Original research article

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
2020, Vol. 30(6) 1499–1505

DOI: 10.1177/1120672119899378
journals.sagepub.com/home/ejo
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Optic atrophy in children: Current causes and diagnostic approach

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Abstract

Background/aims: Optic atrophy is one of the leading causes of sight impairment in children. It frequently poses a diagnostic challenge, as it can be caused by many ocular and systemic conditions. We aimed to determine the current causes of optic atrophy at our centre and to describe the use of investigations, including molecular genetic testing.

Methods: We reviewed the medical records of children with optic atrophy seen at Moorfields Eye Hospital between 2010 and 2015. We recorded demographic data, reason for referral, history, investigations and diagnosis.

Results: We studied 143 cases aged below 16 years. A cause could be identified in all cases. Taking a full history was the most important part of the diagnostic workup, identifying a cause in 96 (67%) children. A developmental disorder of the brain and/or optic nerve, sometimes with retinal involvement, was the commonest cause (n = 33, 23%), followed by inheritable optic neuropathies (n = 27, 19%). Other causes included perinatal insults (n = 18, 13%), post-infectious or post-inflammatory conditions (n = 18, 13%), accidental or abusive trauma (n = 14, 10%) and inheritable retinal dystrophies (n = 13, 9%). Rare conditions included neurodegenerative disorders (n = 7, 5%), skeletal developmental disorders such as rickets (n = 4, 3%), tumours (n = 4, 3%), ischaemic events including large optic nerve head drusen (n = 4, 3%) and toxic events/metabolic conditions (n = 1, 0.7%).

Conclusion: In this series, an underlying cause could be identified in all cases. Taking a comprehensive antenatal, perinatal, postnatal and family history will indicate a probable diagnosis in two-thirds of children, and targeted ancillary tests may identify the cause in most remaining cases.

Keywords

Optic neuropathy, neuro-ophthalmology, neuro-ophthalmic disease, paediatric ophthalmology, genetic disease, congenital abnormalities, inborn errors of metabolism, infections, inflammations

Date received: 1 August 2019; accepted: 15 December 2019

Background

Optic atrophy (OA) is one of the leading causes of sight impairment in children, both in the United Kingdom and worldwide,[1–6] and its prevalence may be increasing.[3] OA in children frequently poses a diagnostic challenge and can be found in up to 38% of children with multiple disabilities.[3] It can be a sign of damage to, or underdevelopment of, the anterior or posterior visual pathways, with thinning of the neural tissue at the optic nerve head. The underlying causes have changed over the last 50 years and are known to vary depending on the population studied. In the 1960s, inherited conditions were the commonest recognised cause.[7] In the 1980s, brain tumours were the leading identifiable cause.[8] In the new millennium, complications of premature birth became the commonest cause[9] and more recently, perinatal events including prematurity.[10]

Currently no treatment is available for OA, but in the near future, there may be treatment for Leber's Hereditary Optic Neuropathy (LHON) and mitochondrial conditions.[11]

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Therefore, timely identification of treatment-eligible patients is required while retinal ganglion cells can still be salvaged. Similarly, identification of systemic associations, such as rickets or diabetes insipidus/diabetes mellitus/optic atrophy (DIDMOA or Wolfram syndrome), is important. In addition, all children with sight impairment benefit from early support, enabling visual habilitation and access to educational support.[12–15]

This evaluation describes the causes of OA in children at our tertiary eye care facility in London, UK, and the findings of investigations, including neuroimaging, visual electrophysiological and molecular genetic testing.

Methods

This work had Trust approval (CA16/ONSP/04) as a service evaluation. In October 2016, we searched the electronic patient record system (Open Eyes) at Moorfields Eye Hospital for relevant cases, using the following individual search terms: 'optic atrophy' or 'disc palor' or 'disc pallor' or 'optic neuropathy' or 'pale disc'. We included consultations, between 1 January 2010 and 31 December 2015, of children younger than 16 years. We excluded cases for whom no assessment details were available, and cases of glaucoma, microphthalmia and retinal detachment. We recorded demographic details including age at presentation, gender, clinical details, cause for presentation, antenatal and postnatal medical history, family history, clinical and ancillary test findings and diagnosis.

