontinence, and dementia that classically characterizes iNPH, however, a lumbar puncture (LP) with evacuation of Cerebrospinal Fluid (CSF) (26 cc) has been used as a diagnostic test. After the evacuation of CSF, symptoms related to the patient's dysarthria and swallowing difficulty were significantly improved for 15 days. We repeated LP with evacuation of CSF (36 - 50 cc) 5 times in order to help our patient, because the neurosurgeons and anesthesiologists denied to put a shunt. However, the duration of the improvement at the last LP was only 3 days. Finally, after an extensive clinical and laboratory examination we had a patient with bulbar symptoms and signs at the beginning with ventricular enlargement and good transient response to CSF evacuation. At the follow up she progressed to Amyotrophic Lateral Sclerosis (ALS) with a repeat expansion in C9ORF72 which can be present in both ALS and idiopathic iNPH.

Keywords: *Amyotrophic Lateral Sclerosis; Normal Pressure Hydrocephalus; C9ORF72*

Introduction

Idiopathic normal pressure hydrocephalus is a syndrome, which typically has a clinical presentation of gait/balance disturbance, often accompanied by cognitive decline and/or urinary incontinence. It is considered common but remains under investigated. There are no uniformly accepted diagnostic criteria and therapeutic guidelines. Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron (MN) disease. Its primary cause remains elusive, although a combination of different causal factors cannot be ruled out. There is no cure, and prognosis is poor. Although novel ALS genetic variants have been identified, the shared genetic risk between ALS and other neurodegenerative disorders remains poorly understood. We present a woman 56 years old with bulbar symptoms and enlargement of the ventricles who had transient responses to CSF evacuations. After an extended neurophysiological exam and the patient's deterioration the clinical diagnosis of ALS was confirmed. Finally, a repeat expansion in C9orf72 was identified which can be present in both ALS and iNPH.

Case Presentation

A 56-year-old female was admitted 7/10/2019 to the 1st University Department of Neurology of AHEPA hospital, Aristotle University of Thessaloniki, presenting with dysarthria and slow speech 4 - 8 months prior to her present hospitalization with rapid deterioration. The patient initially experienced slow and slurred speech 4 - 8 months prior to her present admission, following by dysarthria and hypernasal voice speech, which was gradually deteriorating. She also reported a difficulty in swallowing liquids, accompanied by cough. The patient reported only allergy in pollen and dust from her personal medical history and no family medical history was recorded. She is a heavy smoker, starting at the age of 13 years. The current consumption of tobacco cigarettes is approximately 20 cigarettes per day. No alcohol consumption was reported.

Her medication at home was Aflen 300 mg 1 x 2 and Nortolan (Nimodipine) 30 mg 1 x 1.

Neurological examination (7/10/2019): A neurological examination revealed slow saccadic eye movements, dysarthria, difficulty in swallowing liquids, slow speech, hyperactive gag reflex, hyperactive jaw jerk reflex and positive response of a primitive reflex, the palmo-jaw reflex (L > R). Mild fasciculations of tongue were also present. Her vision was 5/10 of the right eye and 4.10 of the left eye. Hyperactive deep tendon reflexes (L > R) especially of the left upper limb were also noted. Hoffman sign was present, but the extensor response of the plantar reflex (Babinski sign) was absent. The function of fissures was normal. Muscle strength was rated 5/5 for both upper and lower limbs and the muscle tone was normal. Sensation was also normal. During cerebellar examination, a mild dysdiadochokinesia and dysmetria was noted at the left upper limb as well as an intention tremor and resting tremor of the left hand. No gait/balance disturbance, cognitive decline and/or urinary incontinence were present.

Diagnostic procedure: Prior to her admission to the clinic, the patient had undergone two hospitalizations, over a time span of four months, throughout the course of which various diagnostic tests were performed to pinpoint the cause of her condition.

Based on the significant enlargement of the ventricles and the cerebral atrophy (not compatible with age of the patient), that were detected by a brain MRI scan, performed by an independent laboratory before her admission to our hospital, we thought the possibility of a diagnosis of idiopathic Normal-Pressure Hydrocephalus with bulbar symptoms (NPH) (Figure 1).

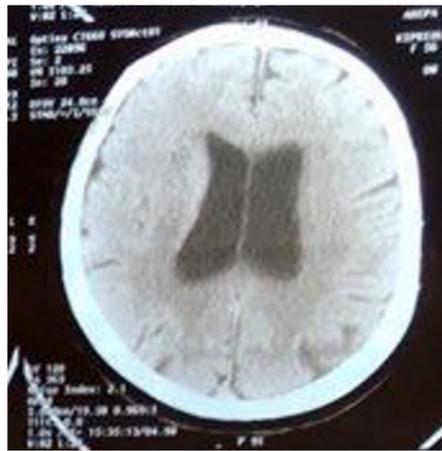


Figure 1: Enlargement of the ventricles not compatible with the age of our patient.

