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Recognizing differentiating clinical signs of CLN3 disease (Batten disease) at presentation

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Abstract:

Purpose: To help differentiate CLN3 (Batten) disease, a devastating childhood metabolic disorder, from the similarly presenting early-onset Stargardt disease (STGD1). Early clinical identification of children with CLN3 disease is essential for adequate referral, counselling and rehabilitation.

Methods: Medical chart review of 38 children who were referred to a specialized ophthalmological centre because of rapid vision loss. The patients were subsequently diagnosed with either CLN3 disease (18 patients) or early-onset STGD1 (20 patients).

Results: Both children who were later diagnosed with CLN3 disease, as children who were later diagnosed with early-onset STGD1, initially presented with visual acuity (VA) loss due to macular dystrophy at 5–10 years of age. VA in CLN3 disease decreased significantly faster than in STGD1 ($p = 0.01$). Colour vision was often already severely affected in CLN3 disease while unaffected or only mildly affected in STGD1. Optic disc pallor on fundoscopy and an abnormal nerve fibre layer on optical coherence tomography were common in CLN3 disease compared to generally unaffected in STGD1. In CLN3 disease, dark-adapted (DA) full-field electroretinogram (ERG) responses were either absent or electronegative. In early-onset STGD1, DA ERG responses were generally unaffected. None of the STGD1 patients had an electronegative ERG.

Conclusion: Already upon presentation at the ophthalmologist, the retina in CLN3 disease is more extensively and more severely affected compared to the retina in early-onset STGD1. This results in more rapid VA loss, severe colour vision abnormalities and abnormal DA ERG responses as the main differentiating early clinical features of CLN3 disease.

Omtale fra / Review from BattenDiseaseNews.com:

Compared to children whose vision loss is due to Stargardt disease, those with juvenile Batten (CLN3) disease have more extensive retinal pathology leading to a distinctively more rapid loss of visual acuity, color blindness, and poor retinal responses to light, a study reports.

Recognizing the early clinical characteristics of Batten disease, which can be similar to early onset Stargardt (STGD1), can help clinicians in making an accurate diagnosis and starting appropriate treatment.

According to the researchers, this analysis — done in children with macular degeneration evident at around age 6 — is "the most extensive overview of the ophthalmological characteristics early in Batten disease described so far." The study, "Recognizing differentiating clinical signs of CLN3 disease (Batten disease) at presentation," was published in *Acta Ophthalmologica*.

Symptoms of juvenile Batten are similar to those of early onset STGD1, an unrelated rare genetic disorder that causes vision loss due to macular degeneration.

The lack of distinguishing clinical features make diagnosing Batten a challenge, often resulting in a diagnostic odyssey that delays a start of proper care for this severe metabolic disorder, and the possibility of better outcomes for patients and their families.

Researchers in the Netherlands sought to identify clinical features that could distinguish juvenile Batten disease from early onset STGD1.

Clinical data on 38 children with rapid vision loss, referred to a specialized ophthalmologic center between 1987 and 2019, were reviewed. Visual acuity was assessed using the best-corrected visual acuity (BCVA) of both eyes (VODS), where lower VODS indicates poorer vision.

Of these 38 patients, 18 were later diagnosed with Batten disease and 20 with early onset STGD1. Children with Batten disease had a slightly earlier age of onset (mean age, 6.4) while the mean age of those with STGD1 was 7.5. Loss of visual acuity was more pronounced at onset in Batten than in STGD1 patients, with a mean VODS of 0.2 and 0.3, respectively.

The slight differences in age and vision clarity at onset were not sufficient to differentiate between the diseases, and significant clinical overlap was observed.

During the first year after disease onset, however, visual acuity loss in Batten disease progressed significantly faster than in early onset STGD1.

"[W]hile the VA [loss of visual acuity] itself may not be clearly different between CLN3 disease and early-onset STGD1 at presentation, the velocity of the vision loss clearly is different — already within the first year of follow-up," the researchers wrote.

Problems with color vision, particularly red-green color blindness, were also far more severe in Batten patients, distinguishing most of these children from those with STGD.

Tritan (blue-green) color vision deficiency was also more severe in Batten, although not to the same degree as red-green color vision loss.

The degree of both visual acuity loss and color blindness in Batten were both significant enough to distinguish the disease from early onset STGD1, the researchers noted.

The presence of pale optic discs — a sign of optic atrophy — and narrowed retinal arteries was observed in 70.5% and 88.2% of Batten patients tested, respectively, compared to 10% and 10.5% of early onset STGD1 patients. (Optic discs represent the beginning of the optic nerve, and are also the entry point for the major blood vessels that supply the eye).

While the outer photoreceptor layer of the retina was severely affected in both conditions, only Batten patients showed abnormalities in the inner retina. (The retina is the innermost, light-sensitive layer of tissue of the eye, thanks to the presence of photoreceptors that are sensitive to light.)

A full-field electroretinogram (ERG) was used to analyze the retina's electrical activity in response to light stimuli. The seven tested juvenile Batten patients had a distinct abnormal electrical response suggestive of retinal dysfunction, including dramatically reduced or absent responses to specific dark-adjusted light flashes. No such abnormalities were observed in 11 tested early onset STGD1 patients, in whom ERG response was normal or only mildly reduced.

"Importantly, to distinguish between CLN3 disease and early-onset STGD1, a dark-adapted ERG must be included" as a diagnostic test, the study stated.

These data also suggest that these observed abnormalities result from inner retina dysfunction, in some cases prior to the photoreceptor loss that is characteristic of Batten.

"Using a deep phenotyping approach, we unveiled that compared to early-onset STGD1 … the retina in CLN3 disease is affected more extensively … and more severely, resulting in several consistent clinical and electrophysiological differentiating features of CLN3 disease," the researchers wrote.

Three of these features, they added, "most clearly aided us to distinguish CLN3 disease from early-onset STGD1: dramatically rapid loss of vision, severe colour vision deficiency (both indicative of severe cone involvement) and absent or electronegative DA [dark-adjusted] ERG responses."

They concluded that their work "may aid clinicians in differentiating between two rare but clinically relevant disorders of the retina … based on their presenting clinical characteristics only. This differentiation allows early identification of children with CLN3 disease which is essential for adequate referral, counselling and rehabilitation."