Where best corrected visual acuity (BCVA) was recorded as 'counting fingers', we assigned a value of 2.1 logMAR; for 'hand movements', 2.4 logMAR; for 'light perception', 2.7 logMAR; and for 'no light perception' or 'ocular prosthesis/artificial eye', 3 logMAR.[16] For 'fixing and following', we assigned the value equivalent of light perception, that is, 2.7 logMAR. We collated data in a Microsoft Office Excel 365. Statistical analysis was descriptive, presenting the proportions at diagnoses. To summarise patient age and BCVA, we calculated median and interquartile range (IQR), as data were not normally distributed.

Results

We identified 228 cases of OA in children aged below 16 years over the 6-year period. Review of the full electronic, and where available, paper-based records, resulted in 143 cases with sufficient details to be included in this evaluation (Figure 1).

Demographic details and visual function

Of the 143 children, 77 were boys (54%) and 66 girls (46%). Median age at first presentation was 5.9 (IQR = 2–8.3) years. In 101 cases, laterality was recorded; 83 (58%) were bilateral and 18 (13%) unilateral. BCVA or degree of visual behaviour transformed into logMAR values was available for 95 children. In these, median (IQR) BCVA in the worse affected eye was 1.0 (0.63–1.65) logMAR, and in the better-seeing eye, 0.7 (0.22–1.1) logMAR.

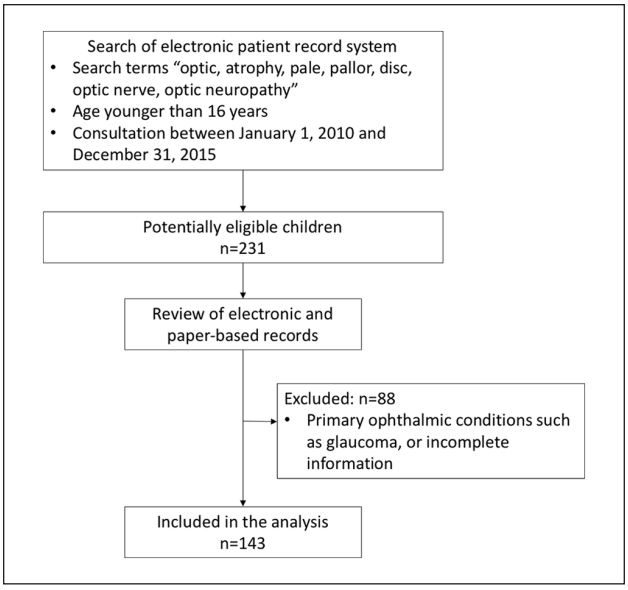

Figure 1. Medical records search and information retrieval.

Referral, presentation and causes

We identified two broad types of referral and presentation: in Group 1 (n = 118), parents, carers or healthcare professionals had noticed signs of reduced vision (including possible nystagmus or manifest strabismus) in one or both eyes, without a possible underlying cause being mentioned in the referral; in Group 2 (n = 25), children were referred to determine the visual impact of a known or suspected condition, or a family history of potential OA (Table 1).

However, on re-taking a full history, it was apparent that in Group 1, 71 of 118 children had either a previously identified relevant condition or a relevant family history (Table 2). Thus, in 96 (67%) of 143 children in this cohort, a condition or family history had been previously identified.

Among children in Group 1, 71 (60%) had bilateral and 12 (10%) had unilateral OA; in 35 (30%), information on laterality was not available (Table 2). In Group 2, bilateral OA was less frequent, occurring in 11 (44%) of 25 cases, and 5 (20%) were unilateral; details on laterality were not recorded in 9 (36%); 23 (16%) of 143 children had a family history of the same condition: 14 OA, 4 retinal dystrophy, 4 developmental eye/optic nerve/brain disorders and 1 a neurodegenerative condition (Tables 2 and 3).

