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CASE REPORT

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# Bulbar-onset amyotrophic lateral sclerosis in a patient with genetically confirmed Huntington's disease: a case study

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## Abstract

**Background** The rationale for this paper is a description of a patient from Southeast Europe with genetically confirmed Huntington's disease (HD), coexisting with sporadic, bulbar-onset amyotrophic lateral sclerosis (ALS). To the best of our knowledge, the total number of reported cases with confirmed coexistence of HD and ALS is less than 20. Thus, it is an extremely rare condition speculated to be in a range from 2 to 6 per billion, and data from this part of the World are completely missing.

**Case presentation** Here we report a 72-year-old female with a family history of HD who had generalized chorea and hyperreflexia. Using the PCR-based test for the detection of the CAG triplet repeat expansion, the presence of HD was confirmed. After several months, our patient had progressively developed dysarthria and dysphagia, followed by spastic quadriparesis, generalized muscle wasting, spontaneous fasciculations and sialorrhea. The diagnosis of definite ALS was established based on the patient's neurological status, electromyography findings and current El Escorial criteria.

**Conclusions** Our study emphasizes the need for the recognition of the co-occurrence of clinically distinct and rare genetic disorders, such as HD and ALS. New insights from the studies dealing with these rare topics could significantly contribute to the contest of new gene therapy trials.

**Keywords** Huntington's disease, Amyotrophic lateral sclerosis, Bulbar-onset ALS, Co-occurrence, Co-existence

## Background

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder, which is defined by motor neuron loss in brain cortex, brainstem, and the spinal cord [1]. Similar to other neurodegenerative diseases, ALS occurs sporadically in the majority of cases. However, in 5–10% of patients ALS is considered familiar, where the disorder might be inherited in an autosomal-dominant, occasionally in a recessive or X-linked manner [1]. On the other hand, Huntington's disease (HD) is a single gene autosomal-dominant neurodegenerative disorder caused by an expansion of the trinucleotide CAG repeat mutation in the *Huntingtin* gene (HTT), localized on chromosome 4 [2]. Cardinal HD manifestations

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are progressive motor dysfunction, preceded or followed by cognitive decline and typical behavioral changes [2]. Although both diseases are part of the neurodegenerative spectrum, they are clinically and neuropathologically distinct entities. Both diseases are considered to be rare, with the prevalence of ALS reaching approximately 6 cases per 100,000 persons, while Huntington's disease occurs in 2.7 per 100,000 inhabitants worldwide [3]. Thus, their co-occurrence is extremely rare and up to now only fifteen cases of HD with ALS signs were reported worldwide [3, 4]. However, none of the reported cases was from this part of Europe.

The aim this article is a description of a female patient from Southeast Europe with genetically confirmed HD, coexisting with sporadic, bulbar onset ALS, with a focused literature analysis.

## Case presentation

A 72-year-old female patient, with a family history of HD, was admitted to the Neurology Clinic in Belgrade due to the appearance of a year-long lasting, brief, involuntary and unpredictable limb movements. Her mother and sister died in their late sixties/seventies due to genetically confirmed HD (38 and 42 repeats, respectively), and her nephew had genetically confirmed HD as well (the number of repeats is not known). Her family history and pedigree were negative for other neurodegenerative diseases (including motor neuron disease and dementia), and relevant psychiatric disorders, and there was no clear data about any degree of consanguinity in the family history. Her neurological examination revealed generalized chorea and lower limb hyperreflexia without spasticity. No presence of muscle weakness or atrophy was noted during the initial hospitalization. All laboratory findings (including biochemical, immunological, serological, and viral status, tumor markers, vitamin B12 and markers of thyroid function) were unremarkable. The patient's cardiologic status was also normal. Neuropsychological testing was performed, and it showed a significant reduction in attention, divergent verbal memory, problems with confrontational naming, and visuo-constructive functions, which are all in accordance with cognitive deficits typical for HD. Moreover, a mild degree of depressed mood and apathy was observed, and the Mini-Mental State Examination (MMSE) score was 24. In addition, global brain atrophy (including mild *nucleus caudatus* atrophy) along with scarce white matter hyperintensities was noted on brain magnetic resonance (MR) imaging. Finally, the PCR-based test for detecting the CAG triplet repeat expansion revealed an expanded allele (40 repeats) in the HTT gene, which, in addition to patient's clinical presentation and family history, confirmed the presence of HD.

