SCIENTIFIC REPORT

Batten disease: features to facilitate early diagnosis

J Collins, G E Holder, H Herbert, G G W Adams

Br J Ophthalmol 2006;**90**:1119–1124. doi: 10.1136/bjo.2006.091637

Aims: To ascertain the clinical and electrophysiological features in patients with juvenile neuronal ceroid lipofuscinosis (jNCL/Batten disease) and to identify those features that facilitate early diagnosis.

Methods: Nine patients with jNCL were identified retrospectively and their case notes reviewed. All had undergone an extensive clinical examination, including electrophysiology. Blood and molecular genetic testing confirmed the diagnosis.

Results: Age at onset ranged from 4–8 years. At presentation, two of nine patients had normal fundi; only two of nine patients had a bull's eye maculopathy. The electroretinogram (ERG) findings in this series included undetectable rod specific ERGs, an electronegative maximal response, reduced and delayed cone flicker ERGs, reduction in the b:a ratio in the photopic single flash ERG, and an undetectable pattern ERG. Vacuolated lymphocytes on peripheral blood film testing were present in eight of nine patients. Five of eight patients were homozygous for the 1.02 kb deletion on the *CLN3* gene on molecular genetic testing; two of eight patients were heterozygous for that deletion.

Conclusion: jNCL should be considered in children of 10 years and under presenting with visual loss and fundal changes ranging from normal through to pigmentary/atrophic changes or a bull's eye maculopathy. Electrophysiology may suggest jNCL. Although currently untreatable, early diagnosis is important to institute appropriate counselling and support.

The neuronal ceroid lipofuscinoses (NCL) are the commonest neurodegenerative disorders occurring in children and have an autosomal recessive pattern of inheritance.[1] Batten in 1903 described two siblings with progressive macular dystrophy and cerebral degeneration[2] and his name subsequently became associated with the juvenile form. Zemen and Dyken introduced the term NCL in 1969 and suggested that the autofluorescent material, which accumulated within neurons and other cell types in these disorders, had histochemical properties similar to the lipopigments ceroid and lipofuscin.[2 3] It has recently been demonstrated that this material is two thirds protein.[3]

Clinical features, including age of onset and the presence/ultrastructural appearance of this lysosomal storage material, have traditionally classified NCLs as infantile, late infantile, juvenile, and adult. The term Batten disease should refer only to the juvenile onset form of NCL, but this eponym has been applied to all NCLs.[1] Current genetic classification of NCLs distinguishes eight different disorders, which often encompass clinical heterogeneity.[4] Two genes, *CLN1* and *CLN2*, encode for lysosomal proteases palmitoyl protein thioesterase 1 and tripeptidyl peptidase 1, respectively. Lysosomal membrane proteins of currently unknown function are encoded for by *CLN3*, *CLN5*, *CLN6*, and *CLN8*.[5] The majority of cases of juvenile onset NCL are caused by mutations in *CLN3* which maps to chromosome 16p21.[6] To date 31 mutations in this gene have been reported, the commonest of which is a 1.02 kb deletion that is present on approximately 85% of disease chromosomes.[7] Juvenile phenotypes have also been observed following mutations in the *CLN1* and *CLN2* genes.[4] The primary biochemical defect in these disorders is yet to be ascertained and to date there is no available treatment.

It is juvenile NCL (jNCL) that is of particular interest to the ophthalmologist as these children usually present with rapidly progressive visual failure between the ages of 4–10 years, generally leading to legal blindness within 3 years.[1] The incidence of jNCL is estimated at up to one in 25 000 with an increased prevalence in north European populations.[6] It is an important cause of childhood blindness in the United Kingdom as up to 25% of the children registered as blind each year presenting with retinal or macular disease may have jNCL.[1]

