**PEDIATRIC HORNER’S SYNDROME – IS INVESTIGATION FOR UNDERLYING MALIGNANCY ALWAYS REQUIRED?**

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**ABSTRACT**

OBJECTIVE

Horner’s syndrome (HS) is characterised by a triad of ocular miosis, ptosis and anhidrosis. HS may be a subtle sign of occult pathology in otherwise asymptomatic children, neuroblastoma (NBL) being the commonest associated malignant tumour. Despite such knowledge the incidence of underlying malignancy in children with HS remains unclear and robust evidence to guide best clinical practice is sparse. We performed a systematic review of the literature with the aim of identifying the incidence of NBL in children with HS of unknown aetiology, and establishing if screening for NBL should be routinely performed in this patient population.

METHODS

Systematic review of the literature (PubMed and Ovid/Medline database, 1961-2018).

RESULTS

The initial search identified 334 manuscripts, of which eight studies were included in the final analysis. All reports were single-centre retrospective studies without control groups and included a total of 152 patients (age range 0-20 years). All studies investigated patients with HS but without previously established diagnosis. In the studies included, 17 out of a total of 152 patients were diagnosed with a space occupying lesion. 12 out of the 152 patients were subsequently detected with NBL.

CONCLUSION

HS in children may be the first sign of occult malignancy. We report the first systematic review that comprehensively investigates the incidence of malignancy in this unique patient cohort. We show that HS of unknown aetiology in children warrants further investigation(s) to exclude an underlying space occupying lesion. This should include cross-sectional imaging of the brain, neck and thorax, plus urinary catecholamines for prompt diagnosis and treatment.

**MANUSCRIPT**

**INTRODUCTION**

Horner’s syndrome (HS) is characterised by a triad of ocular miosis, ptosis and anhidrosis, and was first described by Friedrich Horner in 1869 [1]. It occurs following disruption of the oculosympathetic pathway. This pathway provides the sympathetic innervation to the eye, through three orders of neurons which are located 1) central in the hypothalamus, 2) preganglionic in the thoracic spinal cord and 3) postganglionic in the superior cervical ganglion. [2] Extent of symptoms i.e. development of complete HS or isolated miosis depends on the level of disruption of the pathway. HS can be evaluated pharmacologically using the so-called “cocaine test” because cocaine acts as an inhibitor of noradrenaline re-uptake into the presynaptic sympathetic neuron. 2.5% - 5% cocaine eye drops are applied to the eye of a patient and anisocoria is measured 1 hour afterwards. In HS, the absence of sympathetic activity through denervation will not allow for dilatation of the miotic eye to occur, because sympathetic activity is absent due to denervation. HS is diagnosed if anisocoria is greater than 1 mm 1 hour after cocaine application. [3]

Most papers classify HS as either congenital or acquired. Causes of congenital HS include birth trauma, anomalies of the carotid artery, tumours and idiopathic occurrence [4]. Most frequently, new onset HS occurs post-operatively or as a result of trauma. Of greater concern, new onset HS may be the first subtle sign of underlying pathology in otherwise asymptomatic children. In such cases, neuroblastoma (NBL) is thought to be the most commonly associated malignant tumour [5]. Despite such knowledge, robust evidence to guide best clinical practice for investigating children with HS of unknown cause is sparse. Both the incidence of NBL and the overall incidence of occult malignancy in these children remain unclear. We performed a systematic review aimed to (1) identify the incidence of NBL in children with HS of unknown aetiology, and (2) establish if screening for NBL should be routinely performed in this patient population.

**METHODS**

*Search strategy*

The methodology of this study was designed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [6]. We electronically searched the PubMed, EMBASE and OVID databases from inception to December 2017 for the Medical Subject Headings (MeSH) terms as follows: For the aspect of HS, we used the MeSH terms “claude bernard horner syndrome” or “acquired horner syndrome” or “horner s syndrome” or “horner syndrome” or “horner s syndrome, pupil” or “horner syndrome, pupil” or “horner's syndrome” or “horner's syndrome, pupil”. For the diagnosis of NBL, we used the MeSH terms “neuroblastoma” or “neuroblastomas” or the text word term "neuroblastic tumor" or "neuroblastic tumour" or “neuroblastoma”. We restricted manuscripts to English language publications only.

Our initial search yielded 334 abstracts. These were screened based on our inclusion and exclusion criteria (table 1). Included studies were investigating the underlying diagnosis in participants presenting with a new onset of HS. Participants were aged from birth to 20 years. In order to explicitly investigate the incidence of NBL in children with HS, we only included studies where the underlying diagnosis at presentation was not known. We excluded case reports, and studies that investigated the incidence of HS in children with known NBL, post-operative HS, and HS due to birth trauma. Reference lists of identified articles were manually searched to identify additional studies.

The methodological quality of the included studies was assessed independently by two researchers (S.B. and P.F.) and scored according to the MINORS criteria [7]. The MINORS tool was chosen as a validated tool designed to identify and assess high quality non-randomized studies. The MINORS scale includes several items derived from indices of quality of randomized trials, but also allows for extra points if the study is a comparative one. In the case of score discrepancy of more than two points, discussions took place between the two investigators and consensus was reached.

