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A New Family of Boucher-Neuhauser Syndrome: Coexistence of Holmes Type Cerebellar Atrophy, Hypogonadotropic Hypogonadism and

Retinochoroidal Degeneration: Case Reports and Review of Literature

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Abstract. The association of familial hypogonadism with progressive cerebellar ataxia is only rarely encountered, and the exact link between the symptoms remains unknown. We report here two sisters presenting with Holmes type cerebellar ataxia, hypogonadotropic hypogonadism and retinochoroidal degeneration recently diagnosed as Boucher-Neuhauser syndrome. There was consanguinity between
the parents of the affected individuals and the condition seemed to be inherited as an autosomal recessive defect. On endocrinological examinations, in both cases, the responses of LH and FSH to LH-RH (100 jug) were impaired even after repetitive stimulation with LH-RH (400 jig, 7 days), suggesting that the hypogonadism was due to a primary pituitary disturbance. Impaired GH responses to GRF (100 ug) and insulin-induced hypoglycemia (0.1 U/kg) were also noted. The two sisters shared an almost identical clinical and endocrinological picture. Their karyotypes were 46, XX. They had been treated for primary and secondary amenorrhea at the age of 20 years and neurological problems had started at the
age of 30 years. This unique family displays clinical evidence of a possible common mechanism responsible for a progressive hypothalamo-pituitary and cerebellar impairment of late onset.

Key words: Cerebellar ataxia, Hypogonadotropic hypogonadism, Retinochoroidal degeneration, Estrogen, GH deficiency
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SYSTEMATIC cerebellar degeneration is often dif-
ficult to clarify with any precision, and in most
cases, the etiology remains unknown. Corticocer-
ebellar atrophy (CCA) and olivocerebellar atrophy (OCA) most probably represent the same degener-ative disorder. They are characterized by the appearance of a pure, progressive pan cerebellar

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syndrome associated with an autosomal dominant pattern of inheritance. Occasionally sporadic cases and cases with autosomal recessive inheritance also

may occur. The age of onset is usually in the fourth to sixth decades, but onset as early as the second and as late as the seventh decade has been report-ed. The abnormality appears first in the legs, resulting in unsteadiness of stance and a gait of a peculiar wavering, lurching character typical of cerebellar ataxia. This phenomenon has been cor-related with the localization of changes in the superior vermis of the cerebellum and adjacent parts of the cerebellar cortex. With more extensive

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cerebellar involvement, a disturbance in the artic-
ulation and rhythm of speech occurs that may progress to total incomprehensibility, and the arms likewise become ataxic. In advanced stages, there
may be weakness of the legs, rigidity, nystagmus,
and oculomotor palsies. Optic atrophy occurs fre-

quently in some families, but not in others. Reflexes may be reduced or hyperactive. Ankle clonus and extensor plantar responses are found in some cases. Mental deterioration may occur late. Holmes [1] first described three brothers and a sister with this

disease entity. He also demonstrated the associa-tion of hypogonadism with cerebellar ataxia. Since then various combinations of cerebellar ataxia and

hypogonadotropic hypogonadism have been re-ported [2-19], but the exact link between the symptoms has remained unknown. Limber et al. reported the association of spinocerebellar or cere-bellar ataxia, hypogonadotropic hypogonadism and chorioretinal dystrophy as an autosomal single gene disorder on the basis of three documented familial cases, and termed it Boucher-Neuhauser syndrome, using the name of the first authors of two earlier reports [14]. Recently, we examined two sisters who seemed to suffer from a condition

almost exactly compatible with this syndrome, and had the opportunity to perform a careful endocri-nological evaluation. Here we report a new variant of Boucher-Neuhauser syndrome.