Early diagnosis of jNCL by the ophthalmologist has several implications. In particular, it allows families to receive the appropriate counselling and also enables appropriate provision of educational and family support. The diagnosis is based on clinicopathological findings and can be confirmed by molecular genetic testing. Retinal signs include bull's eye maculopathy, peripheral pigmentary or atrophic changes, disc atrophy, and attenuation of retinal arterioles.[2] However, fundus examination at presentation may be normal causing great diagnostic difficulty. Features including behavioural changes, cognitive impairment, motor disturbance, and seizures follow the ophthalmic signs. The disease follows an inexorable path to death in the second or third decade.[1] Analysis of the peripheral blood film demonstrates vacuolated lymphocytes with the characteristic fingerprint profile pattern on ultrastructural appearance. The diagnosis is confirmed by molecular analysis of the *CLN3* gene, with the majority of disease alleles having the common 1.02 kb deletion. Electrophysiological testing may facilitate the early diagnosis of jNCL and electroretinograms (ERGs) typically demonstrate an electronegative waveform under both scotopic and photopic conditions.

A series of patients with jNCL is reported and their clinical, electrodiagnostic, blood, and molecular genetic findings ascertained to identify features for early investigation and diagnosis of this condition. We also highlight the need for support measures to be available once the diagnosis has been made. Some data on three of these patients have previously appeared.[8 9]

MATERIALS AND METHODS

The case notes of 11 patients with NCL were reviewed. Patients were identified from records within the family support services at Moorfields Eye Hospital (MEH) and from

Abbreviations: ERG, electroretinogram; jNCL, juvenile neuronal ceroid lipofuscinosis; NCL, neuronal ceroid lipofuscinoses

the electrophysiology department database searching for records with a diagnosis of Batten disease.

All patients had an extensive clinical examination, which included visual acuity assessment, comprehensive ophthalmic examination with dilated funduscopy and electrophysiology. All patients underwent electrophysiological testing based on the ISCEV standard, with variations in some because of their young age, seven of which were performed at our institution and two elsewhere.

In order to confirm the diagnosis, examination of a peripheral blood film for the presence of vacuolated lymphocytes and electron microscopy to observe for fingerprint inclusions were performed. In addition, patients underwent molecular genetic testing to identify the common 1.02 kb deletion in *CLN3*. Four patients also underwent testing for leucocyte enzymes to exclude infantile and late infantile NCL.

Other investigations performed included magnetic resonance imaging (MRI) scans, skin biopsy, and an echocardiogram in one patient who had pre-existing cardiac problems, which showed stable mitral valve incompetence. Electroencephalograph (EEG) testing was performed in four patients.

All patients were referred to a developmental paediatrician, paediatric neurologist, clinical geneticist, family support service, and low vision aid services. In addition, they were given information regarding various support groups in the United Kingdom such as the Batten Disease Association.

RESULTS

General patient data and ophthalmic features are shown in tables 1 and 2. Neurological features are summarised in table 3.

The age at which diagnosis of jNCL was made ranged from 6–11.5 years (mean 8.7 years). The time between presentation to an ophthalmologist and diagnosis of jNCL ranged from 6 months to 4 years (mean 1.3 years). Other provisional diagnoses had included cone/rod dystrophy, macular dystrophy and retinal dystrophy.

The results of electrophysiological tests are detailed in table 4. Note the high prevalence of electronegative waveforms under both scotopic and photopic conditions in the full field ERGs. Pattern ERG, reflecting macular function, was undetectable in five of six and showed residual activity in only one eye of one patient. Examples of ERG recordings from three patients in this series are demonstrated in figure 1.

Vacuolated lymphocytes on peripheral blood film testing were present in eight of nine patients. Fingerprint inclusions were observed in six of the eight in the blood film alone and in two on both blood film and skin biopsy. Five out of eight patients were homozygous for the 1.02 kb deletion on the *CLN3* gene on molecular genetic testing. Two patients were heterozygous for the same 1.02 kb deletion. Other mutations in these two heterozygous patients were not identified. No genetic abnormality was identified in one patient. This patient also showed no vacuolated lymphocytes on peripheral blood testing. The diagnosis of an atypical variant of jNCL was formed on the basis of characteristic clinical, neurophysiological, and magnetic resonance imaging (MRI) findings. EEG was reported as highly characteristic of Batten disease, showing runs of large amplitude and slow wave and spike complexes.[1] MRI scanning demonstrated cerebellar atrophy and white matter abnormalities. One patient, the oldest in the series, did not undergo molecular genetic testing. Fingerprint inclusions were identified on blood film and skin biopsy in this patient. Leucocyte enzymes were assessed in four of nine children, but no abnormality was detected. Of the four patients who underwent EEG testing, two had developed grand mal seizures and another absences.