The most frequent cause of OA, found in 33 (23%) of 143 children, was the developmental disorder of the brain, optic nerve, some including retinal involvement (Table 3).

Table 1. Reasons for referral in this cohort of children with pale optic nerve heads/optic atrophy.

	n	%
Referred for concerns about vision or related problem	118	83
Suspected reduced or poor vision in one or both eyes, or strabismus or nystagmus	116	81
Facial asymmetry, one eye looks bigger	1	1
Headaches	1	1
Referred to evaluate impact of known conditions	25	17
Abusive or accidental eye/orbital/optic canal or head trauma	10	7
Incidental finding of pale or swollen optic nerve heads	7	5
Family history of optic atrophy or retinal dystrophy	3	2
Prenatal developmental condition, such as microcephaly	2	1
Perinatal brain insult from prematurity/ intraventricular haemorrhage/hydrocephalus	2	1
Tumour	1	1
Total	143	100

Table 2. Known pre-existing conditions or relevant family history emerging when taking the history in those 118 referred for concerns about vision or related symptoms.

	n	%
Known pre-existing condition or relevant family history	71	60
Prenatal developmental condition, such as microcephaly	17	14
Perinatal brain insult from prematurity/ intraventricular haemorrhage/hydrocephalus	16	14
Family history of optic atrophy or retinal dystrophy	13	11
Postnatal infection/inflammation: meningitis/ encephalitis/ventriculitis/optic neuritis	7	6
Abusive or accidental eye/orbital/optic canal or head trauma	4	3
Postnatal toxic/metabolic/endocrine condition: vitamin D deficiency/rickets, other skeletal conditions (dysplasia), orbital conditions	5	4
Neurodegenerative condition	4	3
Tumour	1	1
Etoposide for Burkitt lymphoma	1	1
History of visual loss after aortic surgery	1	1
Learning difficulties	1	1
Post-infectious/inflammatory optic nerve pallor: neuromyelitis optica (Devic)	1	1
No relevant previously known condition	47	40
Total	118	100

An inheritable optic neuropathy was identified in 27 (19%), perinatal insult in 18 (13%), post-infectious or post-inflammatory conditions in 18 (13%), accidental or abusive trauma in 14 (10%), and an inheritable retinal dystrophy in 13 (9%). Rare conditions included neurodegenerative disorders in 7 (5%), skeletal developmental disorders including rickets, tumours, ischaemic events including large optic nerve head drusen in 4 (each 3%) and toxic events/metabolic conditions in 1 (0.7%) (Table 2).

Initial diagnostic assessment

The diagnostic workup for children in Group 1 (referred for possible reduced vision) included taking a detailed medical history of the pregnancy, delivery, perinatal events, postnatal development and family history. This was followed by orthoptic assessment of visual acuity, refraction and fundoscopy. Additional tests included visual evoked potential (VEP), electroretinogram (ERG) and neuroimaging (typically magnetic resonance imaging (MRI)). Computed tomography (CT) was carried out for suspected skeletal abnormalities, including osteopetrosis and microcephaly, or when MRI was contra-indicated. Molecular investigations included tests for specific mutation analysis (dominant optic atrophy, LHON, DIDMOA) or whole-exome or whole-genome sequencing (Genomics England). In Group 2, for whom the principal clinical question was to determine their current level of visual functioning, neuroimaging had typically already been undertaken prior to referral. Molecular testing was undertaken if it had not been carried out already.

