Choroidal neovascularisation in children

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► Additional tables (containing full details of the studies in tables 1 and 2) are published online only at http://bjo.bmj.com/content/vol92/issue4

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ABSTRACT

Choroidal neovascularisation (CNV) is a rare but important cause of visual impairment in children. There have been considerable recent advances in our understanding of both the pathogenesis and the management of this sight-threatening complication. New treatment modalities for these neovascular lesions make early recognition very important for timely management and preservation of vision. This review highlights the causes and current management options available for this condition in children.

Choroidal neovascularisation (CNV) is characterised by the growth of new blood vessels that originate from the choroid through a break in Bruch's membrane into the sub-retinal pigment epithelium (sub-RPE) or subretinal space. The neovascular membrane usually occurs at the macula or at the margin of the optic disc and often leaks blood and fluid, resulting ultimately in photoreceptor cell death. The most common cause of CNV in adults is age-related macular degeneration, the leading cause of blindness in Europe and North America. In younger adults, CNV is usually associated with ocular disorders such as chorioretinal inflammation, choroidal rupture, angioid streaks, high myopia and retinal dystrophies.[1 2] The development of CNV in children is rare, and in many cases the cause is uncertain.[3] The aim of this paper is to review current knowledge relating to the aetiology and management of CNV in children.

INFLAMMATORY CNV

The most common cause of CNV secondary to inflammation in children is presumed ocular histoplasmosis syndrome (POHS).[3] This is a clinical diagnosis and relies on the presence of typical clinical findings of atrophic chorioretinal scars at the macula and retinal periphery, peripapillary atrophy, and the absence of signs of inflammation of the vitreous or anterior segment.[4] In POHS, CNV characteristically develops in early to mid-adult life, but retrospective case series indicate that about 3–4% of CNVs in POHS develop in patients below the age of 20 years.[4–6] The CNV may manifest at multiple sites, especially at peripapillary and subfoveal locations.

Another important cause of inflammatory CNV in children is ocular toxoplasmosis (fig 1). The frequency of CNV in this disorder is difficult to ascertain because affected patients usually have scotomas subsequent to retinochoroiditis and are often ignorant of further visual loss from CNV.[7] Although the frequency of CNV in ocular toxoplasmosis in children is uncertain, most case series of CNV in children include this diagnosis.[8 9]

Rubella retinopathy is benign, non-progressive and asymptomatic unless it is complicated by the development of CNV at the macula.[10–12] Other reported causes of inflammatory CNV in children include presumed sarcoidosis, toxocara canis, Vogt–Koyanagi–Harada syndrome and chronic uveitis.[9–13]

OPTIC NERVE HEAD ANOMALIES

The first case of CNV in children with optic nerve head abnormalities was reported by Gass[14] in a 4-year-old child with optic nerve head drusen. This complication is, however, rare. In a retrospective series of 40 children with optic nerve head drusen with a follow-up of 44 months, Hoover *et al*[15] noted that only one child developed CNV. Other conditions of the optic nerve that are associated with CNV in childhood include optic nerve coloboma,[16] optic nerve pit[17] and morning glory syndrome.[18] Peripapillary CNV is also a rare complication of chronic papilloedema[19] and malignant hypertension.[20]

TRAUMATIC CHOROIDAL RUPTURE

CNV is a rare but significant cause of visual loss complicating choroidal rupture.[21 22] The proximity of the rupture to the centre of the fovea and the length of the rupture are risk factors for the development of CNV.[23]

RETINAL DYSTROPHIES

CNV has been reported in a number of retinal dystrophies and may be symptomatic during childhood. These include Best disease,[24 25] North Carolina macular dystrophy,[26] Stargardt disease and choroideraemia.[27–29]

MISCELLANEOUS CAUSES

Childhood CNV has been reported in association with high myopia, angioid streaks and choroidal osteoma. Myopic CNV can occur at any age, although it is rare in the paediatric age group.[30] This may be because predisposing factors such as RPE atrophy and lacquer cracks take time to develop.[31] Angioid streaks are rarely reported in children, and, when they do occur, they are rarely associated with CNV.[3] CNV has also been reported in children with choroidal osteoma[32 33] and combined hamartoma of the retina and retinal pigment epithelium.[34]

IDIOPATHIC CNV

When there is no clinical evidence of a predisposing abnormality, the CNV is termed idiopathic. All case series of CNV in children include idiopathic cases. The CNV is usually unilateral. No risk factors have been identified.[35]