DISCUSSION

This report details the phenotypic features in a series of patients with jNCL. The results of molecular genetic analysis and the key electrophysiological findings that facilitated early diagnosis of the disorder are described.

The age of onset of visual failure ranged from 4–8 years (mean 6.4 years) with presentation to an ophthalmologist at 5.5–8.5 years (mean 7.3 years), which is comparable to an earlier series in which the peak incidence of visual failure was 6–7 years with a range of 4–10 years.[2] Two of nine patients had developmental or behavioural problems before visual deterioration; one child had behavioural problems noted at the age of 3 years—that is, 4.5 years before the onset of visual failure and a second child had problems with speech and walking at the age of 3 years, 2 years before the onset of visual failure. The time taken from presentation to an ophthalmologist to the diagnosis of jNCL ranged from 6 months to 4 years (mean 1.3 years). This time scale compares well in relation to other metabolic diseases such as adult Refsum syndrome; one recent study on adult Refsum reported an average delay of 11 years between presentation to an ophthalmologist and diagnosis.[10]

Overall, seven of nine patients presented with definite symptoms and signs of visual failure/reduced visual acuity. In two of nine patients there was documentation of behavioural problems and speech/walking difficulties at the age of 3 years. It could not be ascertained therefore, whether the presenting feature in these two children was visual failure. Common additional ocular symptoms in this series were night blindness and photophobia (table 2). Seven of nine patients had been provisionally diagnosed with other retinal disorders before the diagnosis of jNCL. These included cone/rod dystrophy, macular dystrophy, and retinal dystrophy. As most of these children present with visual failure it is quite plausible that the cause may be attributed to another retinal disorder rather than NCL until the clinical features progress;

Table 1 General patient data

Patient	1	2	3	4	5	6	7	8	9	Mean
Current age	10	13	9	8	16	13	6	10	17	
Male/female	F	M	F	M	M	F	M	F	F	
Consanguineous parentage	No	No	No	No	No	No	Yes	No	No	
Age onset visual failure	7.5	5	4	7	7	8	5	6	8	6.4
Age at presentation to ophthalmologist	5 (squint) 7.5	7	8	7	8	8.5	5.5	6.5	3 (Duane) 8.0	7.3
Age at diagnosis	8.5	11	9	7.5	11.5	9	6	7	8.5	8.7
Presentation with visual failure?	Behaviour problems age 3	Yes	Yes	Yes	Yes	Yes	Speech/walking problems age 3	Yes	Yes	