Case 1

Case Reports

A 52-year-old woman, the product of a normal pregnancy and delivery, was admitted for evalua-tion of an unsteady gait, recurrent bone fractures and hypercalcemia. There was consanguinity be-tween the parents. They are second cousins. The patient never menstruated. She first noticed un-steady gait and hair loss at about the age of 20. She had been treated for primary amenorrhea for 6 years since the age of 28 years, and had had a child at the age of 35. Renal dysfunction and hy-percalcemia were diagnosed at the age of 41. At 46, she suffered from compression fractures of the lumbar vertebra twice. Around the same time, she first recognized visual problems. Besides case 2 (an elder sister), an elder brother is known to

have suffered from similar neurological problems
although endocrinological examinations have not
yet been performed. On examination, she looked
older than her chronological age. Her height was
153 cm and her weight 51.6 kg. Vital signs were normal, but pubic and axillary hair was scarce. There was temporal baldness. Visual acuity was
0.1 in both eyes and fundoscopy revealed retin-
ochoroidal degeneration. Intelligence was normal.
On neurological examination, a fine tremor of the upper limbs was noted. She had normal olfaction. The main abnormal findings were dysarthria, axi-
al and appendicular ataxia and wide-based gait.
Her speech was ataxic and slurred. She had bilat-
eral horizontal nystagmus of lateral gaze. Other
cranial nerves were intact. The tendon reflexes
were symmetrical and no pathological reflexes were
noted. A heel-knee test revealed decomposition
and a finger-nose test was dysmetric. The sensory
system was not disturbed. Romberg's sign was
not present.

Case 2

A 57-year-old woman, an elder sister of case 1, was the product of a normal pregnancy and deliv-
ery. Menarche commenced at the age of 15 years.
She noticed progressive loss of libido while her
periods became irregular and scarce, leading to
amenorrhea. She had been treated for amenor-rhea since the age of 35, and had had a child at the
age of 37. She noticed progressive gait instability
followed by disequilibrium and speech difficulties
at the age of 35. On examination, she looked older than her chronological age. She was 148 cm tall and weighed 49 kg. Vital signs were normal, pu-
bic and axillary hair was scarce. There was
temporal baldness. Neurological evaluation dis-closed normal mental status and cranial nerve
functions, including the sense of smell. Sensory
examination was normal. Visual acuity was 0.1 in
both eyes and fundoscopy revealed retinochoroi-
dal degeneration. Speech was ataxic and slurred. There was no evidence of muscle wasting, but some
hypotonia of the limbs was evident. She showed
occasional dysmetria, minimal dysdiadochokine-
sia, marked ataxia in the heel-knee test, an ataxic
wide based gait, difficulty in heel-to-toe walking with falling. Romberg's sign was not present.

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Laboratory evaluation

The laboratory data on admission in case 1(Ta-ble 1) were as follows: The serum level of calcium (Ca) was high (10.5 mg/dl), while urinary Ca ex-cretion was extremely low (9.2 mg/day), resulting in exaggerated decrease in the Ca clearance/creat-inine clearance ratio (Cca/Ccr) (0.0014). In

addition, the uric acid clearance/creatinine clear-ance ratio (CuA/Ccr) was also decreased (0.037). A moderate decrease in renal function was noted

(Ccr: 43 ml/min). Marked hyperlipidemia and hy-peruricemia were also found (total cholesterol: 367 mg/dl, triglyceride:1453 mg/dl, uric acid: 9.4 mg/ dl). Blood gas showed metabolic acidosis. For other routine chemistries, urinalysis data were all normal. The karyotype was 46 XX.

Table 1. Laboratory data in cases 1 and 2

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The laboratory data for case 2 are also shown in
Table 1. The serum Ca level was at the normal

upper limit (10.0 mg/dl), but enhanced urinary
Ca excretion was noted (145.6 mg/day). Ccr was normal. Moderate hyperlipidemia and hyperuri-
cemia (total cholesterol: 263 mg/dl, triglyceride: 296 mg/dl, uric acid: 6.8 mg/dl) were found. CUA/ Ccr was slightly decreased (0.069). For other rou-tine chemistries, the urinalysis was normal. The karyotype was 46 XX.

Endocrinological evaluation

The serum basal hormone levels of both patients are summarized in Table 2. The low estradiol (E2) levels, together with low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are consistent with hypogonadotropic hypogonadism. Serum progesterone levels were below the normal lower limit. Serum growth hormone (GH) and somatomedin C levels were also low. In case 1, serum levels of intact parathyroid hormone (PTH), m-PTH, c-PTH were slightly elevated. The basal levels of other hormones were almost all within