### Follow-up period

Several months after the hospital discharge, our patient developed progressive dysarthria, dysphagia and hypersalivation, which lead to the second hospitalization at the Neurology Clinic. Her neurological examination, apart from previously noted generalized chorea, demonstrated generalized muscle wasting, with spontaneous body and tongue fasciculations, mild bulbar palsy and discrete sialorrhea. Diffuse hyperreflexia and bilateral extensor plantar responses were noted at the examination as well. All ancillary tests mentioned initially were conducted again (including the tumor markers and most common paraneoplastic antibodies). Since the serum neuroplastic/paraneoplastic antibody panel was negative, and the patient did not have any suggestive clinical signs and symptoms, further screening for malignancy was not indicated. Moreover, a rare entity such as paraneoplastic ALS is typically not presented with bulbar palsy or upper motor neuron sings at onset. All repeated neuropsychological and radiological analysis have not shown any major deviations compared to the previous studies.

Electromyography and nerve conduction studies (EMG and NCS) revealed the presence of active denervation and chronic neurogenic lesions of the 7th and 8th cervical nerve root bilaterally, in addition to the presence of fasciculations in the 8th cervical root region and fibrillation potentials in other cervical and cranial segments (genioglossus muscle was tested). Observed electrophysiological findings in other two regions (thoracic and lumbosacral) were normal. Comprised with progressive upper and lower motor signs in two different body regions, the patient initially fulfilled the El Escorial criteria for laboratory supported probable ALS with bulbar onset. Genetic testing for the most common mutations in *C9orf72*, *SOD1*, *FUS* and *ANG* genes (most frequent ALS genes in the Balkan region) were all negative. At the EMG and NCS follow-up examination after six months, the patient had ALS consistent lesions in all four body regions (now consistent with definite ALS according to the El Escorial criteria), which was in accordance with the further observed clinical deterioration. These findings further support the typical bulbar onset ALS propagation in a "caudal manner". Patient has received non-invasive ventilation and percutaneous gastrostomy.

Informed consent for publication of the data was obtained from the patient's closest relative.

## Discussion

To the best of our knowledge, the total number of patients with confirmed or even suspected coexistence of both HD and ALS reported in to-date literature, is around 20 (comprised 15 definite cases and around five

probable cases) [2–12]. The first reported case with both HD and ALS diagnosis was described in 1996 by Rubio et al. and it included a male patient with genetically confirmed HD (at the age of 57) and with histopathological post-mortem confirmed ALS (at the age of 81) [3]. It was unclear at that time whether this case merely represented the occurrence of two separate entities or did the prolonged HD pathology led to motor neuron dysfunction. However, although reports on this issue are present, it is still an extremely rare, speculated to be in a range from 2 to 6 per billion [5, 6], and data from this part of the World are completely missing.

One must agree that these numbers are still quite low for scientists to draw relevant conclusions, but a review by Fung et al. has revealed several common features among reported cases [7]. When compared to them, our patient is a "mirror image" of these cases—except for the fact that she had an older than average HD onset (72 years of age), with lower end of the numbers of repeats compared to HD patients without ALS (40 CAG repeats in the HTT gene). ALS symptoms developed several months after the HD diagnosis was made and the disease had a rapid-progressive course. On the other hand, most of the reported cases had spinal onset ALS, while our patient was diagnosed with bulbar onset. Thus, the fast development of ALS symptoms in our patients could be explained not only by the possible synergistic degeneration processes of both HD and ALS, but also with the bulbar onset form of ALS which is known to progress faster that the spinal variant.

Although the proposed direction in almost all papers is: "HD with later ALS development", Pradat et al. have described the other way around, with a 40-year-old man who developed progressive choreic movements 6 years after the diagnosis of clinically definite ALS [13]. It was hypothesized that a prolonged course of ALS in their patient led to degeneration of extrapyramidal structures with subsequent occurrence of a hyperkinetic movement disorder. Nota bene, chorea has been described in ALS patients without HD, but the exact pathophysiology behind movement disorders in these patients still remains unclear.