Table 2 Ophthalmic features

Patient	1	2	3	4	5	6	7	8	9	Total
Visual acuity on presentation to MEH	6/60, 6/12	HM	6/60, 3/60	6/12,6/12	CF, 1/60	6/18, 6/18	Not fixing/following	6/60, 6/60	3/60, 3/60	
Symptoms reported										
Poor night vision	*	*	NR	*	NR	*	*	NR	NR	5/9
Photophobia	NR	*	NR	NR	NR	*	NR	*	NR	3/9
Difficulty reading	NR	NR	NR	NR	*	NR	NR	*	NR	2/9
Poor colour vision	NR	NR	NR	NR	*	NR	NR	NR	NR	1/9
Presenting funduscopic signs										
	Bilateral bull's eye maculopathy and peripheral atrophic retinopathy	Bilateral pigmentary maculopathy and peripheral pigmentary retinopathy	Bull's eye maculopathy and arteriolar attenua tion	Peripheral pigmentary retinopathy	Optic atrophy, arteriolar attenuation, macular and peripheral pigmentary retinopathy	Normal fundus on presentation	Subtle retinal changes	Atrophic maculopathy and peripheral pigmentary retinopathy	Normal fundus on presentation	
Signs										
Bull's eye maculopathy	†	–	†	–	‡	‡ , age 9	Subtle right maculopathy*	–	–	4/9
Pigmentary maculopathy	–	†	–	‡	†	–	–	–	–	3/9
Atrophic maculopathy	–	‡	–	–	‡	–	–	†	–	3/9
Peripheral atrophic retinopathy	†	‡	–	–	–	‡	–	–	–	3/9
Peripheral pigmentary retinopathy	–	†	–	†	†	–	* subtle	†	–	5/9
Bone spicules	–	‡	–	–	–	–	–	–	‡	2/9
Arteriolar attenuation	–	‡	†	‡	†	–	–	–	‡	5/9
Optic atrophy	–	‡	–	‡	†	–	–	–	‡	4/9
Overlooking/eccentric viewing	–	*	–	*	*	*	–	–	–	4/9
Abnormal Ishihara	*	*	*	*	*	*	ND	*	*	8/8
Constricted visual field	*	ND	ND	*	*	ND	ND	ND	ND	3/3
Other	Convergent squint	Nystagmus			Nystagmus	Normal fundus on presentation	Alternating exotropia, nystagmus		Normal fundus on presentation Right Duane with esotropia age 3	
Other/initial diagnosis before NCL	Rod-cone dystrophy	Rod-cone dystrophy	Cone, cone-rod or macular dystrophy	Retinal dystrophy	Cone dystrophy	Non-organic visual loss	Retinal dystrophy	Macular dystrophy	Non-organic visual loss	

*Symptom/sign present. †Fundal sign on first presentation. ‡Subsequent fundal feature/finding. –, Feature not present.
MEH, Moorfields Eye Hospital; NCL, neuronal ceroid lipofuscinoses; NR, feature not reported; ND, no data available.

Table 3 Neurological symptoms and signs

Patient	1	2	3	4	5	6	7	8	9
Cognitive	Slow learning	Learning difficulties, low IQ, reduced cognitive skills: verbal and non-verbal	Dyslexia, non-verbal learning disorder	Learning difficulties	Learning difficulties, dyslexia	No neurological symptoms/signs	Developmental regression, Communicates with single words	No neurological symptoms/signs	No neurological symptoms/signs
Motor	Poor coordination, Feeding difficulties	Problems standing unsupported on 1 leg, Slurred speech	Coordination of complex motor skills difficult	Difficulty writing	Change in gait/poor coordination/rigidity, slurred speech, reduced deep tendon reflexes in lower limbs	–	Walking with support only, Reduced muscle tone, Hyperreflexia lower limbs, Ankle clonus	–	–
Behavioural	Aggressive behaviour/ outbursts, Poor sleeping	–	Psychological assessment age 5 – temper/outbursts	Poor sleeping, erratic behaviour/aggressive outbursts	–	–	–	–	–
Seizures	Vague episodes	No	No	Absences EEG requested	Yes, grand mal	No	Absences	No	Yes Grand Mal
EEG?	No	No	No	Requested	Yes	No	Yes	Yes	Yes
Age of onset	–	–	–	8	10	–	–	–	–
Time after onset visual failure	–	–	–	1 year	3 years	–	–	–	–

–, Not applicable/no data available. EEG, electroencephalogram.

neurological/behavioural features develop; or the possibility of Batten disease is raised by the ERG (table 3). Two of the nine patients were thought to have a functional visual disorder initially as a reason for reduced visual acuity.