Visual field assessment was carried out infrequently, reflecting the absence of tests that young children and those with developmental impairment can undertake. Of children who could co-operate with visual field tests, 18 (53%) of 34 had field defects. Pupillary assessment was recorded in 91 children, with a finding of unreactive or slowly reactive pupil in 16 (18%), and a check for relative afferent pupillary defect, present in 12 (14%) of 86. Colour vision assessment was carried out in 34 children, with defective colour vision detected in 22 (65%); 19 underwent optical coherence tomography (OCT), of which 14 (74%) had retinal nerve fibre layer thinning and 1 (5%) thinning of the ganglion cell complex.

In most cases of isolated retinal dystrophy or optic neuropathy without a family history, there were no concerns regarding the child's development or general health. However, full diagnostic workup including assessment by a paediatrician and neuroimaging revealed additional findings in 22 (36%) of 61 children.

Additional investigations

Additional investigations were guided by the history and clinical findings (Table 4). Visual electrodiagnostic tests and neuroimaging were the most commonly performed additional investigations and, together with OCT, had the

Table 3. Causes of optic nerve pallor/optic atrophy in this cohort.

	n (%)	n	Laterality		
			Bilateral	Unilateral	Not available
Developmental eye/optic nerve/brain malformation	33 (23)		23	6	4
Including those with additional conditions					
Microcephaly chorioretinal atrophy		1			
Cerebellar-retinal degenerative disorder		1			
Retinal dystrophy: Dandy Walker syndrome plus cone dystrophy		1			
Retinal dystrophy: Knobloch syndrome		1			
Microcephaly plus FEVR		1			
Retinal dystrophy – microcephaly syndrome		1			
Congenital hypdrocephalus secondary to posterior fossa arachnoid cyst		1			
No definitive diagnosis (possible Ohdo syndrome)		1			
Plus aniridia		1			
Inheritable optic atrophy	27 (19)		19	1	7
No molecular diagnosis		7			
OPA1/dominant		7			
Dominant, no molecular diagnosis		3			
OPA1/dominant PLUS hypopituitarism and congenital bone (forearm) abnormalities		1			
LHON		5			
DIDMOAD		4			
Perinatal insult (including hydrocephalus), cerebral visual impairment, optic nerve head pallor	18 (13)		11	1	6
Post-infectious/inflammatory optic nerve pallor (including optic neuritis)	18 (13)		3	2	13
Post-infectious/inflammatory optic nerve pallor PLUS white matter lesions		1			
Post-infectious/inflammatory optic nerve pallor: meningitis neuroretinitis		1			
Postnatal accidental or abusive trauma	14 (10)		3	4	7
Inheritable retinal dystrophy	13 (9)		11	0	2
Isolated, unspecified		7			
Isolated, CSNB		1			
Isolated, Leber congenital amaurosis		1			
Isolated, Stargard		1			
Isolated, X-linked retinoschisis		1			
Plus incontinentia pigmenti, Peutz–Jeghers syndrome		1			
Plus Heimler syndrome		1			
Neurodegenerative disease	7 (5)		5	0	2
Diagnosis unknown		1			
Juvenile Batten disease (CLN3)		1			
Peroxisomal disorder (Zellweger spectrum)		1			
Possibly HMSN (Charcot–Marie–Tooth)		1			
Progressive encephalopathy with oedema, hypsarrhythmia and optic atrophy		1			
Brown–Vialetto–Van Laere syndrome		1			
Sandhoff disease		1			
Skeletal malformation including rickets	4 (3)		4	0	0
Tumour	4 (3)		2	2	0
Ischaemic, including drusen	4 (3)		1	1	2
Toxic/metabolic	1 (1)		0	1	1
Total	143 (100)				

LHON: Leber's hereditary optic neuropathy; DIDMOAD: diabetes insipidus/diabetes mellitus/optic atrophy/deafness; FEVR: familial exudative vitreoretinopathy; CSNB: congenital stationary night blindness; HMSN: hereditary motor and sensory neuropathy.

Table 4. Additional investigations carried out in this cohort of 143 children with optic atrophy.