The postmortem pathological confirmation of HD and ALS coexistence was evaluated in a small number of reports [3, 5]. For instance, Tada and collaborators hypothesized that an altered polyglutamine protein aggregation might not only be a provoking factor in the development of ALS with inclusions (specifically TDP4 positive inclusions), but also could contribute to neuronal loss in patients with HD [5]. Furthermore, specimens in other studies demonstrated neuronal loss and gliosis in substantia nigra, globus pallidus, nucleus subthalamicus and with immunohistochemically confirmed ubiquitin inclusions in motor neurons [6, 8, 14]. Nevertheless, although these disorders share the process of neurodegeneration, their combined pathophysiology still remains unclear and needs further pre- and post-mortem investigations.

It is already known that both HD and ALS, like most of other neurodegenerative disorders, are characterized by an aggregation of misfolded proteins [15]. HD is characterized by aggregation of a specific protein—Huntingtin, while aggregations in ALS comprise different proteins. In order to prevent/stop pathological protein aggregation, cells have evolved different families of molecular chaperones [15]. However, their regulatory and mechanisms of functioning are still poorly understood. Recent studies in 2022 tried to identify whether lack or function of different chaperones in both HD and ALS could be the reason for their co-occurrence. These studies could be a very corner stone of the new era in which chaperones could be used as potential therapy targets in neurodegenerative disorders.

A single genetic mutation might have profound consequences in neurodegenerative disorders, as seen in ALS and HD. It is of note that more than 20 causing genes have been identified in patients with sporadic and familial forms of ALS, while HD is a single gene autosomal-dominant disorder. A hexanucleotide repeat expansion in *C9orf72* gene is the most common genetic cause of ALS worldwide identified to-date. It accounts for approximately 30% of cases and manifesting predominantly with bulbar symptomatology and cognitive decline in some patients [8]. In addition, it was recently discovered that *C9orf72* gene mutation are the most frequent cause of HD phenocopies with negative HTT gene, further underlining the possible co-pathology and combining pathophysiological mechanisms of these groups of different neurodegenerative disorders [16]. However, our patient screened negative for *c9orf72* mutation. The mutation in the *FUS* gene has also been characterized by the presence of intracellular aggregates and it was found apart from ALS in patients with different movement disorders [17]. However, our patient was negative for this and all other investigated mutations as well. The knowledge about the genetic disease background is crucial not only from the point of predicting the course of the disorder, but also from the point of gene therapy development. For instance, recent studies have shown that the CRISPR technique in the central nervous systems of mice turned off the production of mutant proteins that can cause ALS and HD [18].

Our case study encounteres some limitations. A post-mortem study was not performed, and genetic testing included only a limited number of (although the most common) gene mutations. Regardless of this

disadvantage, our case underlines the need for the recognition of the co-occurrence of different and rare genetic disorders.

## Conclusions

Our study underlines the need for recognition of unexpected co-occurrence of different and rare diseases, such as HD and ALS. This case report is an update of previously reported data since it underlines the possibility of appearance of bulbar-onset ALS with HD, fulfilling the data from this part of the World. We also suggest that HD patients should be evaluated on a regularly basis and screened for atypical signs. New insights from the studies dealing with these rare topics could significantly contribute to the contest of new gene therapy trials.

### Abbreviations

| | |
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| ALS | Amyotrophic lateral sclerosis |
| ANG | Angiogenin |
| c9orf72 | Chromosome 9 open reading frame 72 |
| CRISPR | Clustered regularly interspaced short palindromic repeats |
| EMG & NCS | Electromyography and nerve conduction studies |
| FUS | Fused in sarcoma |
| HD | Huntington's disease |
| MR | Magnetic resonance |
| PCR | Polymerase chain reaction |
| SOD1 | Superoxide dismutase 1 |
| TDP-43 | TAR DNA-binding protein 43 |

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Not applicable.

### Author contributions

The paper was conceptualized by IB (Ivo Bozovic) and ZS. The formal analysis was done by IB (Ivo Bozovic) and SG. The investigation and data curation were done by IK, AP, and VI. The original draft preparation was done by IB (Ivo Bozovic), SG and IK. The review and editing were done by IB (Ivana Basta), SP and ZS. The project was supervised by ZS.

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### Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Declarations

### Ethics approval and consent to participate

This research was approved by the Ethical Board the Neurology Clinic, University Clinical Center of Serbia. Informed consent for participation/publication of the data was obtained from the patient's closest relative.

### Consent for publication

Each author has read and approved the final manuscript version for submission.

### Competing interests

The authors report no conflict of interest.

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## Publisher's Note