Bull's eye maculopathy is commonly reported in the literature on jNCL.[1 11 12] However, only two of nine patients presented with this feature, with a further two patients subsequently developing a bull's eye lesion. In one patient who initially had a normal fundal appearance this was apparent one year after the development of visual failure. The other patient had a pigmentary maculopathy at presentation, followed by atrophic changes before eventually developing a characteristic bull's eye maculopathy (table 2). Two patients had a normal fundal appearance on presentation and were originally suspected of functional (non-organic) visual loss. This highlights that these changes may emerge with time and may not be apparent at the time of presentation with visual failure. Spalton *et al* also noted the low number of patients with a bull's eye maculopathy at presentation.[2]

Visual field constriction was present in three of three children in this series who underwent visual field testing. This may be an underestimate of the true number as testing in young children can be difficult or unreliable. Four patients had eccentric viewing, which would appear similar to the feature described previously as ''overlooking,'' where children held their eyes in a raised position when attempting to fixate on a target. This was considered to be due to the relative preservation of the superior peripheral retina.[2]

The contribution of electrodiagnostic testing to diagnosis, further investigation and management of disease in the paediatric ophthalmology population has previously been described.[13] The early electrophysiological tests performed in many of these patients raised clinical suspicion of jNCL, prompting further diagnostic tests to be performed. The ERG findings in this series included an unrecordable rod specific ERG, an electronegative maximal response, reduced and delayed cone flicker ERG, an undetectable pattern ERG, and an abnormal photopic ON/preserved photopic OFF response, in keeping with but extending those previously described.[8] Perhaps the feature most suggestive of jNCL is a markedly reduced b:a ratio in the single flash photopic ERG with additional a-wave delay. The electronegative ERG is consistent with the inner retinal localisation of the gene product for CLN3.[8 11] An electronegative ERG may also be observed in conditions such as X linked congenital stationary night blindness and juvenile X linked retinoschisis,[11 14] but the combination of clinical features and other aspects of the ERGs do not usually result in confusion.

In addition to the cognitive decline, progressive motor disturbance and behaviour changes were noted in six of nine patients. Two of nine patients were noted to have problems with sleeping. These patients were both noted to have peripheral pigmentary or atrophic retinal changes (table 3)

In this series, 89% of patients (eight of nine) demonstrated vacuolated lymphocytes and fingerprint inclusions on electron microscopic testing (in two patients also on skin biopsy), a higher percentage than in previous series.[2 15] Two patients were found to be heterozygous for the 1.02 kb deletion of the *CLN3* gene; five others were homozygous and to date the genetic mutation has yet to be identified in a further patient. Diagnosis in this patient rested on the clinical findings, neurophysiological and MRI testing, which were characteristic of jNCL. The phenotype for patients heterozygous for the common 1.02 kb deletion differs from that of patients homozygous for this deletion in that the course of the disease is slower and some individuals may develop visual loss only into early adult life. This slower progression is possibly because the unknown mutation on the other allele does not abolish CLN3 activity completely.[4 16]

Table 4 Electrophysiology

Patient	1	2	3	4	5	6	7	8	9
Rod specific ERG	Undetectable		NP		Undetectable	NP	NP	Severely Subnormal	NP
Maximal response	Negative		Negative		Undetectable	Negative	Residual	Negative	Negative
Cone flicker ERG	Subnormal/ delayed		Delayed		Undetectable	Altered waveform, preserved amplitude	Undetectable	Subnormal	Subnormal, delayed
Photopic ON/OFF	Reduced b:a −ve ON, Preserved OFF		Reduced b:a −ve ON, Preserved OFF		Undetectable NP	Reduced b:a −ve ON, Preserved OFF	Reduced NP	Reduced b:a NP	Reduced b:a NP
PERG	Undetectable		Undetectable		NP	Undetectable RE, residual LE	Undetectable	Undetectable	Undetectable
VEP	NP		Delayed		NP	Delayed	Residual	NP	Undetectable
Previous ERG/ comments	Said to be normal elsewhere age 5	All ERGs said to be undetectable elsewhere	Photopic ERGs done as EUA	Previous ERG elsewhere age 7 – retinal dystrophy	Previous ERGs age 7, 9 elsewhere. First said to show cone, 2nd rod-cone dystrophy	The 30Hz flicker ERG waveform was in keeping with loss of ON response, preservation of OFF response			

ERG, electroretinogram; PERG, pattern electroretinogram; VEP, visually evoked potential; EUA, examination under anaesthesia; NP, not performed.