*Data Extraction*

Data extraction included study characteristics (citation, country, study design and sample size), baseline population characteristics (age, gender, definition of HS), outcomes (underlying diagnosis of NBL, underlying diagnosis of other tumour or space occupying lesion).

*Statistical Analysis*

Due to the small number of included studies, and the significant heterogeneity observed, data was expressed in cumulative tables for study characteristics, demographics, and outcomes risk(s).

**RESULTS**

Our initial search identified 334 manuscripts. Out of these, eight studies fulfilled the full-text inclusion criteria and were included in the analysis (figure 1). These studies were all retrospective cohort studies [6 – 13]. The studies included a total of 152 patients. Age of patients was heterogeneous (range: infant to 20 years of age). Study characteristics and demographics are detailed in table 2.

*Outcomes*

The definition of HS was variable amongst the published studies (table 2). Some papers only included patients with a positive cocaine test. Due to the scarcity of data available we decided therefore to include all studies even if HS was not defined or verified through a positive cocaine test.

Studies were assessed for quality using the MINORS score [11]. The scores achieved by the different studies were low throughout. Table 2 shows the scores for individual studies.

Overall, a space occupying lesion was detected in 20 out of the 152 patients included in the published studies.

NBL was diagnosed in 12 out of the 152 patients. A ‘new’ malignancy was detected in 17 out of the 152 patients (table 3). These other lesions diagnosed here included: rhabdomyosarcoma (n=1), Ewing’s Sarcoma (n=1), ganglioneuroma (n=1), astrocytoma (n=1), metastatic tumour nodule (n=1), juvenile xanthogranuloma (n=1), intraorbital hemolymphangioma (n=1) and brain stem vascular malformation (n=1).

**DISCUSSION**

HS is caused by disruption of the oculosympathetic pathway through a multitude of causes. HS may be the first sign of underlying undiagnosed malignancy, NBL being the most common lesion. Although this fact is well recognized, robust data on the true incidence of NBL in this patient cohort is lacking.

This study is to the best of our knowledge the first systematic review study to comprehensively investigate the incidence of NBL (and occult malignancy) in pediatric patients with new onset HS. We herein crucially demonstrate - suspicion of HS of unknown aetiology in pediatric patients regardless of age should mandate investigation(s) to exclude an underlying space occupying lesion. In this systematic review we found that more than 1 in 10 children presenting with newly diagnosed HS had a malignant space occupying lesion, most commonly NBL. In some of the included studies, the incidence was much higher notably 27%. [8]

Limitation(s) of this study were the quality of evidence available in publications. The studies therefore eligible for inclusion were few in number and heterogenous, both from a clinical and methodological point of view. Patients included in the studies were of a broad age range, and the methods applied for diagnosis of HS were variable from study to study. The MINORS scores achieved by the different studies are low throughout, and quantify the clinical and methodological heterogeneity.

Small patient populations with a variable definition of HS were also encountered.

It is well known that negative results are published less frequently, a problem which is also referred to as “publication bias”. Therefore, it is possible that some case series with isolated, idiopathic HS were not been published and hence would have not been retrievable in a literature search. This is a common problem encountered when undertaking systematic reviews in general, and should be mentioned here for completion.

Some studies included patients from infancy. Although it is widely assumed the most common cause of HS in infants is resultant from birth injury at delivery, several newborns in the studies we analysed were diagnosed with congenital NBL and associated HS. These findings therefore strongly infer that HS observed in the neonatal period must also warrant further investigations (as in all patient age groups) unless there is a clear history of birth trauma in a baby .

*Recommendations for ‘ patient work-up ‘*

No agreed consensus protocol(s) currently exist for the clinical work-up of newly diagnosed HS in children. Most papers recommend a physical examination which is not well defined. Controversy exists with regards to requirements for either ( i ) urinary catecholamines analysis and ( ii ) imaging studies (chest radiograph , ultrasound , CT scan, MRI). [2, 14]

This systematic review confirms NBL as the most common malignant lesion detected in children with new-onset HS. We strongly recommend that ‘work-up’ should include urinary catecholamines as a rapid, non-invasive, low cost investigation. However, urinary catecholamine levels may be normal in some cases of NBL and therefore this should not wholly deter clinicians on their decision making as to whether imaging should or should not be obtained. [16] Suspicion of a pathological lesion should prompt cross-sectional imaging of the entire oculosympathetic pathway including head, neck and chest. [2] Magnetic resonance tomography (MRI) scans of the head, neck and chest are the investigation(s) of choice. [16, 17] A flow chart algorithm recommendation for investigating new onset HS in infants and children is shown in Figure 2 .