	Number/proportion of children undergoing investigation		Diagnostic yield	
	n	%	n	%
Flash/pattern ERG	77	54	34	44
Flash/pattern VEP	72	50	63	87.5
Neuroimaging	64	45	43	67
Molecular genetic testing	40	28	15	37.5
Optical coherence tomography of retina and/or optic nerve head	19	13	14	74
Blood tests	16	11	4	25
Lumbar puncture (opening pressure)	10	7	1	10

ERG: electroretinogram; VEP: visually evoked potentials.
Visual electrodiagnostic tests and neuroimaging were the most commonly performed additional investigations and, together with optical coherence tomography, had the highest diagnostic yield.

highest diagnostic yield. Of those who underwent neuroimaging (n = 64), 61 had MRI and 3 computer tomography scans, which revealed abnormalities of the brain and/or orbit in two-thirds of children.

Targeted molecular testing delivered a definitive diagnosis in over one-third of children tested (15 of 40). Blood tests for metabolic conditions showed increased serum glucose, abnormal serum calcium, hyperthyroidism and deficiency in insulin-like growth factor 1 in four children only. Blood tests for infectious diseases were requested for five children, but were negative in all cases.

Discussion

This is the first large case series of OA in children in the United Kingdom, carried out at a centre providing secondary and tertiary eye care for the largest metropolitan area in Europe. The principal findings of this evaluation are that in all cases of OA, an underlying cause could be identified, and that taking a full history is of paramount importance, to guide further investigations.

The leading cause of OA in children was the developmental disorder of the brain and/or optic nerves. This is a change from historical series where hereditary causes were the leading cause,[7] and more recent series were tumours,[8] and premature birth[9,10] was the most common underlying cause.[17]

The importance of full history has been reported by previous studies.[18–20] In our series, this was the most important part of the diagnostic workup, and this has relevance for referring clinicians. Once obtained, the detailed antenatal, birth, medical and family history allows targeting of investigations. This meant that neuroimaging, electrodiagnostic testing (EDT) and genetic testing had a high diagnostic yield. The final outcome was that, here, a cause could be identified in all cases. This appears to be part of a secular trend, with resolution rising from half of the cases in the 1960s[7] to 89% in the 1980s[8] and 96% in the 1990s.[9]

Neuroimaging certainly facilitates the diagnosis of intracranial pathology,[7,8] and in a series of isolated clinically unexplained OA, its diagnostic yield in the detection of tumours was 20%.[19] In our series, targeted imaging detected intracranial pathology in 67%, confirming that neuroimaging can be used selectively, minimising the radiation burden of CT and the need for general anaesthetic for MRI in young children.

EDT helps differentiate retinopathy and post-retinal pathology, both in our and previous series.[21–23] Genetic testing provided a molecular diagnosis in 15 of 40 children (38%) tested, which is similar to the reported clinical sensitivity of genetic screening for hereditary optic neuropathies.[24] Other cases took part in the 100,000 Genomes Project (http://www.genomicsengland.co.uk) and/or the Deciphering Developmental Disorders project,[25] which will help increase the genetic yield in the future. Blood tests for infectious diseases and metabolic workup should be performed as guided by the history and clinical signs. As with other series, we found that in most cases, routine blood tests are not required.[18]

Our evaluation is limited by its design as a retrospective review of medical records, which means that for some parameters, information was missing. Another limitation arises from our site being a stand-alone eye hospital, as children with complex needs are more likely referred to specialist children's hospitals with an embedded eye clinic. However, as we have supporting paediatricians on site, and provide a service across all childhood eye conditions, we suspect that our findings may be generalizable to other settings.