MRI also revealed a small number of limited volume, subcortical and periventricular white matter lesions, this is the reason for her medication, and a small nasopharyngeal cyst arising from midline of the nasopharynx. Although, the enlargement of the ventricles did not meet the criteria of iNPH, -Evans' index was 0.3- (NPH is characterized by increased values of Evans' index > 0.3), CSF fluid flow in MRI was normal, and the patient did not appear the triad of gait apraxia/ataxia, urinary incontinence, and dementia that classically characterizes NPH, a lumbar puncture (LP) with evacuation of CSF (26 cc) has been used as a diagnostic test. After the evacuation of CSF, symptoms related to the patient's dysarthria and swallowing difficulty were significantly improved for 15 days. We repeated LP with evacuation of CSF (36 - 50 cc) 5 times in order to help our patient, because the neurosurgeons and anesthesiologists denied to put a shunt. The duration of the improvement at the last LP was only 3 days.

Ophthalmological assessment was also performed. The fundus exam was normal considering the right eye, with sharp margins of the optic disc. On the contrary, a mild blurring of the disc margins were noticed in left eye. Vision was rated 5/10 for the right eye and 4/10 for the left eye. These findings were compatible with nuclear cataract in both eyes.

ENT examination has shown marginal velopharyngeal insufficiency, reduced pharyngeal contractility, decreased vocal fold mobility and reduced tongue pressure. Chest x-ray was normal as well as routine blood test exams.

The patient underwent a neuropsychological assessment and her cognitive function received a score of 29/30 on the Mini-Mental State Examination (MMSE) Scale. The Glasgow Coma Scale (GCS) was 15/15. Furthermore, the Functional-Cognitive Assessment Scale (FUCAS) score was 42. The last test examines activities of daily living directly from the patient [1].

During the second hospitalization, (10/12/2019) an extended electrophysiological evaluation has taken place. A minimum, routine motor and sensory conduction studies along with late responses were performed in upper and lower extremities. Compound muscle action potential (CMAP) amplitudes of both left median and ulnar nerves were decreased, whereas distal latencies and conduction velocities remained relatively intact. Motor amplitudes of the abductor pollicis brevis (APB) were decreased more than the amplitude from the abductor digiti minimi (ADM) ($APB/ADM = 0,42 < 0.6$) indicating Amyotrophic Latera Sclerosis (ALS). APB/ADM is $< 0,6$ in 40% of patients with ALS vs. 5% in normal individuals. Sensory conduction studies remained intact in all examined peripheral nerves of upper and lower extremities. An extensive EMG evaluation has also been performed. Spontaneous activity such as fibrillation potentials, positive sharp waves and fasciculations, were prominent in all examined muscles (upper limbs, lower limbs and bulbar muscles). Because of these last results of EMG the neurosurgeons and anesthesiologists denied to put shunt for management of NPH. The patient was also investigated, by means of somatosensory evoked potentials (EPs). Cervical SEPs from the median nerve and cortical SEPs from the median and tibial nerve were recorded, showing borderline latency values of N/P37 EPs and normal latency values of N9, N/P13 and N19 EPs.

In the third and most recent hospitalization, (28/1/2020) an MRI scan of the spinal cord (cervical portion, thoracic and lumbar spine) was performed. A two-level cervical segments stenosis was noticed between C5-6 and C6-7, and a mild disk protrusion. There was also a mild disk protrusion from segment L1 to segment S1 without significant spinal cord or nerve root compression. A small Tarlov cyst has been visualized at the S2 vertebral body.

We did a genetic examination and a repeat expansion in C9orf72 was identified. During the last neurological examination of the patient we found except bulbar symptoms and signs, symptoms and signs also from UMN and LMN.

Discussion

Idiopathic normal pressure hydrocephalus diagnosis is based on relevant history and clinical examination, appropriate imaging findings and physiological testing. The clinical picture of idiopathic normal pressure hydrocephalus may occasionally be difficult to distinguish from that of Alzheimer's dementia, subcortical ischemic vascular dementia and Parkinson's disease. No CSF or imaging biomarkers are currently fulfilling the criteria required to aid in the diagnosis of this condition. Our patient had only ventriculomegaly at the age of 56, with a significant improvement of her bulbar symptoms after CSF evacuations. There were not gait and balance disturbance, cognitive dysfunction, and urinary symptoms. She had no previous personal and family medical history, and signs and symptoms restricted to the bulbar muscles including progressive dysarthria, slow speech and difficulty in swallowing developed 4 - 8 months prior her first hospitalization.

It is well known that about 25% of patients with ALS have complaints connected with bulbar muscles as the first symptom. Upper Motor Neuron (UMN) dysfunction was present including brisk jaw, gag, and primitive reflexes, as well as Lower Motor Neuron (LMN)

involvement as neurophysiological investigations revealed. The presence of both UMN and LMN signs in the same region (bulbar region) is characteristic of amyotrophic lateral sclerosis (ALS) [2]. Electromyography (EMG) and nerve conduction studies were used to support the diagnosis of ALS. Conduction studies have shown muscle wasting affecting the lateral hand (thenar) out of proportion to the medial hand (hypothenar). This pattern, known as split-hand syndrome is common in ALS patients. Kuwabara., *et al.* 1999 have shown that the extent of motor unit loss was significantly greater in the APB than ADM [3]. Later, Kuwabara., *et al.* 2008, have shown decreased APB/ADM amplitude ratio in 41% of ALS patients, compared to only 5% of normal persons and 4% of disease controls [4].