**CONCLUSION**

We report the first comprehensive systematic review study highlighting the incidence of NBL (and other lesions) in children with new-onset HS. Although the papers identified are few in number and heterogeneous, this study crucially shows that HS of unknown aetiology in children should prompt detailed investigation(s) to exclude underlying space occupying lesion(s). An algorithm is provided which may usefully guide clinicians in the ‘work-up’ of these patients.

**WHAT IS ALREADY KNOWN ABOUT THIS TOPIC**

* Horner’s syndrome (HS) is characterised by a triad of ocular miosis, ptosis and anhidrosis.
* HS may be a subtle sign of occult pathology in otherwise asymptomatic children.
* Neuroblastoma (NBL) and other malignancies may be the cause for HS.

**WHAT THIS STUDY ADDS**

* This is the first systematic review study investigating the incidence of NBL (and occult malignancy) in pediatric patients with new onset HS.
* More than 1 in 10 children presenting with newly diagnosed HS have a malignant space occupying lesion, most commonly NBL.
* HS of unknown aetiology in children should prompt detailed investigation(s) to exclude underlying space occupying lesion(s).

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| Inclusion Criteria | Exclusion Criteria |
| * Investigating the underlying diagnosis in patients with new onset HS
* “new onset” defined as previously not diagnosed with HS
* Only patients not previously diagnosed NBL or other solid tumour
* Study population < 20 years
 | * Non-english language
* Investigating HS due to other causes (post-operative, post-traumatic, birth trauma, and others)
* Study population > 20 years
* Review papers of studies already included
* Case reports, expert opinions
 |

Table 1: Inclusion and exclusion criteria (NBL = neuroblastoma)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Type of study | Number of patients | Age (Years, Mean, Range) | Criteria used to diagnose Horner’s Syndrome | Combined MINORs Score |
| Sauer et al, Neurology 1976. [8] | RCS  | 7 | 3.8 (range 0 – 10) | No definition | 2.5 |
| Woodruff et al, J Pediatr Ophthalmol Strabismus 1988. [9] | RCS  | 10 | 2.1(range 0 – 8) | Narrowing of the interpalpebral fissure + ipsilateral miosis with anisocoria | 1.5 |
| Jeffery et al, J AAPOS 1998. [10] | RCS  | 11 | 6.9(range 0.1 – 4.1) | Unilateral miosis +/- ptosis + positive cocaine testing | 6.5 |
| George et al, Br J Ophthalmol 1998. [11] | RCS | 23 | Not specified | Anisocoria and ptosis +/- heterochromia or facial anhydrosis | 4.5 |
| Mahoney et al,Am J Ophthalmol 2006. [12] | RCS | 28 | 2.04 (range 0.12 – 8.83) | Unilateral miosis +/- ptosis + one of the following: 1) obvious pupillary dilatation lag in the dark, 2) positive cocaine test, 3) iris heterochromia, 4) ipsilateral facial anhydrosis, 5) neck surgery | 6.5 |
| Smith et al, Arch Ophthalmol 2010. [13] | RCS | 9 | Not specified | Miosis +/- ptosis and one more of: 1) pupillary dilatation lag 2) iris heterochromia 3) anhydrosis 4) history of trauma to neck | 5.5 |
| Kadom et al, Pediatric Radiol 2015. [14] | RCS | 38 | 4.1(range 0 – 20) | Unilateral miosis + at least one of: ipsilateral ptosis, ipsilateral heterochromia, positive cocaine block | 3.5 |
| Martin et al, Eur J Ped Neurol 2017. [15] | RCS | 26 | 0.24 (range 0 – 0.6) | Isolated miosis with dilatation of the miotic pupil on cocaine test +/- associated signs | 5.5 |

Table 2: Study Characteristics and Definition of Horner’s Syndrome (RCS – retrospective cohort study)

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Incidence of NBL | Incidence of Malignancy | Overall incidence of space occupying lesion |
| Sauer et al, Neurology 1976. [6] | 0/7 (0%) | 1/7 (14%) | 1/7 (14%) |
| Woodruff et al, J Pediatr Ophthalmol Strabismus 1988. [7] | 2/10 (20%) | 2/10 (20%) | 2/10 (20%) |
| Jeffery et al, J AAPOS 1998. [8] | 2/11 (18%) | 3/11 (27%) | 4/11 (36%) |
| George et al, Br J Ophthalmol 1998. [9] | 2/23 (9%) | 3/23 (13%) | 3/23 (13%) |
| Mahoney et al,Am J Ophthalmol 2006. [10] | 4/28 (14%) | 5/28 (18%) | 6/28 (21%) |
| Smith et al, Arch Ophthalmol 2010. [11] | 0/9 (0%) | 0/9 (0%) | 0/9 (0%) |
| Kadom et al, Pediatric Radiol 2015. [12] | 1/38 (3%) | 2/38 (5%) | 2/38 (5%) |
| Martin et al, Eur J Ped Neurol 2017. [13] | 1/26 (4%) | 1/26 (4%) | 2/26 (8%) |

Table 3: Numbers of patients with diagnosis of Neuroblastoma, other malignancies, or other space occupying lesions in the studies