Optic neuropathy in late-onset neurodegenerative Chédiak–Higashi syndrome

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ABSTRACT
Background The classic form of Chédiak–Higashi syndrome (CHS), an autosomal recessive disorder of lysosomal trafficking with childhood onset caused by mutations in LYST, is typified ophthalmologically by ocular albinism with vision loss attributed to foveal hypoplasia or nystagmus. Optic nerve involvement and ophthalmological manifestations of the late-onset neurodegenerative form of CHS are rarely reported and poorly detailed.

Methods Case series detailing ophthalmological and neurological findings in three adult siblings with the late-onset form of CHS.

Results All three affected siblings lacked features of ocular albinism and demonstrated significant optic nerve involvement as evidenced by loss of colour and contrast vision, central visual field loss, optic nerve pallor, retinal nerve fibre layer thinning by optical coherence tomography (OCT) and abnormal visual evoked potential, with severity corresponding linearly to age of the sibling and severity of neurological disease. Further, unusual prominence of a ‘third line’ on macular OCT that may be due to abnormal melanosomes was seen in all three siblings and in their father. Neurological involvement included parkinsonism, cerebellar ataxia and spastic paraparesis.

Conclusions This report expands the ophthalmological phenotype of the late-onset neurodegenerative form of CHS to include optic neuropathy with progressive vision loss, even in the absence of ocular albinism, and abnormal prominence of the interdigitation zone between cone outer segment tips and apical processes of retinal pigment epithelium cells on macular OCT.

INTRODUCTION
Chédiak–Higashi syndrome (CHS) is an autosomal recessive disorder of lysosomal trafficking caused by mutations in LYST.1–2 The classic form of CHS, which accounts for >80% of cases, is of childhood onset and is characterised by immunodeficiency and recurrent infections, hemophagocytosis and pigmentary changes affecting skin and hair and resembling oculocutaneous albinism. Severe immunodeficiency and lymphohistiocytosis are frequently fatal or life threatening. Neurological involvement may occur in 10% of infantile cases.3–5 Nonsense or other disruptive mutations account for the majority of childhood-onset cases.6 In 10–15% of cases, a late-onset neurodegenerative phenotype with minimal to no immunological dysfunction occurs. These cases have been historically associated with missense mutations or small intragenic deletions that do not disrupt the reading frame.6,7 Classic neurological disease in attenuated forms, and also observed in classic infantile disease decades after haematopoietic stem cell transplantation,9 includes peripheral neuropathy, cerebellar ataxia and progressive cognitive decline. A parkinsonian syndrome, spinocerebellar degeneration and cranial nerve palsies can also occur.1–3 Optic neuropathy as the primary cause of vision loss has not been previously described in CHS. We report three siblings with a late-onset neurodegenerative phenotype with optic nerve involvement and unusual findings on macular optical coherence tomography (OCT).
Acids and plasma serology for human T-lymphotropic virus (HTLV)-1 and HTLV-2 were non-diagnostic. Genetic testing for spinocerebellar atrophy types 1, 2, 3 and 6, autosomal dominant optic atrophy, Leber hereditary optic neuropathy, several hereditary spastic paraplegias and various hereditary forms of parkinsonism was unrevealing. Skin biopsy revealed cutaneous amyloid deposition. Light microscopy of hair shafts showed abnormal melanin clumping and peripheral blood smear revealed cytoplasmic granules characteristic of CHS. Sequencing of LYST revealed a novel homozygous 6 base-pair in-frame deletion at exon 43, confirming the diagnosis of CHS.

The proband had four siblings, two of whom had similar symptoms. The elder of the two affected brothers (sibling 2, S2) was 35 years old and had a history of mild learning difficulties at school and recent onset parkinsonism; his younger brother (sibling 3, S3) was 29 years old with a history of insidiously progressive spastic paraparesis initially attributed to a spinal arteriovenous malformation (AVM), but who had shown progressive motor decline despite embolisation of the AVM 2 years earlier. None of the three affected siblings had visual complaints. The same homozygous LYST deletion was confirmed in both affected brothers, and heterozygosity for the deletion was confirmed in both parents and two unaffected siblings. Homozygosity for the mutant LYST allele thus segregated with the disease phenotype, confirming the diagnosis of attenuated CHS in all three affected adult siblings.

At age 43, S1’s visual acuity was 20/80 OD and 20/100 OS, and colour vision had deteriorated to no control (Ishihara) both eyes (OU). Goldmann visual field (GVF) revealed complete loss of the I2 and I3 isopters (figure 2A). Retinal nerve fibre layer (RNFL) OCT (Spectralis) revealed bilateral RNFL thinning, more marked temporally (figure 2B). Electroretinogram (ERG) was normal. Visual evoked potential (VEP) waveforms were extinguished.