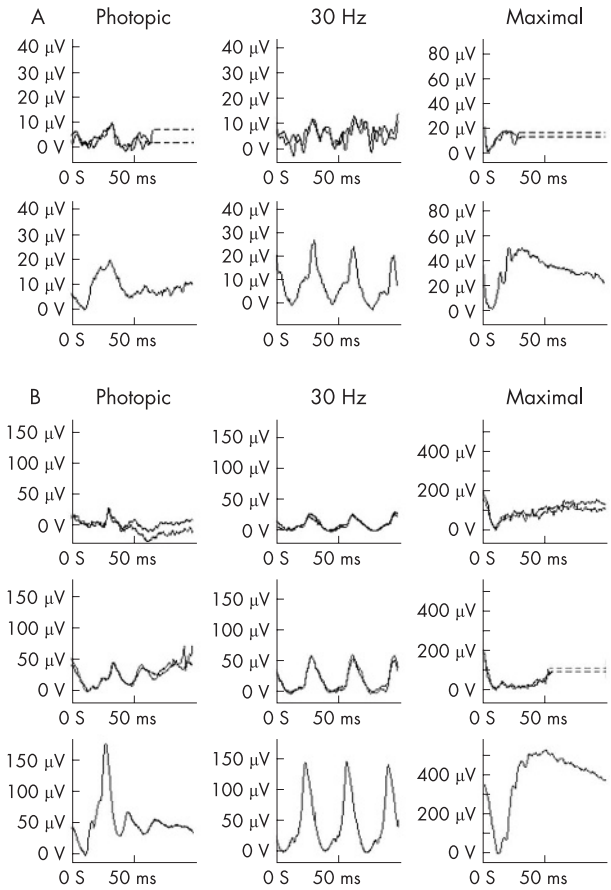

Figure 1 (A) ERGs recorded using a surface electrode on the lower eyelid. The upper trace is from patient 3, the lower trace from a normal child. Note the reduction in the b:a ratio in the photopic single flash ERG; the delayed and reduced 30 Hz flicker ERG; and the profoundly electronegative bright flash dark adapted ERG (maximal). Broken lines have been used to replace blink/eye movement artefact. (B) ERGs recorded using corneal gold foil electrodes. The upper traces are from patient 8; the middle traces are from patient 6 the lower traces are from a normal subject. The ERG characteristics are similar to those described above with additional amplitude changes in the photopic ERG of patient 8. Broken lines have been used to replace blink/eye movement artefact.

In the early series by Spalton *et al*, diagnosis was often delayed until the onset of seizures, with the delay in diagnosis ranging from 1–9 years.[2] None of their patients had undergone standardised electrophysiological testing, and our data suggest that early electrophysiology raises the possibility of jNCL, which can then be confirmed by molecular genetic testing. Many of the patients in the current series had not developed seizures at the time of molecular diagnosis.

Although jNCL is currently untreatable, it is important to make the diagnosis at the earliest opportunity to inform families and institute appropriate counselling. Planning for the supportive care of the affected child (including the family) may then be put into place. These patients should be managed by a multidisciplinary team, including a paediatrician, paediatric neurologist, ophthalmologist, family doctor, clinical geneticist, and a family support or equivalent unit. Severe vision impairment registration and low vision aid services are practical ways of providing help. Other measures may include educational statementing to ensure local authority provision of classroom support, especially important if the child is to stay within the mainstream school system. Families may gain much benefit from support groups such as the Batten Disease Association.

In summary, a diagnosis of Batten disease (juvenile neuronal ceroid lipofuscinosis) should be considered in children of 10 years and under presenting with unexplained visual loss in the presence either of a normal fundus or a bull's eye maculopathy. A low threshold should exist for further investigation, particularly electrophysiology, which in the present series contributed to earlier diagnosis than in earlier reports, often enabling confirmatory laboratory and genetic tests to be performed sooner than would otherwise have occurred. A non-organic cause for visual loss should not be assumed until electrophysiology has demonstrated normal function despite symptoms that suggest otherwise. A multidisciplinary approach has benefits to the management and ongoing support of these patients.

