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Original Article

Etiology-based strabismus classification scheme for pediatricians

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ABSTRACT

Background. Pediatricians are regularly involved in the initial examination of children presenting with strabismus, a common ocular condition occurring in 3% of children. The objective of this review was to gain insight into pediatric residents, fellows and attendings' understanding of strabismus, and to propose an etiology-based strabismus classification scheme to aid this understanding.

Methods. A survey was conducted in a single Department of Pediatrics in a university academic institution in order to assess the degree of understanding of the classification, etiology and nomenclature of strabismus. A targeted literature review, pertinent to our classification scheme for strabismus in the pediatric age group, is provided to clarify the various underlying etiological conditions for pediatricians.

Results. The surveyed cohort (n=26) consisted of 10 (38.5%) attendings and 16 (61.5%) pediatricians-in-training. Although 69% of survey participants felt comfortable performing an ocular motility evaluation, only 19% had a clear understanding of the underlying etiology of strabismus, 8% had a clear understanding of strabismus nomenclature and none of the participants had clear knowledge of a classification scheme of strabismus. We propose an etiologic-based strabismus classification scheme with streamlined nomenclature geared towards Pediatricians to facilitate the management of pediatric patients with various ocular misalignments. Eight major categories of this classification scheme include (1) physiologic, (2) comitant, (3) paralytic, (4) sensory, (5) syndromic, (6) orbital, (7) supranuclear and (8) pseudostrabismus.

Conclusions. Pediatricians at all levels of professional experience have a limited command of strabismus. An etiology-based classification scheme of strabismus may assist in understanding the underlying causes and facilitate the management of strabismus in the pediatrician's office.

Key words: strabismus classification, strabismus etiology, pediatric strabismus.

Strabismus is a common ophthalmic condition in children, with a prevalence around 2-3%.[1-3] Pediatricians should promptly identify ocular motor disorders in children for two main reasons: strabismus may be the only sign of a critical ocular, neurologic or systemic disease with significant health implications[4], and an ocular misalignment may lead to irreversible amblyopia and loss of binocularity if treatment is delayed beyond the age of visual plasticity.[5-6]

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An ocular motor disorder may be observed as a crossing in of an eye (esotropia), a drifting out of an eye (exotropia), a vertical misalignment (hypertropia or hypotropia), or an incomplete rotation of an eye. Pediatricians are often the first medical providers to encounter infants or children who have strabismus, and have a pivotal role in the identification and referral of these patients.

The term strabismus in medical texts is often narrowly defined to describe an ocular motor problem in which the eyes are not properly aligned. Ophthalmologists tend to use a broader usage to include any type of eye muscle disturbance that may not necessarily include

a misalignment of the eyes, such as in a gaze palsy or apraxia.

Various classification schemes exist for strabismus, most of which are penned by pediatric ophthalmologists for use within the ophthalmology community.[7] These same schemes show up in primary care texts, and classify strabismus in terms of direction of misalignment, whether constant or intermittent, as comitant versus incomitant, as patterns with over- or under-actions of oblique extraocular muscles, as a relationship to accommodation, as excesses or insufficiencies of convergence or divergence, and in terms of age of onset or laterality.[7] Confusing nomenclature such as high accommodative convergence/accommodation esotropia or divergence excess exotropia may show up in these types of schemes. Also, these classification schemes provide little insight as to why patients develop the strabismus, the necessity for early referral or the expected work-up.

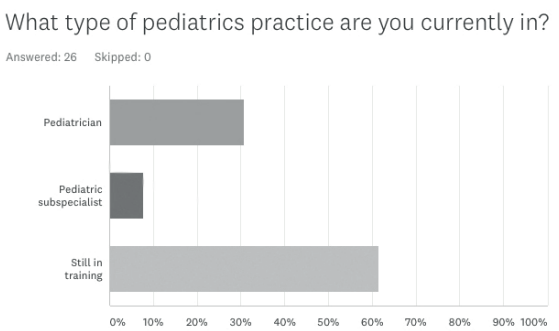
In the present study, we aimed to construct a clinically relevant classification of strabismus to simplify the differential diagnosis and work-up of pediatric patients for pediatricians and primary care physicians. In order to assess the current understanding of strabismus conditions by the pediatricians, we undertook a survey of the pediatrician faculty and pediatric residents/fellows at our academic institution to see if these individuals had a working knowledge or comfort level in understanding strabismus. We propose an alternative etiology-based classification scheme for strabismus with simplified nomenclature tailored towards the needs of pediatricians in dealing with this disorder.

