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H63D Syndrome Type-1
What you should know about it (2023)

Abstract

In most practices, clinics and professional societies, a homozygous H63D gene mutation was and is generally considered relatively harmless, since carriers of this mutation very rarely develop classic ferritin-related hemochromatosis. Ferritin levels are usually normal or even rather low in these patients, so everything seems fine. Due to the fragmentation of medicine into many specialties, on a meta-level, hardly anyone has noticed that people with a homozygous H63D mutation can develop a very severe disease, H63D Syndrome. The key to understanding the phenotype is non- transferrin-bound iron, or NTBI. H63D Syndrome is a separate phenotype (clinical picture) of a homozygous mutation of the HFE gene H63D, which is otherwise known to cause at best a mild classical hemochromatosis. H63D syndrome, however, is not just another type of hemochromatosis, it is a serious syndrome caused by non- transferrin bound iron (NTBI) which is the result of an elevated transferrin saturation (50-100%) due to hypotransferrinemia which is the consequence of a homozygous mutation of HFE gene H63D.

Definition

H63D Syndrome is a rare clinical phenotype which is based on a homozygous H63D mutation of the HFE gene is based. This mutation is associated with various syndromes H63D Syndrome is the only known specific expression of a homozygous HFE-H63D mutation. The homozygous HFE-H63D mutation is the cause of classical and treatable hereditary hemochromatosis. H63D Syndrome is independently a distinct entity, the incidence in homozygous carriers of the H63D mutation is about 10%.

Pathomechanism

Due tue hypotransferrinemia or other forms of another dysfunction of the main iron transporter protein the transferrin saturation raises to levels of >50% which automatically leads to the formation of non-transferrin bound iron (NTBI) which is toxic and a trigger for oxidative (micro-)inflammatory processes, especially in parenchymal tissue, sodium, potassium and magnesium channels, as well as in the substantia nigra and, to a lesser extent, on the basal ganglia (brain structures). The transferrin value is pre - and postprandial stable in many patients (static transferrin). Free iron of the NTBI type (labile iron pool) can therefore enter the before-mentioned tissues and cause microinflammations and/ordegenerative changes through oxidation cascades. NTBI iron overload primarily affects nerve cells in the substantia nigra, normally leading to a slow but progressive degeneration. In addition, in many H63D Syndrome patients there is a non-specific activation of the innate immune system which additionally leads to spontaneously occurring, passive autoimmune reactions of variable type and severity.

Variants

There are patients with a homozygous H36D mutation whose symptoms are not exclusively caused by NTBI-type iron but by other oxidative inflammatory cascades. They show an almost identical clinical picture. To better distinguish them, the International H63D Syndrome Research Consortium has proposed the name "H63D Syndrome type 2" for the use in clinical settings.

Symptoms

The most visible signs of H63D Syndrome include neurological symptoms:

- Variable motor disturbances, in the late course possibly also
- Parkinson's symptoms (especially of the non-motor type)
- Postural instability analogous to Parkinson's disease
- Narcolepsy often with cataplexy - when a degenerative and irreversible brain damage has already manifested.
- Thinking disorders. Often highly severe and usually primarily obsessive in nature, compatible with dysfunction of the basal ganglia. They are - especially in the early phase of the disease - in the sense of a wrongly misdiagnosed as "mental illnesses". If thought disorders are in the foreground, a timely diagnosis is therefore often delayed.
- Tic disorders. Variable, with strongly fluctuating course occurring, often Tourette-like.
- Hyperkinesias, sometimes with danger of self-injury
- Disordered REM sleep patterns with danger of self-injury.
- Dementia syndromes of various degrees of severity from mild cognitive impairment to full-blown dementia, most compatible with a Lewy body dementia Clinically relevant changes occur in 30% to 60% of H63D patients, depending on the study. The variability is due to non-standardized measurement methods and cut-off values conditioned, especially in mild cognitive impairment.
- Cognitive impairment. This aspect is often masked by power reserves over time (months to years), especially in previously cognitively strong patients, but can occur under high sensory and complex content input can lead to considerable failures in everyday life and occupation.
- Decrease of the intelligence quotient and executive functions despite preserved selective performance in diagnostically relatively well definable areas

- Impairment of the executive functions with preserved long-term memory.
- The occurrence or worsening of narcolepsy with a decrease in tic symptomatology is indicative of the progression of brain damage.

Symptoms in other organ systems

- Cardiac damage and cardiac dysfunction, especially conduction defects and arrhythmias occasionally leading to
- Chronic heart failure
- Liver damage (even in the early course often an unexplained steatosis)
- Excessive episodes of the innate part of the immune system with highly variable autoimmune reactions, including phases of decreased defense of the adaptive immune system.
- Fibrosis on various organ systems, including the skin.
- Disturbed motility in the digestive system, mostly with chronic constipation
- Testicular atrophy in male patients, sometimes with degenerative signs in sonography
- Skin symptoms of variable nature (including impetigo, itching)
- Hyperreactivity
- Hydradenitis suppurativa
- Rare: Renal involvement
- Eye disease
- Oxidative microinflammatory processes induced by NTBI
- Hearing loss

etc.