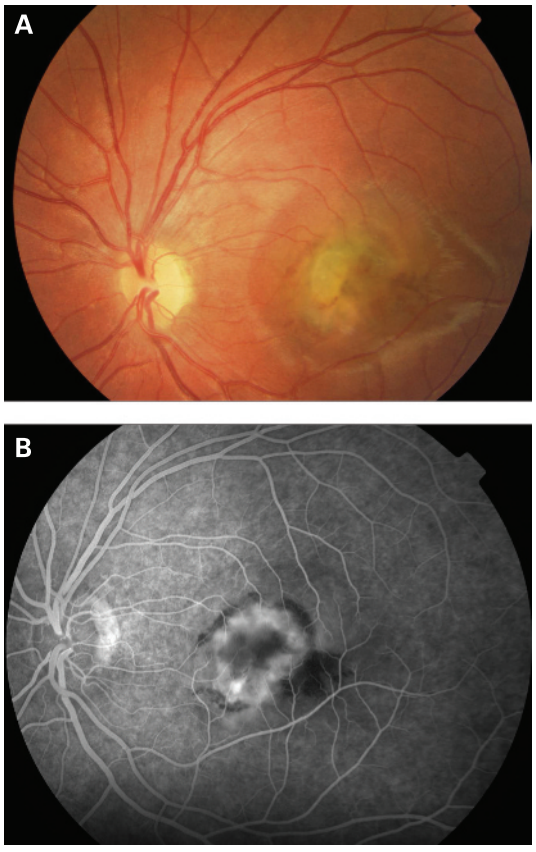

Figure 1 (A) Subfoveal choroidal neovascularisation in the left eye secondary to presumed toxoplasmosis. (B) Fluorescein angiographic appearance of the subfoveal choroidal neovascularisation. Consent for publication of this figure has been obtained.

TREATMENT OF CNV

The decision whether to treat CNV occurring in children is particularly difficult because of the late presentation, paucity of natural history data, and lack of clinical trials in children. The four main options are observation, thermal laser photocoagulation, submacular surgery and photodynamic therapy (PDT) with verteporfin. The proven efficacy of novel anti-vascular endothelial growth factor (VEGF) agents, such as pegaptanib sodium and ranibizumab, in age-related macular degeneration will lead to a debate about whether such agents are safe to use in children.

Observation

As CNV is rare in children, the natural history of the condition is not well described. In a series reported by Goshorn *et al*,[36] 58% (11/19) of untreated patients underwent spontaneous involution, with a final visual acuity of better than 20/50. However, in their series, 90% of patients with initial visual acuity of less than 20/200 achieved final visual acuity of less than 20/80. The CNVs were of multiple causes, and five of the 11 CNVs were extrafoveal or peripapillary.

When the natural history of various causes of inflammatory CNV in children is analysed, about half the patients retain a visual acuity of 20/200 or better in POHS,[5] and the visual prognosis of CNV secondary to toxoplasmosis and rubella is poor, with most patients having a final visual outcome of 20/200 or worse.[7 10–12] Natural history data are lacking for other rarer causes of inflammatory CNV in children. There are no outcome data on CNV in optic nerve head drusen in children, and it is difficult to translate the visual outcome data from adults with this condition, as the results are conflicting. Wise *et al*[37] noted a rapid progression of the CNV towards the macula in a case series of 23 patients and recommended early photocoagulation. Harris *et al*,[38] however, reported spontaneous involution of CNV in most cases. The visual prognosis of CNV in Best's disease in children is good compared with other retinal dystrophies, which generally have a poorer visual prognosis.[24 27] Although idiopathic CNV has been reported to have a better visual outcome than age-related macular degeneration, the case series did not include any children.[39]

Table 1 Photodynamic therapy in children

Study	Number of patients
Mauget-Faysee *et al*.[9]	6
Mimouni *et al*[53]	3
Giansanti *et al*[41]	5
Farah *et al*[40]	1
Oliveira *et al*[54]	1
Silva *et al*[55]	2
Potter *et al*[42]	1

Laser photocoagulation

Laser photocoagulation of extrafoveal and juxtafoveal CNV can usually safely be performed in teenagers and older cooperative children using similar techniques to those used in adults. Laser treatment is technically demanding in younger children. Laser photocoagulation using an indirect ophthalmoscopic delivery system is routinely used in children with peripheral retinovascular abnormalities, but is not suitable for juxtafoveal treatment because of the high risk of an inadvertent foveal burn.

