The ROYAL COLLEGE of OPHTHALMOLOGISTS

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Anisocoria in Children

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Anisocoria is a common finding in infants and children. Many cases have no serious cause; however, it is important not to miss rarer conditions such as neuroblastoma, which may present after a difference in pupil size is noted. Examination of infants and small children is a particular challenge and at younger ages it may be more difficult to determine whether findings are congenital or acquired. This article aims to outline a straightforward approach to the investigation and management of children with anisocoria, with particular emphasis on Horner syndrome. Additionally, the article highlights evidence that topical apraclonidine, often used to help determine the cause of anisocoria, has the potential for severe systemic adverse effects in infants, and so if used should be prescribed with caution.

Physiological anisocoria

Classically defined as a difference of 0.4 mm or more in the pupil sizes of an individual in the absence of ocular or neurological pathology, physiological anisocoria is said to occur in 20% of the adult population. However, more recent work has indicated that smaller degrees of anisocoria may be seen in almost ¾ of the adult population, exacerbated in dim light[1]. There are limited studies on paediatric anisocoria, but work by Suh et al indicates that a difference in the pupil sizes could be the 'normal' situation in children, with only 7% of 592 children showing no difference in pupil size between their two eyes[2]. However, these authors note that larger degrees of anisocoria are less commonly encountered in children, with only 3.7% showing an anisocoria greater than 1.3 mm. Larger amounts of anisocoria should therefore alert a clinician to the possibility of a more serious underlying cause. The assessment of pupil size in children is further complicated by factors such as fatigue and distress potentially influencing pupil size.

Horner syndrome

This classical triad of a 1-2 mm ptosis (due to a non-functioning Mullers muscle), miosis (most pronounced in the dark due to a non-functioning dilator pupillae) and anhydrosis (seen if the causative lesion is proximal to the superior cervical ganglion) occurs if there is disruption of oculosympathetic innervation, anywhere along its course from the hypothalamus, through the cervical sympathetic chain, along the carotid artery and into the orbit. Heterochromia is a well-known feature of congenital Horner syndrome, with the affected iris lighter in colour as melanin formation is thought to be sympathetically controlled. However, melanocytes continue to migrate into the iris even postnatally, so heterochromia may only come to light at the age of 9 months or even later. Heterochromia is also not seen in blue-eyed individuals, even where there is a congenital Horner syndrome. There are also rare reports of heterochromia in cases of acquired Horner syndrome, which again emphasises the importance of taking a thorough history in individuals with anisocoria[3], as heterochromia does not invariably indicate a benign causation.

A key question to ask early in the evaluation of any child with Horner syndrome is to determine whether it is congenital or acquired. Where there is suspicion that Horner syndrome is acquired and the causation uncertain, it must be investigated. The concern is missing a serious underlying pathology. Recent studies indicate surgery to be the most common cause for Horner syndrome, followed by birth trauma (more common in earlier series, which may reflect improvements in obstetric techniques) and mass lesions including neoplasia (16%)[4]. A major concern when seeing a child with Horner syndrome is the possibility that it may be caused by neuroblastoma. This is the commonest extracranial tumour in children below the age of 5 years, arising from primordial neural crest cells in the adrenal medulla (commonest site) and sympathetic ganglia. A prompt diagnosis is key, with infants diagnosed within the first year of life having better survival than children aged 1-4 years. A study by Musarella et al[5] reported that almost 1 in 5 children with neuroblastoma had ocular findings, and in 8.1% of all cases it was the presenting symptom. While most children presented with orbital signs secondary to orbital metastases, Horner syndrome was present in 3.4% of all cases of neuroblastoma, and was the presenting problem in 2%. Importantly, children with Horner syndrome had a better survival rate and were more likely to have localised disease. The importance of making a prompt diagnosis in young children with Horner syndrome due to the possibility of neuroblastoma is therefore clear.

In older children with acquired Horner syndrome, clinical examination and investigation is often more straightforward. Clinical assessment of any ocular condition is more challenging in an infant, and ascertaining the presence of a ptosis and characteristics of any anisocoria can be very difficult. George et al outlined their experience of 23 babies presenting with Horner syndrome in the first year of life[6]. In the majority of cases (70%), no underlying cause was found. Two children had an undisclosed underlying pathology on further investigation; one child with an acquired Horner and progressive iris heterochromia had a neuroganglioma of the lung apex and another child with raised urinary vanillylmandelic acid (VMA) had a cervical neuroblastoma. To assess an infant with Horner syndrome, these authors therefore recommended taking a thorough history, performing a clinical examination (including a systemic examination with a paediatrician/paediatric neurologist) and urinary VMAs. They recommend reserving further investigations for cases where Horner syndrome is acquired, or where there are other neurological signs or a cervical mass.