Material and Methods

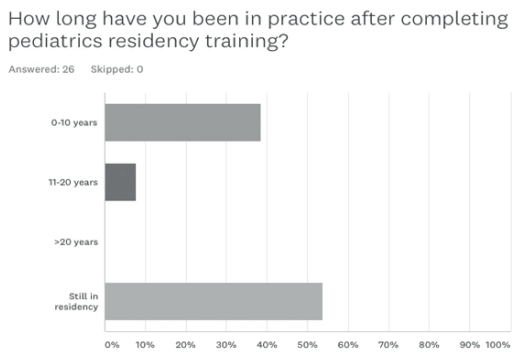
This cross-sectional survey was conducted on Pediatrician attendings and Pediatric trainees in a single university-based Department of Pediatrics. The demographics of the physicians surveyed are presented in Figure 1. A five-question survey was administered through a web-based portal (i.e. surveymonkey.com) in a blind fashion during a 4-week period (July-August 2019). The survey questions are presented in Table I, and the questions sought to identify the participant's level of comfort and knowledge regarding strabismus. No patient data was extracted and therefore an IRB approval was not required for this survey.

Data sources

A PubMed data search was conducted between the years 1980 and 2020, utilizing the key words "strabismus", "strabismus classification",



ANSWER CHOICES	RESPONSES	
Pediatrician	30.77%	8
Pediatric subspecialist	7.69%	2
Still in training	61.54%	16
TOTAL		26



ANSWER CHOICES	RESPONSES	
0-10 years	38.46%	10
11-20 years	7.69%	2
>20 years	0.00%	0
Still in residency	53.85%	14
TOTAL		26

Fig. 1. Demographics of physicians who participated in the survey according to current practice/training status.

and "strabismus etiology". Targeted searches based on the articles found through the initial PubMed query were additionally conducted. Publications written in a language other than English were not analyzed, apart from those that had abstracts provided in English.

Results

The preliminary survey that served as the basis for the current review consisted of 26 physicians; 16 were pediatricians in training and 10 were attendings of the same department (Fig. 1). Of the surveyed physicians, 50% were comfortable with performing an eye screening exam on a pediatric patient and 69% were comfortable with performing an ocular motility examination. No physician surveyed had a clear understanding of a classification system of strabismus and only 19% had an understanding as to the etiology of strabismus in children. Furthermore, the majority (92%) of the surveyed population did not have a clear understanding of strabismus nomenclature. The response rates of pediatricians in training versus attending pediatricians are presented in Table I.

In the light of these results, a clinically relevant classification scheme was proposed to assist pediatricians with improving their understanding of the underlying causes of strabismus (see below and Table II). Eight major categories of this classification scheme include (1) physiologic, (2) comitant, (3) paralytic, (4) sensory, (5) syndromic, (6) orbital, (7) supranuclear and (8) pseudostrabismus, provided in more detail in the following section.

Discussion

Our proposed classification scheme for strabismus is clear and concise, and provides a sense of the importance of identifying strabismus in the pediatric patient, the need for prompt referral and the possible work-up. It should be emphasized that the role of the pediatrician is not to assign an etiology to the strabismus, but to identify and refer, as the skills and knowledge for assigning an etiology in these cases require advanced training in ophthalmology.

Particular important clinical clues for *expedited* referral in suspected cases of strabismus include an acute onset, presence of diplopia, limited ocular rotations, visual impairment, leukocoria, pupillary abnormalities, proptosis, ptosis, signs of ocular inflammation or other neurologic findings.[8] Many forms of strabismus, including comitant strabismus, may present either as alternating strabismus where either eye will be used for fixing on objects of interest or non-alternating strabismus where there will be a dominant eye that will be used for fixation.