Photodynamic therapy

A few case series and reports have described the results of PDT for CNV in children (table 1; a more detailed table can be found online). Visual acuity improved in most children. The two cases in which there was deterioration despite PDT were due to toxoplasmosis. Unlike PDT in adults, most children needed only one session. No serious systemic adverse events were noted in any patients. However, pronounced RPE alterations and atrophy were noted in five cases.[9 40 41] The causes of CNV in these cases were idiopathic (n = 2; ages 13 and 15 years), toxoplasmosis (n = 2; ages 10 and 12 years) and Vogt–Koyanagi–Harada syndrome (n = 1; age 9 years). The combination of PDT with intravitreal triamcinolone for a myopic subfoveal CNV membrane in a child improved vision but resulted in increased intraocular pressure.[42] PDT appears to be a promising treatment in young patients with subfoveal CNV.

Submacular surgery

CNV in children usually develops from a solitary site and is subretinal rather than sub-RPE. These factors contribute to a

Table 2 Submacular surgery in children

Study	Number of patients
Sears *et al*[26]	12
Uemura and Thomas[44]	17
Jain *et al*[25]	3
Mateo *et al*[51]	2
Sulu *et al*[52]	1
Inoue *et al*[34]	1

favourable outcome with surgical management.[43] As controlled and randomised trials are not practical given the rarity of cases, extrapolation from case series is the most useful way of assessing this treatment option. Table 2 shows the cases managed surgically in children reported in the literature (a more detailed table can be found online).

Most children had preoperative vision of less than 20/100, and submacular surgery gave very encouraging results, with 92% improving vision. Thirty-two of the children had subfoveal membranes. Postoperative recurrence of CNV was noted in nine cases (25%). Uemura *et al*[44] lasered the extrafoveal and juxtafoveal recurrent CNV, and second surgery was performed in subfoveal recurrence. One patient had moderate loss of vision due to loss of RPE at the time of surgery.

Other treatments

Several new therapeutic agents are now being used for CNV secondary to age-related macular degeneration. The results of intravitreal injections of anti-VEGF agents such as pegaptanib sodium (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin) are promising in adults and are associated with few side effects. However, it is difficult to assess the relevance of such data, acquired in elderly adults, to its use in children.

The VEGF molecule subserves important regulatory roles in endothelial differentiation in several organ systems during embryonic development[45] including fetal brain. It also plays a role in angiogenesis and the regulation of vascular permeability.[46] Hypoxic injuries upregulate expression of VEGF and its receptors on vascular endothelium, neurons and astrocytes, resulting in a process of physiological repair by normalising vascular perfusion to metabolic demand. Anti-VEGF agents given intravitreally may be found at low levels in the blood,[47] and this has led to concerns that this may be associated with increased risk of stroke in patients treated for age-related macular degeneration, especially in those with a previous history of stroke.[48]

Little is known about the role of VEGF in normal brain development, in part because of the lethality of any related knockout animal.[49] However, the effects of VEGF on brain repair give clues to the pleiotropic role of VEGF in brain development. Recent observations show that VEGF acts both as a common signalling linkage between the major cell types in nervous tissue and help in the maintenance and development of the blood–brain barrier.[50] The effects of suppressing these functions in children remain unclear. Another concern about using these agents in children is a lack of data about drug metabolism; this may be different in children from adults, and adverse events may occur that are not predictable from the adult experience.

The logistics of administering regular intravitreal injections in children, which may need general anaesthesia, should also be considered. Given the rarity of CNV, it will be extremely difficult to carry out a randomised controlled trial of these new agents in children, but one possible way forward would be to encourage all clinicians using anti-VEGF treatment "off label" in children to report results and complications in a common format to a central registry, so that outcomes of treatment and side effects could be evaluated in a larger series. There is currently no good evidence base, and clinicians need to make decisions about treatment on the basis of a risk–benefit analysis in each individual case. Children and parents should be counselled about the experimental nature of the treatment and possible risks.

CONCLUSIONS

The cumulative evidence from case series and reports provide valuable information on the natural history of visual outcome in children with CNV. It is, however, difficult to determine the likely benefits of therapy over the natural history of CNV in children. Of all the treatment modalities, submacular surgery shows the most encouraging results to date. Long-term studies are needed to assess the efficacy and side effects of treatment with PDT in children. The newer anti-VEGF agents should be used with caution in children, and only after a detailed discussion with parents about the possible side effects. Clinical trials of these and other novel treatments in children are probably not realistic, given the extreme rarity of the condition, but centralised reporting of the effects of treatment and side effects should lead to greater understanding of the best treatment strategy in childhood CNV.

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Patient consent: Consent for publication of fig 1 has been obtained.

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Notes