normal limits. Pituitary hormone responses to

provocation tests in both cases are shown in Table
3. Serum LH and FSH, measured by Spac-S LH and FSH kit (Daiichi Radioisotope Lab, Tokyo), did not respond to a single intravenous (iv) injection of LH-releasing hormone (LH-RH) (100 jig) even after repetitive stimulation with LH-RH (400 jig) for 7 days, suggesting that the hypogonadism was due to a primary pituitary disturbance. Serum GH responses, measured with a GH kit [Daiichi] (Daiichi Radioisotope Lab), to insulin-induced hy-poglycemia (regular insulin 0.1 U/kg) were impaired, while GH responded slightly to GH-re-leasing factor (GRF) (100 jig) in case 1 and the GH response to GRF tended to be restored after repet-itive stimulation with GRF (100 µg, 7 days) in case
2. The serum adrenocorticotropin (ACTH) re-sponse, measured with an Allegro ACTH kit (Nihon Medi-Physicus, Takarazuka), to insulin-in-duced hypoglycemia (regular insulin 0.1 U/kg) exhibited a delayed pattern. The serum thyrotro-pin (TSH) response, measured with a TSH RIABEAD II kit (Dinabot, Tokyo) and the serum prolactin (PRL) response, measured with a Spac-S PRL kit (Daiichi Radioisotope Lab), to iv injection of thyrotropin releasing hormone (TRH) (500 jig)

Table 2. Endocrinologica 1 fin d ings

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were normal.

Radiological evaluation

Magnetic resonance imaging (MRI) of the brain showed marked cerebellar atrophy, while the brain stem was intact (Fig. 1). There was no evidence of parathyroid gland swelling on echogram, comput-
ed tomography (CT) or technetium-thallium
subtraction scanning. Since these two sisters had common histories of recurrent bone fractures, bone mineral density (BMD) was evaluated by the dual energy X-ray absorptiometry (DXA) method. The total BMD and L2-L4 BMD of cases 1 and 2 were

0.891 ± 0.01 and 0.896 ± 0.01 g/cm2, respectively (% age matched: 86 ± 3 % and 91 ± 3 %, respective-ly), and 0.738 ± 0.01 and 0.706 ± 0.01 g/cm2, respectively (% age matched: 71 ± 3 % and 75 ± 3 %, respectively), suggesting osteoporotic changes.

Discussion

These cases on presentation shared highly simi-lar clinical histories and symptoms including
hypogonadotropic hypogonadism, retinochoroidal
degeneration and cerebellar ataxia without spinal
tract involvement, all of which are compatible with
Boucher-Neuhauser syndrome. When these cases are considered together with previously reported cases, it may be reasonable to assume that the triad of manifestations, hypogonadotropic hypog-onadism, retinochoroidal degeneration and

Table 3. Endocrine provocation tests in cases 1 and 2

Fig. 1. T1-weighted sagittal imaging (TR, 600 ms; TE, 15 ms) of the brain in case 1
(upper panel) and case 2 (lower panel).
No atrophy of basis points. Cerebellar
atrophy is seen in the superior vermis,
but not in the inferior one.

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cerebellar ataxia, is secondary to a dysfunction of
the same gene, while the possibility that a strong linkage of several gene abnormalities is involved
in the etiology of this syndrome could also be
considered. Besides these common clinical

manifestations of Boucher-Neuhauser syndrome, case 1 exhibited hypocalciuric hypercalcemia. In case 2, the serum Ca level was at the normal upper limit with exaggerated urinary Ca excretion. Fur-thermore, the serum PTH level was not suppressed, suggesting that she may have subclinical hyper-parathyroidism. The existence of consanguinity between the parents suggests an autosomal reces-sive pattern of inheritance. Reported cases of
cerebellar ataxia and hypogonadotropic hypogo-
nadism are reviewed in Table 4. Most families which have been reported are compatible with au-tosomal recessive inheritance, although Volpe et a1, reported a family for which an X-linked reces-sive inheritance was suggested. The association of hypogonadism with cerebellar or spinocerebellar ataxia was first described by Holmes, and in most cases reported since, a deficiency in gonadotropin secretion has been demonstrated. The responses of LH and FSH to LH-RH (100 #g) were impaired even after repetitive stimulation with LH-RH (400 µg, 7 days), pointing strongly to pituitary hypogo-