**Figure 1** Dermatological appearance of patient S1.

**Figure 2** (A) Goldmann visual field (GVF) in patient S1 reveals loss of the I2 and I3 isopters, with constriction of the I4 isopter, more prominent in the right eye. (B) Retinal nerve fibre layer optical coherence tomography (OCT) in patient S1 reveals temporal thinning with borderline superior and inferior thinning. (C) GVF in patient S2 reveals severe central field loss with additional nasal and inferior constriction both eyes (OU). (D) GVF in patient S3 reveals partial loss of central isopters and nasal defects OU.
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Figure 3 Macular optical coherence tomography reveals normal foveal architecture, with the exception of excessive prominence of the photoreceptor-retinal pigment epithelium interdigitation (arrows), in patient S1 (top) and her father (bottom).

Patient S2, at age 38, had acuity 20/40 OD and 20/20 OS, normal colour vision (Ishihara 9/10 OD and 10/10 OS), moderate loss of contrast (Pelli–Robson contrast sensitivity of 0.90 and 1.05 log units OD and OS, respectively), mild bitemporal optic nerve pallor and severe central field loss by GVF with additional nasal and inferior constriction OU (figure 2C). RNFL OCT revealed thinning superiorly, more severe OS. At age 41, multifocal ERG (mERG) in S2 revealed robust central responses and pattern ERG showed normal central retinal activity with loss of the ‘N95’ deflection indicative of loss of nerve fibre layer activity. Patient S3, at age 32, had acuity 20/25 OD and 20/20 OS, normal colour vision and mild loss of contrast (Pelli–Robson contrast sensitivity of 1.05 and 1.20 log units OD and OS, respectively). Fundi appeared normal. GVF revealed partial loss of central isopters and nasal defects OU (figure 2D). ERG was normal and VEP showed mild slowing OU. None of the affected siblings demonstrated clinical findings of ocular albinism. All three affected siblings and their father had normal foveal architecture on macular OCT, with the exception of excessive prominence of the photoreceptor-retinal pigment epithelium (RPE) interdigitation (figure 3).

DISCUSSION
Decreased vision has been reported in the setting of CHS, but has most often been attributed to ocular albinism with foveal hypoplasia and nystagmus, which are frequent features of this disorder.9 10 We describe optic neuropathy as the primary cause of vision loss, as well as an unusual macular OCT finding, in three adult siblings with a CHS late-onset neurodegenerative phenotype in whom ocular albinism was not present. Detailed reports of ophthalmological findings in CHS are scant. There is a single reported, well-detailed case of progressive visual loss with visual field constriction due to retinal pigmentary degeneration in a child with classic, infantile-onset CHS, which was diagnosed clinically and not confirmed with molecular genetic testing.11 Prior to her death in early adolescence, she had ocular albinism with retinal hypopigmentation, progressive complaints of photopsias and night blindness and an extinguished ERG attributed to retinal degeneration. A second recent report describes a child with retained visual function with mixed hyperpigmentation and hypopigmentation of the iris and choroid.12 Optic nerve appearance and function in CHS are very poorly delineated; however, one report describes a child with elevated optic disc margins and progressive deterioration on ERG and VEP testing and a second autopsy report from a child describes optic nerve and retina infiltration by abnormal immature lymphocytes.13 14 In the three affected siblings that we describe, significant optic nerve involvement is suggested by loss of colour and contrast vision, central visual field loss, optic nerve pallor, RNFL thinning by OCT and abnormal VEP, with severity corresponding linearly to age of the sibling and severity of neurological disease. While similar clinical findings may result from macular dysfunction, predominant primary optic nerve dysfunction was suggested by the presence of only mildly abnormal macular OCT in each patient and normal central retinal responses on mFERG and pattern ERG in S2.

The significance of the prominent ‘third line’ on macular OCT in our patients is unclear. This likely represents an unusual prominence of the interdigitation zone between cone outer segment tips and apical processes of RPE cells that extend inwards to encase the cone outer segment tips. Histological RPE characteristics in CHS animal models include a paucity of melanocytes, with those present being atypically large or having abnormal morphology.16 Electron microscopy of cats with CHS reveals cells between the photoreceptor outer segments and RPE, including detached RPE cells with inclusions, giant melanosomes and secondary lysosomal residual bodies.17 Accumulation of these abnormal cell types may explain the prominence of this line in our patients, though the precise pathomechanisms of retinal pathology in CHS remain undefined. Giant electron-dense granules in the RPE of beige mice, which carry a mutation of the LYST gene, contain melanin-like melanosomes and exhibit acid phosphatase activity like primary lysosomes.18 One interesting hypothesis is that this abnormal ‘third line’ is directly related to enlargement of melanosomes in the retina in CHS, as melanosomes are located in RPE cell bodies and their apical processes and have recently been shown to be a primary source of reflectivity in OCT studies.19 20

In summary, the ophthalmological manifestations of CHS are varied. Most commonly, ocular albinism with foveal hypoplasia and nystagmus are seen, though retinal pigmentary degeneration may also occur. This report expands the ophthalmological phenotype of the late-onset neurodegenerative form of CHS to include optic neuropathy with progressive vision loss, even in the absence of ocular albinism or retinal pigmentary changes, and abnormal prominence of the line of interdigitation between outer cone segment tips and apical processes of RPE cells on macular OCT.

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