Conclusion

Clinicians should aim to find an identifiable cause of OA in all cases. Taking a full antenatal, perinatal, postnatal and family history will indicate a probable diagnosis in two-thirds of children, which will then guide further investigations. Based

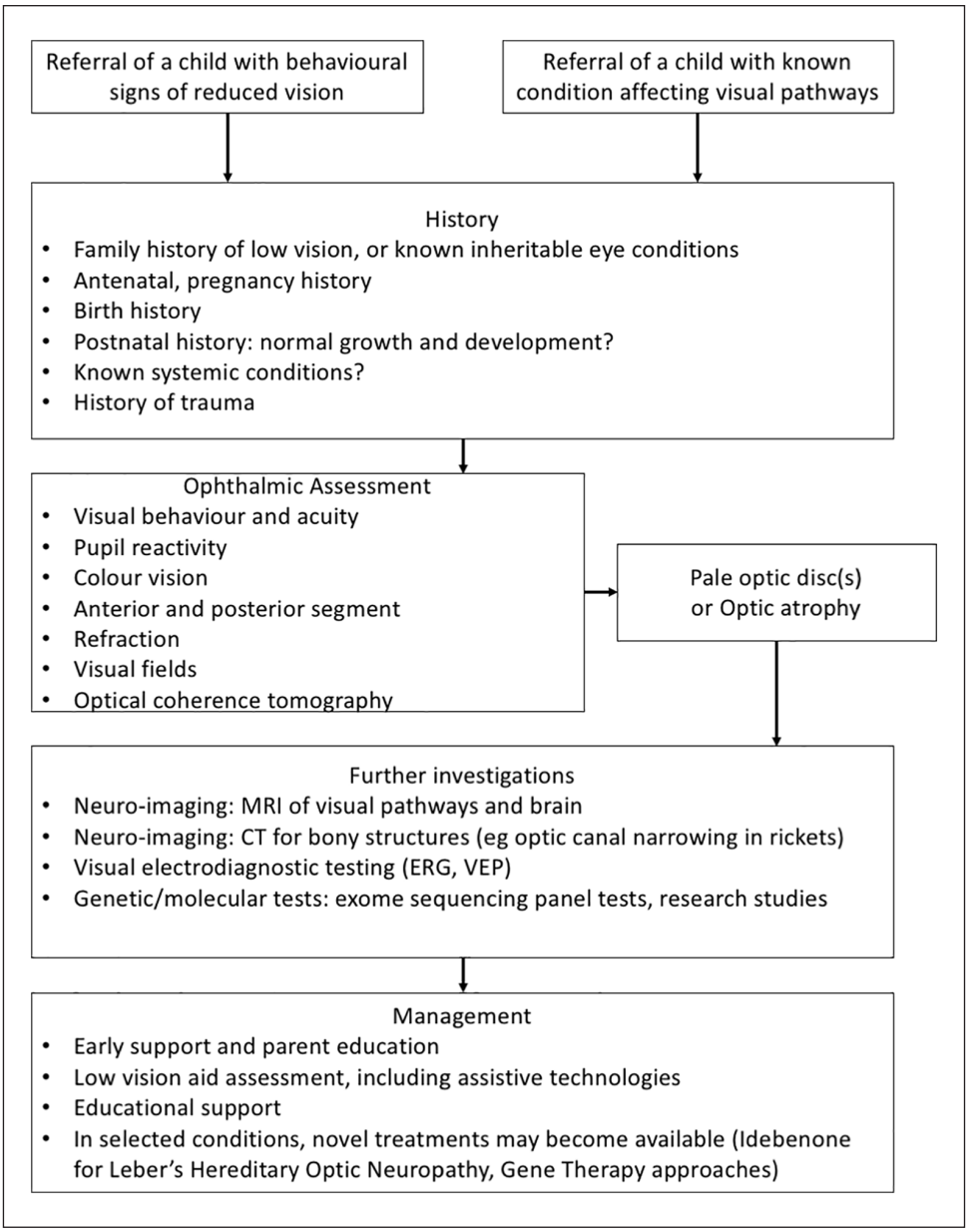

Figure 2. Suggested approach to diagnosis and management of optic atrophy in children.

on the experience presented here, we recommend the diagnostic approach summarised in Figure 2.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: A.D.-N. and H.A.-H. are supported by the National Institute for Health Research (NIHR) Moorfields Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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