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Two sibs with chorioretinal dystrophy, hypogonadotrophic hypogonadism, and cerebellar ataxia: Boucher-Neuhäuser syndrome

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Abstract

We describe two sibs with chorioretinal dystrophy, hypogonadotrophic hypogonadism, and cerebellar ataxia, Boucher-Neuhäuser syndrome, a rare but distinct pleiotropic single gene disorder with an autosomal recessive pattern of inheritance. The cases presented illustrate that this syndrome is still poorly recognised. We provide a review and analysis of previously reported cases and the differential diagnosis, which might aid in the identification of additional cases.

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Keywords: Boucher-Neuhäuser syndrome; ataxia; hypogonadism; chorioretinal degeneration

In 1969, Boucher and Gibberd1 described two sisters with "a combination of several features which although frequently occurring alone or in pairs, rarely occur all in one patient". The features referred to are chorioretinal degeneration, hypogonadism, and ataxia, which at that time did not "conform to any of the recognised syndromes".

Six years later, Neuhäuser and Opitz2 described a new autosomal recessive syndrome combining hypogonadotrophic hypogonadism and cerebellar ataxia. Although ophthalmological examination of two patients described in this study showed retinal pigmentary changes and atrophy, these findings were not considered to be part of the syndrome. The similarities between the cases reported by them and those reported by Boucher and Gibberd1 were therefore not recognised until 1989 when Linber et al.,3 on re-evaluation of one of the patients described by Neuhäuser and Opitz, suggested that this was a specific pleiotropic single gene disorder and named it Boucher-Neuhäuser syndrome.

So far, 17 cases from nine families have been reported, only three of these families in genetic publications.4-9 In the present study, we describe two additional cases and after review of the published reports list the main clinical characteristics of this rare syndrome and its differential diagnosis.

Case reports

CASE 1

The proband, a 31 year old male, was born after a normal pregnancy and delivery. He was seen by an ophthalmologist at the age of 23 years because of slowly progressive visual problems consisting of night blindness and constricting visual fields. His visual acuity was 5/10 in both eyes. Intraocular pressure was 17 mmHg on the right and 18 mmHg on the left. Fundoscopy showed bilateral atrophy of the retinal pigment epithelium and choriocapillaris in the mid peripheral areas, with peripapillary atrophy and retinal pigment epithelium alterations of the maculae. The electro-oculogram was disturbed bilaterally while electrophotography showed no photopic or scotopic responses at all. A fluorescein angiogram indicated central choriocapillaris atrophy. Colour discrimination was not disturbed. The diagnosis of choroideremia was suggested.

At 25 years of age, he was examined because of poor sexual development. He never needed to shave and although he had erections on awakening no ejaculation occurred. His height was 178 cm (25th centile) and weight 65 kg (25th centile). Compared to his trunk, he had relatively long limbs. There was sparse pubic and normal axillary hair with absent chest and facial hair. There was no gynaecomastia and he had a normal masculine voice. He had a very small scrotum and his penis and testicles were small but without anatomical abnormalities. Laboratory tests, including a complete blood count, routine blood chemistry profile, and urine analysis, were within normal limits. Endocrinological studies disclosed hypogonadotrophic hypogonadism. The serum level of testosterone was extremely low (0.86 nmol/l, normal 10-35) and the concentrations of luteinising hormone (LH) and follicle stimulating hormone (FSH) were below the lowest detectable level (<1.0 mIU/ml). There was no response to a single Intravenous dose of LH releasing hormone (LH-RH) even after repeated stimulation with LH-RH for one week, suggesting an abnormal pituitary function. The serum levels of oestradiol, cortisol, prolactin, thyroid stimulating hormone (TSH), and thyroxine (T4) were, however, all normal. Bone age, determined according to Greulich and Pyle, was 15 years 6 months. He was treated with intramuscular hormone injections (250 mg testosterone enantate (Testoviron®) every four weeks). Subsequently, secondary sex characteristics appeared. There was marked increase in facial and pubic hair growth and ejaculation occurred. Since the site of the hormone injections was troubling the patient, the injections were replaced by oral therapy (testo-
The proband's younger sister was born after a rier.

have fundoscopic signs of a choroideremia car­

choroideremia was rejected because of the fun­

nal dystrophy was made. The diagnosis of

doscopy results and because his mother did not

bilaterally. The diagnosis of atypical chorioreti­

was flat. Colour vision examination showed a

scotoma and a decrease of central sensitivity

with anomaloscopic diminished red sensitivity. 