An alternative view is that every child with Horner syndrome should be investigated further, to eliminate the risk of missing a serious underlying cause such as neuroblastoma[7]. To support this viewpoint, Mahoney et al reported 28 children with Horner syndrome with no identified cause (including 24 of who had negative urinary catecholamine testing) who underwent imaging of the oculosympathetic tract. Six of these children were found to have a mass lesion. However, 5 cases were acquired, which to most clinicians would merit further work up. One six-month old baby was noted to have Horner syndrome since 2 weeks of age, which many Ophthalmologists would class as 'congenital'. Clinicians are thus left to balance the risks of investigating a baby under general anaesthetic with the very small risk of missing a serious underlying cause as the cause of a Horner syndrome.

Where Horner syndrome is in doubt

Physiological anisocoria is extremely common, as is a subtle difference in palpebral apertures in young children. It can be difficult to be confident of pupil responses in light and dark, and there is always the concern that one may be dealing with an asynchronous Horner syndrome (where anisocoria and ptosis have different times of onset). There are very few reports of such presentations of Horner syndrome in the literature, but it remains key to warn parents of children with anisocoria to seek urgent assessment of their child if a new ptosis is noted. Topical apraclonidine testing, where a positive test is denoted by a reversal of anisocoria due to denervation hypersensitivity, has become popular in patients of all ages in whom a Horner syndrome is suspected. It is not surprising that this test has been used in babies and young children to exclude the possibility of Horner syndrome. However, there are a number of reports where children have become lethargic and shown cardiovascular instability following administration of both 1% and 0.5% topical apraclonidine following such testing. These cases have been discussed in an Ophthalmic Safety Alert released by the RCOphth in February 2019. Taken together, the oldest child where such an adverse report has been noted is 2 years old. Effects can be delayed for some time after testing, in some cases taking 2 hours for symptoms to manifest. The effects can also be prolongued, lasting 18 hours and in the most severe cases necessitate admission to intensive care. The RCOphth recommendations are summarised below:

RCOphth Recommendations on use of topical apraclondine to test for Horner syndrome

- Apraclonidine 1% should not be used in the diagnosis of paediatric Horner syndrome
- Apraclondine 0.5% should not be used in children below the age of 6 months old in the diagnosis of Horner syndrome and used with extra caution in children below the age of 2 years
- All children under the age of 2 years should remain in the facility for 2 hours following administration of the agent

A suggested approach to assessing the child with suspected Horner syndrome

Take a focused history including:

- Is the Horner syndrome acquired? When were symptoms first noted?
- Has there been any progression of symptoms? - E.g. increasing anisocoria, asynchronous ptosis
- Is the child well? Are there any new neck or abdominal masses?
- Is there a history of birth trauma or neck/chest surgery?

Undertake an examination, in conjunction with a paediatrician/paediatric neurologist (according to local pathways)

- Classical features of Horner syndrome present (1-2 mm ptosis and miosed pupil)?
- Is the anisocoria more pronounced in the dark? Any dilation lag or reverse ptosis (retractor fibres in lower lid are sympathetically innervated) giving the impression of enophthalmos? Is iris heterochromia present?
- Is there anhydrosis on the same side as the Horner syndrome? This indicates there is disruption of sympathetic innervation prior to the superior cervical ganglion and a mass lesion must be excluded, especially cervical
- Are there any other ocular/neurological signs (including cranial nerve palsies and orbital signs)?
- Are there any neck or abdominal masses?

Further investigation

- If there is any suspicion th at the Horner syndrome is acquired, further investigation to rule out a pathology affecting the oculosympathetic pathway must be undertaken (the preferred modalities may differ between centres, but include a MRI of the head and neck, including orbits)
- In cases where the history or examination has revealed any 'red flags' (eg other neurological signs, unwell child) further investigation should be undertaken

Infants with suspected physiological anisocoria

- Where the only finding is isolated aniscoria, the risk of Horner syndrome is very low (N Raoof, unpublished data) but to mitigate the risk of an asynchronous Horner syndrome given that the time of onset is often uncertain, young children can be followed up soon after (suggest 6-8 weeks) to check no progression

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