Rather later in the course, with already structurally altered substantia nigra:

- Urge incontinence in all degrees
- Chronic eosinophilia with possible structural damage to the heart
- Disturbances in the function of the adrenal glands
- Impaired regulation of endocrine organs due to oxidative induced inflammatory processes with functional or structural organ damage due to infiltration processes in the area of the adrenal cortex (primary adrenal insufficiency). As a consequence, a clinically relevant dysfunction of the HPA axis as well as adrenaline synthesis (SAM axis) with erratic adrenaline excesses.
- Damage to the islet cells of the pancreas with possible development of a type-1 like diabetes (Diabetes type 3-C in continental European terminology), or other types of dysregulated insulin secretion.

Cave

Because of the variety of symptoms, the syndrome is usually recognized relatively late, especially if laboratory diagnostics do not reveal all relevant parameters of the iron metabolism metabolism are not obtained.

Diagnostics

The typical constellation of findings is indicative: patients show a postprandial (relatively) unresponsive and in general low transferrin level (hypotransferrinemia) with high transferrin saturation (usually >55 %) and low normal amounts of ferritin. Multiple tests are obligatory due to physiologically induced fluctuations. Mild persistent absolute eosinophilia is sometimes found in rare cases accompanied by an absolute basophilia.

In classic transcranial ultrasound imaging (sonography) the substantia nigra is hyperechogenic as it is seen in Parkinson's disease. Changes due to natural aging processes rule hyperechogenicity in TCS as a diagnostic marker out in patients older than 50 to 55 years of age.

MRI normally remains unremarkable with rare exceptions. A scintigraphy (DAT scan) may also be abnormal. Due to excessive radiation exposure and advances in the field of sonography, DAT scans are nowadays mostly used only in the context of clinical studies.

Pathohistology

The hallmark of H63D Syndrome is the deposition of NTBI iron in the brain and other tissues. This type of iron cannot be stained in histology (e.g. with the Berlin/ Prussian blue reaction). This is a major and very frequent source of error and false-negative findings.

Molecular biology

The homozygous H63D mutation of the HFE gene can be identified by molecular biology using a genetic test genetic test. The detection of a heterozygous mutation excludes H63D Syndrome.

Differential diagnoses

If the clinical situation of the patient is in accordance with H63D Syndrome Type-1 but no homozygous H63D mutation can be detected in the laboratory, other genetic disorders of iron utilization should be considered. Differential diagnoses include:

- Wilson's disease
- various Parkinson’s syndromes
- neurodegeneration with iron deposition in the brain
- anti-NMDA receptor encephalitis
- neuroacanthocytosis
- infectious diseases
- auto-immune diseases
- PANS Syndrome
- early Parkinson’s

Therapy

No causal treatment for H63D Syndrome is currently (2023) available. Free iron not bound to proteins, i.e. NTBI, cannot be removed by phlebotomy and related procedures in a safe and therapeutic way (an important exception being emergency chelation after iron poisoning). Instead, the ‘classic’ patient with rather low ferritin would merely suffer a further drop in his already usually low ferritin level. Free iron not bound to proteins should not be removed by phlebotomy and similar procedures. Instead, the classic H63D Syndrome patient with rather low ferritin would merely suffer a further drop in his already low ferritin level. Dialysis and iron chelators are also ineffective and can cause fatal side effects if used on a regular basis. They further lower the ferritin level, which is often low anyway, without binding the NTBI in the cells in a significant amount.

Dietary control of iron intake thus remains the best prevention against severe symptoms in cases diagnosed in time. If organ damage already exists, a low-iron diet may slow progression somewhat. However, such a diet should only be followed under the supervision of a physician in patients with H63D Syndrome, because an overload of NTBI in the body may coexist with a deficiency of vital ferritin.

To alleviate some symptoms, various drugs can be used - mostly in off-label use. Very high dose NSAIDs (including Aspirin in patients older than 18 years of age) and/or corticosteroids (especially prednisolon). In addition, medical aids such as orthotic, safety helmets, memory aids to help the patient remember important things, whiteboards are useful for writing lists and reminders, calendars for keeping track of appointments and routines, walking aids, wheelchairs, etc.

Social-medical aspects

Often, the patients' linguistic abilities remain normal for a very long time, which means that dementia-related decline is not initially noticeable to their family, peers, and the social environment. H63D Syndrome patients with milder forms of cognitive decline or with isolated impairment of executive functions are often overwhelmed in everyday life. The reason for this is that the long-term memory of the patients is normally never impaired, which the social environment misinterprets as a sign of an intact brain function. Intensive socio-medical counseling of caregivers is therefore an important cornerstone in the management of H63D Syndrome.

Conflicts of interest

None declared.

Peer review

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