Authors' affiliations
J Collins, H Herbert, Moorfields Eye Hospital, London EC1V 2PD, UK
G E Holder, Electrophysiology Department, Moorfields Eye Hospital, London EC1V 2PD, UK

G G W Adams, Strabismus and Paediatric Service, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK

Correspondence to: Miss Gillian G W Adams, Strabismus and Paediatric Service, Moorfields Eye Hospital, City Road, London EC1V 2PD, UK; gill.adams@blueyonder.co.uk

Accepted for publication 16 May 2006

REFERENCES

1 **Taylor D**, Hoyt CS. *Paediatric ophthalmology and strabismus*. Philadelphia: W B Saunders, 2004:702–13.
2 **Spalton D**, Taylor DS, Saunders MD. Juvenile Batten's disease: an ophthalmological assessment of 26 patients. *Br J Ophthalmol* 1980;**64**:726–32.
3 **Ekazi J**, Kominami E. Symposium: The neuronal ceroid-lipofuscinoses (NCL)—a group of lysosomal storage diseases come of age. The intracellular location and function of proteins of neuronal ceroid lipofuscinoses. *Brain Pathol* 2004;**14**:77–85.
4 **Goebel H**, Wisniewski K. Symposium: The neuronal ceroid-lipofuscinoses (NCL)—a group of lysosomal storage diseases come of age. Current state of clinical and morphological features in human NCL. *Brain Pathol* 2004;**14**:61–9.
5 **Goebel H**. Symposium: The neuronal ceroid-lipofuscinoses (NCL)—a group of lysosomal storage diseases come of age. Introduction. *Brain Pathol* 2004;**14**:59–60.
6 **The International Batten Disease Consortium**. Isolation of a novel gene underlying batten disease, CLN3. *Cell* 1995;**82**:949–57.
7 **Mole SE**. The neuronal ceroid lipofuscinoses (NCL)—a group of lysosomal diseases come of age. *Brain Pathol* 2004;**14**:70–6.
8 **Mantel I**, Brantley MA Jr, Bellman C, *et al*. Juvenile neuronal ceroid lipofuscinosis (Batten disease) CLN3 mutation (Chrom 16p11.2) with different phenotypes in a sibling pair and low intensity in vivo autofluoresence. *Klin Monatsbl Augenheilkd* 2004;**221**:1–4.
9 **Marshman WE**, Lee JP, Jones B, *et al*. Duane's retraction syndrome and juvenile Batten's disease—a new association? *Aust N Z J Ophthalmol* 1998;**26**:251–4.
10 **Claridge KG**, Gibberd FB, Sidey MC. Refsum disease: the presentation and oftalmie aspect of Refsum disease in a series of 23 patients. *Eye* 1992;**6**:371–5.
11 **Horiguchi M**, Miyake Y. Batten disease—deteriorating course of ocular findings. *Jpn J Ophthalmol* 1992;**36**:91–6.
12 **Weleber RG**. The dystrophic retina in multisystem disorders: the electroretinogram in neuronal ceroid lipofuscinoses. *Eye* 1998;**12**:580–90.
13 **Woodruff SA**, Fraser S, Burton LC, *et al*. Evaluation of the electrodiagnostic investigation of children using the Greenwich Grading System. *Eye* 2004;**18**:15–19.
14 **Weleber RG**, Gupta N, Trzupek KM, *et al*. Electroretinographic and clinicopathologic correlatieons of retina dysfunction in infantile neuronal ceroid lipofuscinosis (infantile Batten disease). *Mol Genet Metab* 2004;**83**:128–37.
15 **Sinha S**, Satishchandra P, Santosh V, *et al*. Neuronal ceroid lipofuscinosis: a clinicopathological study. *Seizure* 2004;**13**:235–40.
16 **Eksandh L**, Ponjavic VB, Monroe PB, *et al*. Full field ERG in patients with batten/Spielmeyer-Vogt disease caused by mutations in the CLN3 gene. *Ophthalmic Genet* 2000;**21**:69–77.