nadism. It is reasonable to hypothesize that either the LH-RH receptor itself or a post LH-RH recep-tor signaling pathway would be impaired in these cases. Recently, the complementary DNA (cDNA) encoding the LH-RH receptor has been cloned and its sequence has been determined [20-22]. South-ern blot analysis with the cDNA from the leucocytes of these sisters and normal Japanese women with the full length human LH-RH recep-tor as a probe failed to indicate any defect in the LH-RH receptor gene in the patient's sample. Al-though identical southern blot analysis does not exclude a small gene alteration which renders the LH-RH receptor non functional, such as a point mutation within the coding region or a promoter defect, these possibilities seem to be very unlikely. As Boucher-Neuhauser syndrome has many clini-cal features in addition to the loss of LH-RH

responsiveness seen in our patients, it seems likely to that any gene lesion present would be large enough to affect multiple genes and thus would be readily apparent in the southern blot analysis. Further studies will be necessary to clarify the cause of hypogonadotropic hypogonadism. Serum GH responses to insulin-induced hypoglycemia (regu-lar insulin 0.1 U/kg) were impaired in both cases, while in case 1 GH slightly responded to GRF (100

Table 4. Cerebellar ataxia and hypogonadotropic hypogonad ism

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jig) and in case 2 the GH response to GRF tended to be restored after repetitive stimulation with GRF (100 µg, 7 days). The peak ACTH response to in-sulin-induced hypoglycemia (regular insulin 0.1 U/ kg) was obtained at 60 min. This pattern of pitu-itary hormone responses to provocation tests suggests that the defects are not limited to the pi-tuitary but involve the hypothalamus as well. And the absence of lesions in the pituitary and hypo-thalamus on CT and MRI of the brain suggested that the defect is a functional one rather than a structural one.

The two sisters were apparently in a postmeno-pausal state for more than 10 years. Although the exact relationships among the triad of this syn-drome remain unknown, the long term deficiency of estrogen seems to have played an important pathogenetical role in several of the disorders: os-teoporosis, hyperlipidemia, hyperuricemia and, possibly, pituitary unresponsiveness to insulin-in-duced hypoglycemia and GRF. Frantz and Rabkin [23] have postulated that estrogens act to enhance pituitary sensitivity, or that of a higher center, to the GH-releasing effects of physical activity and possibly other stimuli. Impaired responses of GH to insulin-induced hypoglycemia and GRF could therefore be, at least in part, explained by estrogen deficiency. Ma et al. [24] showed that the level of the mRNA for low density lipoprotein (LDL) re-ceptor increased 6- to 8-fold in the liver of rabbits treated with estradiol and that the increase in the receptor number correlated with that in the mRNA. Mabuchi et al. [25] observed, in one patient with heterozygous familial hypercholesterolemia, that the serum total cholesterol and LDL cholesterol

levels were lowered by 63 % and 83 %, respective-ly, during pregnancy, and by 25 % and 40 %, respectively, in the non-pregnant state following treatment with estradiol. They concluded that the reduction in the serum cholesterol during preg-nancy was probably brought about by the action of estrogens. Furthermore, Shiomi et al. [26] have suggested that in homozygous Watanabe heritable hyperlipidemic (WHHL) rabbits, the decrease in serum cholesterol level during pregnancy is close-ly associated with an increase in hepatic LDL receptor activity, and that the increase in hepatic LDL receptor activity during pregnancy may be due to the action of estrogens. In addition, exoge-nous estradiol suppresses the activity of hepatic lipase, which is thought to play a physiological

role in regulating the conversion of very low den-sity lipoprotein (VLDL) and intermediate density lipoprotein (IDL) to LDL, leading to decreased syn-thesis of LDL cholesterol and total cholesterol [27]. On the other hand, it has been well known that there is a sex difference in uric acid metabolism.