Goldmann perimetry showed a large temporal 

fields had narrowed progressively. Her best corrected visual acuity was right 5/10 and left 5/10. Slit lamp examination of the anterior seg­

ments showed no abnormalities. Like her

brother, she had relatively long eyelashes. Fundoscopy showed atrophic retinal pigment epithelium alterations, narrow retinal vessels, and bone spicule-like clumps of pigment depo­position, very similar to the fundoscopic findings of her brother. On electoretinography some photopic rest activity was seen and the electro­
orgram was flat. Colour vision examination showed a

combined blue-yellow and red-green defect

with anomaloscopic diminished red sensitivity.

Intraocular pressure was normal in both eyes.

On electroretinography some photopic rest ac­

tivity was seen while the electro-oculogram

was flat. Colour vision examination showed a

combined blue-yellow and red-green defect

with anomaloscopic diminished red sensitivity.

Goldmann perimetry showed a large temporal

scotoma and a decrease of central sensitivity

bilaterally. The diagnosis of atypical chorioreti­

nal dystrophy was made. The diagnosis of

choroideremia was rejected because of the fun­
doscopy results and because his mother did not

have fundoscopic signs of a choroideremia car­

rier.

CASE 2

The proband's younger sister was born after a

normal pregnancy and delivery. She was first

seen for primary amenorrhoea and poor sexual

development at 21 years of age. On examina­
tion she was 175 cm (80th centile) in height and

58 kg (50th centile) in weight. Breast
development was poor (Tanner 1-2) and only

sparse pubic hair was present. Gynaecological

examination showed hypoplastic external

sexual organs. The vagina and cervix were very

small and the uterus and adnexal structures

were clinically undetectable. A complete blood

count and routine blood chemistry profile

showed no abnormalities. Endocrinological

studies, however, showed hypogonadotrophic

hypogonadism. The serum level of oestradiol

was 0.05 nmol/l (normal 0.11-0.30) and the

concentrations of LH and FSH were 1.2 and

2.9 mIU/ml, respectively (normal LH 3-120,

FSH 5-16). There was no response to a single

intravenous dose of LH releasing hormone.

Serum concentrations of prolactin, cortisol,
testosterone, TSH, triiodothyronine (T3), and

T4 were all within normal limits. Pelvic ultrasound showed a very narrow and small

uterus. It measured 0.5 cm in diameter and

approximately 4.5 cm long. The adnexal struc­
tures could not be visualised properly. A diag­
nostic laparoscopy was performed and showed

normal tubes and ovaries and a normal but

small uterus. Radiographic evaluation of the

sella turcica was unremarkable. The karyotype

was 46,XX. Investigation of mitochondrial

DNA did not show any deletions and the point

mutations known for mitochondrial encephalomyopathy (MELAS) at position 3243 and

3252 and the point mutation known for neuro­

genic muscular weakness with ataxia and

retinitis pigmentosa (NARP) at position 8993

were also excluded.

The patient was treated with an oral contra­

ceptive (Trisequens©) and within three years of therapy breast development and pubic hair

growth both reached Tanner stage 5. The

internal sexual organs however remained small

and on temporary discontinuation of medica­tion no menstrual periods occurred.

At the age of 24 years an ophthalmological

evaluation was performed because she had

noted that in the past three years her visual

fields had narrowed progressively. Her best correct­ed visual acuity was right 5/10 and left

5/10. Slit lamp examination of the anterior seg­

ments showed no abnormalities. Like her

brother, she had relatively long eyelashes. Fun­
doscopy showed atrophic retinal pigment

epithelium alterations, narrow retinal vessels, and

bone spicule-like clumps of pigment depo­
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photopic rest activity was seen and the electro­

oculogram was flat. Colour vision examination showed a

blue-yellow defect with anomalo­

scopically diminished red sensitivity. Visual field

testing on a Goldmann perimeter showed a

large ring scotoma and loss of central sensitivity

bilaterally. The diagnosis was atypical

chorioretinal dystrophy.

Since both brother and sister suffered from

hypogonadotrophic hypogonadism and retinal
degeneration, an inherited syndrome combin­
ing these two conditions had to be considered.

Boucher-Neuhäuser syndrome was a likely
candidate. Therefore, an extensive

neurological evaluation of both patients was

performed. Both the proband and his sister

reported a slight disturbance of balance, first

occurring during childhood. On examination a

disturbed balance and gait was evidently

present in both patients. Furthermore, marked
dystrochokinesis of the hands and an ataxic

heel to shin test was found. Neither patient was

able to walk on their heels, suggesting some

degree of muscle weakness. The deep tendon

reflexes were just elicitable or absent and there

was moderate pes cavus in both patients. A
gaze evoked horizontal and vertical nystagmus

was found in case 2. A reduction of propriocep­
tive sensation, fingertip number writing per­
ception, and dysstereognosis was found in the

proband. Sensory examination was otherwise

completely normal in both patients. Electro­

myogram showed broad complex motor unit

potentials and decreased amplitudes. Nerve

conduction velocities were not disturbed.

