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

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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.¹ 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.¹ In the 1980s, brain tumours were the leading identifiable cause.⁵ In the new millennium, complications of premature birth became the commonest cause⁹ 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.

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

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.
highest diagnostic yield. Of those who underwent neuro-
imaging (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 diag-
nosis 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 second-
ary 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 develop-
mental 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 birth9,10 was the most common underlying 
cause.17

The importance of full history has been reported by pre-
vious studies.18–20 In our series, this was the most impor-
tant part of the diagnostic workup, and this has relevance 
for referring clinicians. Once obtained, the detailed ante-
natal, birth, medical and family history allows targeting of 
investigations. This meant that neuroimaging, electrodiag-
nostic testing (EDT) and genetic testing had a high diag-
nostic 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 1960s7 to 89% in the 1980s8 and 96% in the 1990s.9

Neuroimaging certainly facilitates the diagnosis of 
intracranial pathology,7,8 and in a series of isolated clini-
cally unexplained OA, its diagnostic yield in the detection 
of tumours was 20%.10 In our series, targeted imaging 
detected intracranial pathology in 67%, confirming that 
neuroimaging can be used selectively, minimising the radi-
ation 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 sen-
sitivity of genetic screening for hereditary optic neuro-
pathies.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 fam-
ily history will indicate a probable diagnosis in two-thirds of 
children, which will then guide further investigations. Based

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

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

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

**Declaration of conflicting interests**

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