The average serum uric acid level of men is some-what higher than that of women. Mikkelsen et al. [28] undertook serum uric acid determinations in order to define the distribution characteristics of

serum uric acid levels in a natural population, and to evaluate the importance of age and sex as vari-ables in relation to the serum uric acid level. For

female subjects, there was a slight rise in serum uric acid values beyond puberty but the curve soon falls again and plateaus at a level of about 4.0 mg/ dl until the age of menopause, when in the early fifties it rises gradually to closely approach that of male subjects. It is therefore reasonable to specu-late that estrogens may play a role in preventing the increase in serum uric acid possibly by increas-ing uric acid clearance from the blood or by blocking the synthesis of uric acid. Marked os-teoporosis was also observed in these patients. Estrogen increases bone mass by suppressing bone turnover through several mechanisms as follows: estrogen acts directly on human bone cells through a classical estrogen receptor-mediated mechanism [29, 30]. 17 /3-Estradiol has direct effects on bone consistent with known effects of decreasing bone resorption [31], and estrogen inhibits the produc-tion of interleukin 1, one of the pathogenetical factors in osteoporosis in the monocyte [32]. For the reasons described above, long term estrogen deficiency accelerates osteoporosis and other met-abolic disorders.

The cause of the hypocalciuric hypercalcemia seen in case 1 remains unclear. Usually hypocalci-uric hypercalcemia is a familial disease with autosomal dominant inheritance [33-36]. Most recently, cDNA encoding an extracellular Cat+- sensing receptor has been cloned from the bovine parathyroid gland and well characterized [37]. The cDNA encodes a predicted 120 kd polypeptide con-taining a large extracellular domain and seven membrane-spanning regions characteristic of the superfamily of G protein-coupled cell surface re-ceptors. In addition to parathyroid tissue, the receptor is also expressed in regions of the kidney involved in Cat+-regulated Ca2+ and Mg2+ reab-sorption. Pollak et al. have demonstrated that

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mutations in the human Cat+-sensing receptor gene
cause familial hypocalciuric hypercalcemia (FHH)
and neonatal severe hyperparathyroidism (NSHPT)
[38]. They reported three nonconservative mis-
sense mutations: two occur in the extracellular N-terminal domain of the receptor and the third occurs in the final intracellular loop. However, in this report the existence of familial inherited dis-ease seems unlikely, since case 2, an elder sister of case 1 with almost the same clinical history and symptoms, is assumed to suffer from subclinical
hyperparathyroidism, not hypocalciuric hypercal-
cemia. Roentgenographical findings in case 1
showed no swelling of the parathyroid gland, so

primary hyperparathyroidism also seems unlikely
although a slight increase in serum PTH was noted. Most patients with postmenopausal os-teoporosis have normal or low serum PTH values, but a small subset of osteoporotic patients have increased PTH [39, 40]. Riggs et al. [40] have sug-gested that increased serum PTH in osteoporotic patients is caused by secondary hyperparathyroid-
ism rather than normocalcemic primary
hyperparathyroidism. The fact that case 1 suffered
from renal dysfunction (Ccr 43 ml/min) may sup-
port this hypothesis. It is now established that
native vitamin D is biologically inactive and must undergo hydroxylation at the 25-position in the liver and at the 1-position in the kidney to pro-duce 1, 25(OH)2D, the biologically important, active form of the vitamin [41]. Pike et al. [42] have dem-
onstrated that estrogen modulates renal

25-OH-D3-1 a-hydroxylase, the enzyme responsible for the metabolic conversion of 25-OH-D to 1, 25(OH)2D, leading to increased intestinal Ca ab-sorption. The relatively low serum level of 1, 25-(OH)2D noted in case 1 could therefore also be explained by the lack of estrogen. In consider-ation of these findings, one possible explanation for hypocalciuric hypercalcemia is that exaggerat-ed reabsorption of filtrated Ca (FECa: 0.14%) may be a kind of compensatory adaptation to maintain Ca homeostasis. Although the osteoporotic chang-es estimated by DXA were more prominent in case 2 than case 1, case 2 does not show severe hyper-lipidemia or hyperuricemia, and the serum level of 1, 25(OH)2D is normal. The cause underlying these discrepancies remains to be fully elucidated. We have here reported two very rare cases of Boucher-Neuhauser syndrome associated with var-ious endocrinological disorders. A review of the literature reveals only 3 reports compatible with this syndrome and endocrinological evaluations of

patients with this syndrome were quite incomplete. It is possible that a genetically determined, but as yet unknown, "trophic factor" necessary for the maintainance of normal hypothalamo-pituitary and cerebellar functions may be abnormal or lacking in such patients. It should be emphasized that careful endocrinological evaluation of patients with this syndrome may contribute to a further under-standing of the pathogenetical basis of this new disease entity.

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