MRI of the brain showed evident atrophy of the

cerebellum, most pronounced at the vermis

(fig 1).

The presence of spinocerebellar ataxia in

addition to hypogonadotrophic hypogonadism

and retinal degeneration confirmed the diagno­
sis of Boucher-Neuhäuser syndrome.

FAMILY HISTORY

The proband and his sister were born to

healthy, non-consanguineous parents. In addi­
tion to these affected sibs, their parents had
Boucher-Neuhäuser syndrome

atrophy of the base of the pons.

Cerebellar atrophy can be seen, most pronounced at the vermis (arrows). There is no

IOSCA = Infantile onset spinocerebellar ataxia. For references see text.

4 by Bernard-Weil and Endtz

patient and without additional abnormalities

Retinal degeneration is seen in some patients with Holmes type ataxia.

— — —

Alopecia

— — —

Trichomegaly

Mental retardation

— —

Kapuscinski

remains rare, however. In retrospect, one of the

gonadism, and cerebellar ataxia) in one

sibs with Oliver-McFarlane syndrome

possibility that they are clinical variants of a

Holmes type ataxia, and Boucher-Neuhäuser

features of Oliver-McFarlane syndrome,

Discussion

The occurrence of retinal degeneration, hy­
pogonadism, and cerebellar ataxia has been described in several syndromes with overlap­
ing clinical features (for example, Laurence-

Moon syndrome, Bardet-Biedl syndrome, Al-

ström syndrome, Usher syndrome). However,

these syndromes can be distinguished from

Boucher-Neuhäuser syndrome since they are

complicated by additional features like deaf­

ness, glucose intolerance, mental retardation,

polydactyly, spastic paraplegia, and various
dysmorphic features.12 Disorders more simi­
lar to Boucher-Neuhäuser syndrome are infant­
tile onset spinocerebellar ataxia (IOSCA),13

Oliver-McFarlane syndrome,14 and Holmes
type ataxia15 (table 1). Because of the overlap­
ing features of Oliver-McFarlane syndrome,

Holmes type ataxia, and Boucher-Neuhäuser

syndrome one might even consider the

possibility that they are clinical variants of a

single disorder, particularly considering the

fact that cerebellar hypoplasia was seen once in
two sibs with Oliver-McFarlane syndrome.16

The association of all three disorders (chiori­

etinal degeneration, hypogonadotrophic hy­
pogonadism, and cerebellar ataxia) in one

patient and without additional abnormalities
remains rare, however. In retrospect, one of the

first papers on this subject was written in 1962 by

Bernard-Weil and Endtz1 and before that

Kapuscinski17 and De Mello18 also reported

cases with this triad. However, in these

patients, mental retardation and choreo­

athetosis occurred and the type of hypogo­
nadism was unknown. Lowenthal et al19 re­

ported similar cases, but these patients also

suffered from oligophrenia, anosmia, and

anomalies of amino acid distribution.19 Con­

sidering the complicating features, the patients
described in the latter three articles can proba­
bly not be identified as Boucher-Neuhäuser

syndrome, in contrast to a previous report.17 After further reviewing the published

reports, at least 17 previously reported cases

suffering from Boucher-Neuhäuser syndrome

could be identified.1-10 Below, we list the most

important clinical features (table 2) and
discuss the variable presentation of this rare

syndrome.

Besides the visual problems listed in table 2,

several other symptoms like astigmatism,1 night

blindness,1 photophobia,7 and disturbed depth

perception7 have been described. The onset of

these visual problems varied from the ages of 4
to 46 years.1,6 The main fundoscopic findings

have been extensively described previously by

Salvador et al.10 As stated before,1 the absence

of bone spicule type pigmentation, macular

oedema, and abnormal retinal vessels should
differentiate it from typical retinitis pigmento­
tosa. However, the diagnosis of retinitis pig­

mentosa was suggested in a few cases.1,6

Besides retinitis pigmentosa other diagnoses

like (early) senile macular degeneration,7 reti­
nal chorioretinitis,1 and chordoridermia (present study) have been suggested. In

addition, it seems that independent of the

severity of the observed chorioretinal degen­
eration, the visual outcome varies between

almost no loss of vision and complete blind­

ness. This illustrates the variable presentation

of the ophthalmological manifestations in

Boucher-Neuhäuser syndrome.

