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Prevalence of narcolepsy in patients with H63D syndrome

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Abstract

H63D syndrome is a phenotype of a homozygous mutation of the HFE gene H63D, which is otherwise known to cause at most mild classical hemochromatosis. H63D syndrome leads to an iron overload in the body (especially in the brain, heart, liver, skin and male gonads) in the form of non-transferrin bound iron (NTBI) poisoning. Hallmark symptoms and causal factor for H63D syndrome is a mild hypotransferrinemia with transferrin saturation values >50%. H63D syndrome is an incurable multi-organ disease, leading to permanent disability. Our objective was to detect the prevalence of narcolepsy and narcolepsy with cataplexy in patients with H63D syndrome.

Introduction

HFE mutation H63D is a mutation of the HFE gene characterized by the replacement of histidine by aspartic acid at site 63 of the HH protein. It occurs in about 5% to 10% heterozygous in the normal population, homozygous - regionally different - between 0.2% and 1.5% of all individuals are affected. The effects of this mutation are manifold. In 10% of the carriers of a homozygous mutation an H63D syndrome is found. This is a formation of iron not bound to transferrin (NTBI) caused by hypotransferrinemia and transferrin saturation levels >50%, which causes free iron molecules to penetrate into and damage brain and parenchymal cells. The result is a progressive multi-organ syndrome, mainly affecting the substantia nigra, parts of the basal ganglia, the heart, the liver and the testes. Regarding the causes and other aspects of the syndrome, reliable papers already exist. This small study reports the results of an investigation of the prevalence of the symptoms "narcolepsy" and "narcolepsy with cataplexy" in the context of a clinically manifest H63D syndrome and its role in the diagnosis and course of the disease.^{2, 7, 26}

Narcolepsy and Cataplexy

Narcolepsy is a hypersomnia of central nervous origin. It belongs to the group of sleep disorders. It is divided into narcolepsy with cataplexy ("classic narcolepsy"), narcolepsy without cataplexy ("monosymptomatic narcolepsy") and secondary narcolepsy (as a symptom of brain-organic diseases or brain damage due to accidents or physical trauma). Classic narcolepsy is a neurological disorder and is characterized by the main symptoms of excessive daytime sleepiness and cataplexies. The waking state, NREM and REM sleep and their transitions are affected, with correspondingly complex symptoms. First of all, the attacks of falling asleep, which are irresistible for the affected persons and which can occur during the day in the context of excessive daytime sleepiness, are conspicuous. Furthermore, partial or complete loss of muscle tone may occur in cataplexies, causing falls. This loss of tone occurs when the patient is fully conscious and is triggered primarily (but not exclusively) by strong emotions. Often, in addition, night sleep is not restful due to persistent sleep disturbances through the night, so that sleepiness in the sense of a tendency to fall asleep is compounded by sleep deprivation. Current studies investigate the consequences of chronic sleep deprivation in narcoleptic patients and its effects on metabolism and also on body weight.³⁰⁻³³

Method

We had fully anonymized access to the patient records of 210 patients with confirmed H63D syndrome through the members and institutions active in the framework of the International H63D Syndrome Research Consortium. Those records were systematically screened for symptoms which are consistent with narcolepsy or narcolepsy with cataplexy. Inconclusive data was rated as negative for narcolepsy.

Results

67% of the 100 male patients and 56% of the 110 female patients could be diagnosed with narcolepsy based on their clinical records. The rate was higher in older patients than in younger ones, consistent with the progressive nature of H63D syndrome.

1) *H63D syndrome patients retrospectively diagnosed with narcolepsy:*

<i>Males</i>	67%
<i>Females</i>	56%

2) *H63D syndrome patients diagnosed with narcolepsy and cataplexy*

<i>Males</i>	59%
<i>Females</i>	43%

3) *H63D syndrome patients diagnosed with any kind of chronic sleep disorder*

<i>Males</i>	93%
<i>Females</i>	97%

4) *H63D syndrome patients who suffered from at least one severe injury due to cataplexy*

<i>Males</i>	21%
<i>Females</i>	17%

5) *Onset of narcolepsy (no significant difference between the genders)*

<i>3rd decade</i>	03%
<i>4th decade</i>	17%
<i>5th decade</i>	45%
<i>6th decade</i>	31%
<i>7th decade</i>	04%

6) *Number of narcoleptic episodes per day*

0-1	28%
2-4	49%
>5	23%

7) *H63D syndrome patients with and without damages substantia nigra in TCS brain scan
(TCS results were available for 68 patients with H63D and narcolepsy)*

<i>With abnormal findings in substantia nigra in TCS scan</i>	95.5%
<i>Without damages in abnormal findings in TCS scan</i>	4,5%

Discussion

Once again, it has been shown that narcolepsy with or without cataplexy is a typical symptom of H63D syndrome. It becomes clinically relevant mainly in the 5th and 6th decade of life. To that point, this finding is not surprising to clinicians who treat patients with H63D syndrome. However, the essential new finding that there is a strict correlation with signs of brain injury in our patient population has significance on a broader level. High-quality transcranial ultrasound (TCS) scans or even less reliable scintigraphy are not available in many low-income countries. CT and MRI are without informative value in this case. If our data could be confirmed in a larger study in which patients are actively involved, narcolepsy in H63D syndrome may be used as surrogate marker to confirm brain damage (mainly in substantia nigra and basal ganglia) even without a scan, indicating progression of H63D syndrome from a state with functional symptoms to one with structural damage. Although this does not change the therapeutic approach, structural damage in the brain and/or heart and/or liver and/or testis are important markers of disease progression.

Conclusion

In genetically and clinically confirmed cases of H63D syndrome, the presence of narcolepsy with or without cataplexy is strongly correlated with substantial brain damage, particularly in the substantia nigra and basal ganglia. If confirmed in larger studies, the occurrence of secondary narcolepsy (narcolepsy as a symptom, not as a disease in its own right) could be a reliable surrogate marker for the presence of structural brain damage in patients with H63D syndrome.

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Source of funding and conflicts of interest

No external funding.

No conflicts of interest.

Ethical standards, data safety compliance, patient's rights, and nature of this scientific work

This article is about the scientific classification of defined medical parameters to identify specific symptom clusters. It is not reporting on a clinical trial (or anything similar), especially not a prospective one. All participating subjects gave informed consent for their inclusion. The study was conducted in accordance with the Declaration of Helsinki. Ethical, data protection, and patient rights requirements of the countries from which data were provided or in which these data were

used for research purposes were complied with. The examination results of the participating patients were completely anonymized and transmitted to the study personnel with codes that could not be traced. Thus, at no time were personal data generated that could allow conclusions to be drawn about identities.

Raw data

While this study is in preprint status, raw data from this study is available upon request.

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