Moreover, EMG findings have shown spontaneous activity such as fibrillation potentials, positive sharp waves and fasciculations, in one bulbar muscle and at least in two muscles innervated by different roots and nerves. The combination of clinical and electrophysiological findings supported the ALS diagnosis.

iNPH is clinically characterized by gait disturbance, cognitive impairment, and urinary incontinence, as well as enlargement of the ventricles. Our patient had only enlargement of the ventricles, but there was an improvement of the bulbar symptoms after repeated CSF evacuations. Until 2016 there have been no previous publications regarding the correlation between bulbar dysfunction and NPH [5]. In this recent study preoperatively, 86% (43/50) of patients had swallowing problems and 75% (37/49) had speech problems. Postoperatively, there was significant improvement in swallowing ($p < 0.001$), speech problems ($p = 0.008$), and voice volume ($p = 0.009$) and all triad symptoms were improved. These authors suggest bulbar dysfunction should be regarded as a core symptom that should be considered along with the classic triad in the clinical diagnosis and management of iNPH.

There is another interesting study which was published recently by Eleftheriou., *et al.* [6] which describes a patient with possible iNPH who also developed ALS. This case raises the theory of coexistence of gene-induced etiology at least in some cases and perhaps the question of a genetic link between iNPH and ALS. The authors concluded that it would have been very interesting to make a genetic analysis to see if their patient carried the *C9ORF72* expansion, but unfortunately this was not done. We did it at our patient.

The GGGGCC (G4C2) repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) is the most common cause of familial ALS, frontotemporal lobar dementia (FTLD) and ALS-FTLD, as well as contributing to sporadic forms of these diseases. Screening of large cohorts of ALS and FTLD cohorts has identified that *C9ORF72*-ALS is represented throughout the clinical spectrum of ALS phenotypes, though in comparison with other genetic subtypes, *C9ORF72* carriers have a higher incidence of bulbar onset disease.

Recently, Korhonen., *et al.* [7] presented the prevalence of *C9ORF72* expansion among Finnish iNPH patients. In their study, 487 patients with possible iNPH diagnosis were controlled and 8 patients (1.6%) were carriers of *C9ORF72* expansion. In the same study, there was one patient who was diagnosed with amyotrophic lateral sclerosis (ALS), and in all expansion carriers, the family history was positive for either ALS, iNPH, dementia, psychiatric diseases, gait problems, or a combination of all above mentioned diseases. In this study clinically significant shunt response was detected in 6 out of 7 shunted *C9ORF72* expansion carriers as it happened also in our patient.

Conclusion

Despite extensive diagnostic testing having been performed on the patient, a definitive cause of her condition was difficult to be established. Validated diagnostic, monitoring and prognostic markers of bulbar dysfunction are lacking and clinical assessment practices vary considerably across various centers. We should focus on clinical evidence of UMN and LMN degeneration, which is required for the diagnosis of ALS. With regards to bulbar impairment, clinical UMN signs include pathological reflexes (e.g. hyperactive brisk jaw jerk, gag, and other facial reflexes) and LMN signs encompass muscle weakness, atrophy and fasciculations in the jaw, face, tongue and palate. EMG should be repeated in order to detect progression of the disease. Diagnostic dysphagia instruments and speech measures should also

be useful in order to track the progression of bulbar impairment. In conclusion we had a patient with bulbar symptoms and signs at the beginning with ventricular enlargement and good transient response to CSF evacuation who progressed to ALS with a repeat expansion in C9ORF72.

Bibliography

1. Kounti F, *et al.* "Functional cognitive assessment scale (FUCAS): a new scale to assess executive cognitive function in daily life activities in patients with dementia and mild cognitive impairment". *Human Psychopharmacology* 21.5 (2006): 305-311.
2. De Carvalho M., *et al.* "The Awaji criteria for diagnosis of ALS". *Muscle and Nerve* 44.3 (2011): 456-457.
3. Kuwabara S., *et al.* "Dissociated small hand muscle involvement in amyotrophic lateral sclerosis detected by motor unit number estimates". *Muscle Nerve* 22.7 (1999): 870-873.
4. Kuwabara S., *et al.* "Dissociated small hand muscle atrophy in amyotrophic lateral sclerosis: frequency, extent, and specificity". *Muscle Nerve* 37.4 (2008): 426-430.
5. Chankaew E., *et al.* "Bulbar dysfunction in normal pressure hydrocephalus: a prospective study". *Neurosurgical Focus* 41.3 (2016): E15.
6. Eleftheriou A., *et al.* "A patient with idiopathic normal pressure hydrocephalus and amyotrophic lateral sclerosis. Coincidence or a genetic link between the diseases?" *European Journal of Medical Case Reports* 4.5 (2020): 157-160.
7. Korhonen VE., *et al.* "Prevalence of C9ORF72 expansion in a large series of patients with idiopathic normal-pressure hydrocephalus". *Dementia and Geriatric Cognitive Disorders* 47.1-2 (2019): 91-103.

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