In addition to the more common neurological
findings in Boucher-Neuhäuser syndrome

(table 2), dysmetria,2,4-7 dysdiadochokinesia,2,7 frontal headaches,2 and

pes cavus1,2,4 have also been reported. Absent

as well as increased deep tendon reflexes have

been observed. The neurological symptoms are

often slowly or non-progressive. Although in

most cases the first neurological symptoms

occurred in the third decade of life,1,3,6,10 the

onset of cerebellar ataxia started before 15

years of age in at least seven patients.1,3,5,7 The late onset or recognition of the ataxic symp-

Table 1 Prominent clinical features and differential diagnosis of the cases described

<table>
<thead>
<tr>
<th>Features</th>
<th>Boucher-Neuhäuser syndrome</th>
<th>IOSCA</th>
<th>Holmes type ataxia</th>
<th>Oliver-McFarlane syndrome</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioretinal degeneration</td>
<td>+</td>
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<tr>
<td>Cerebellar ataxia</td>
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<td>+</td>
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<tr>
<td>Hypogonadotrophic</td>
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<td>Hypogonadism</td>
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<td>Hypergonadotrophic</td>
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<td>Hypogonadism</td>
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<tr>
<td>Mental retardation</td>
<td>+</td>
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<td>+</td>
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<td>-</td>
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<tr>
<td>Trichomegaly</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Alopecia</td>
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<tr>
<td>Prenatal onset growth retardation</td>
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<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

IOSCA = Infantile onset spinocerebellar ataxia. For references see text.
Retinal degeneration is seen in some patients with Holmes type ataxia.19

Figure 1 T1 weighted MRI scan of the brain of the proband (A) and his sister (B). Cerebellar atrophy can be seen, most pronounced at the vermis (arrows). There is no atrophy of the base of the pons.

three sons, all in good health. The family

history was otherwise unremarkable.
toms can make the diagnostic process very difficult and the dyad of hypogonadotrophic hypogonadism and retinal degeneration without additional symptoms does not conform to any diagnosis. In fact, we found only one report describing such an association.\textsuperscript{9} These authors described three sisters with hypogonadotrophic hypogonadism and retinitis pigmentosa. In addition to these sisters a prepupertal younger brother with retinitis pigmentosa was mentioned. Since the age of these patients did not exceed 22 years, it is not unlikely that the ataxic symptoms were recognised later in life, like the patients of the present study, but only a re-evaluation of these cases will prove this assumption to be correct.

In contrast to the ocular and ataxic symptoms, the endocrinological findings became evident at the time puberty was expected. Primary amenorrhoea, poor development of sexual organs, and sparse growth of secondary sexual hair prompted the diagnosis of hypogonadism. On testing, LH and FSH were deficient in all reported cases\textsuperscript{1,10} (present study). The absence of a response to LH releasing hormone injections strongly suggests a disturbed pituitary function\textsuperscript{1,8} (present study). The pattern of TSH and prolactin response to TRH plus the GH response to two male subjects in infertility. Azoospermia has been reported in some patients provide evidence for an additional symptom of Boucher-Neuhäuser syndrome. The patient was "assumed to be under postmenopausal state for over 10 years", and this lack of oestrogens seemed to play an important role in the pathogenesis.\textsuperscript{15} Furthermore, one sister of this patient with almost the same clinical history and symptoms had no hypercalcaemia.\textsuperscript{1,9}

Besides the observation that the tissues involved are all of neuroectodermal origin, the exact link between the three disorders (chorioretinal degeneration, hypogonadotrophic hypogonadism, and cerebellar ataxia) remains unknown. All the reported cases provide evidence that this triad represents a specific pleiotropic single gene disorder with an autosomal recessive pattern of inheritance. Males and females are equally affected and all cases are sibs in a single generation with unaffected parents. In addition, consanguinity was present in three of the reported families\textsuperscript{1,7,8} and the karyotypes of all tested subjects were normal\textsuperscript{1,3} (present study). However, the nature of the gene involved and the role it plays in the pathophysiology is still unknown. Recently, a single 5.5 kb mitochondrial DNA deletion was found in lymphocytes of a patient with ataxia, hypogonadism, choroidal dystrophy, and other symptoms.\textsuperscript{21} Mitochondrial metabolism deficiency in a patient with Holmes type ataxia and hypogonadism has been reported before,\textsuperscript{15} and also the occurrence of ataxia and retinal degeneration in patients with mitochondrial myopathy has been reported.\textsuperscript{22} Investigation of mitochondrial DNA of one of the patients reported in the present study, however, did not show any abnormalities.

Until specific tests are available, the diagnosis of Boucher-Neuhäuser syndrome must be made on the basis of clinical findings. The identification and description of additional cases is important to improve our understanding of this rare syndrome and to distinguish between other disorders associating hypogonadism or retinal degeneration with ataxia.

Table 2  Clinical manifestations of Boucher-Neuhäuser syndrome*
We thank Dr H J Troelstra (Department of Neurology, Catharina Hospital, Eindhoven, The Netherlands) for his careful evaluation of both patients.