Table I. Responses to survey questions regarding the perception of pediatricians towards strabismus.

Questions	All participants (n=26)		Pediatricians in-training (n=16)		Attendings (n=10)	
	Response, n (%)		Response, n (%)		Response, n (%)	
	Yes	No	Yes	No	Yes	No
1. Do you feel comfortable performing a screening eye exam on a child?	13 (50)	13 (50)	4 (25)	12 (75)	9 (90)	1 (10)
2. Do you feel comfortable performing the ocular motility portion of the exam?	18 (69)	8 (31)	12 (75)	4 (25)	6 (60)	4 (40)
3. Do you have a clear understanding of the classification system of strabismus?	0 (0)	26 (100)	0 (0)	16 (100)	0 (0)	10 (100)
4. Do you have a clear understanding as to the etiology of strabismus?	5 (19)	21 (81)	1 (6)	15 (94)	4 (40)	6 (60)
5. Do you have a clear understanding as to the strabismus nomenclature?	2 (8)	24 (92)	2 (13)	14 (87)	0 (0)	10 (100)

Table II. Proposed classification scheme for strabismus geared towards pediatricians.

Type of strabismus	Feature	Work-up
1. Physiologic misalignment of early infancy	Resolves by 6 months of age; mostly exodeviations	None
2. Comitant (Essential)	Onset: 3 mo.-6 years; full ocular motility; often intermittent onset	Ophtho w/u required
3. Paralytic	Limited ocular motility; diplopia may be reported in older children	Required (imaging and neurology w/u)
4. Sensory	Visual loss in one or both eyes; may have absent red reflex	Ophtho w/u required
5. Syndromic	Limited ocular motility; noted in early infancy	Ophtho w/u required
6. Orbital	Associated with proptosis ± limited ocular motility	Ophtho w/u and imaging required
7. Supranuclear (Neurologic)	Associated with neurologic findings; abnormal gaze findings may be present	Required (imaging and neurology w/u)
8. Pseudostrabismus	Negative cover-uncover test result; epicanthal folds or flat nasal bridge noted on exam	None

Ophtho: ophthalmology, w/u: work-up.

Non-alternating strabismus may be an ominous sign potentially indicative of an underlying amblyopia, structural pathology such as cataract, optic nerve hypoplasia or retinal pathology, or both in the non-fixing eye of the strabismic patient.

Etiology-based Strabismus Classification Scheme for Pediatricians

1. Physiologic strabismus: Misalignment of the eyes in early infancy is a feature of normal development.[9,10] Normal ocular alignment is a learned process that should be complete by around 4-6 months of age. In one study, out of 2271 newborns, 67% showed some exotropia, 30% had straight eyes, 1% had esotropia and 2% had variable angle misalignments changing between exo- and esotropia.[9] All esotropes were noted to resolve by 2 months and almost all exotropes (97%) were resolved by 6 months of age.[9] Thus, esotropia that persists beyond 3 months of age and exotropia that persists beyond 6 months of age should be considered non-physiologic and then referred. A key feature of physiologic strabismus is full ocular rotations, and so if rotations are seen to be limited by voluntary movements or Doll's head maneuver, another etiology needs to be considered with an early referral.

2. Comitant strabismus: Term used by ophthalmologists to denote the commonly occurring childhood-type, benign strabismus. The word "comitant" was first introduced to describe an ocular horizontal misalignment that showed the same degree of misalignment in center, right and left positions of gaze, with no regard as to the etiology of the misalignment. The term has evolved with time to mean an etiologic grouping that includes the whole gamut of childhood-onset strabismus that does not require a neurologic or orbital work-up.[8] Key features include the same degree of misalignment in center, right and left positions of gaze, full ocular rotations, and no structural changes to the globe or orbit. Vertical misalignments and oblique extraocular muscle dysfunction often co-exist. Non-alternating comitant strabismus could indicate the presence of visual impairment.

The etiology is actually idiopathic, but probably represents a variety of dysfunctions of central nervous system (CNS) centers of ocular motor coordination and/or sensory centers of binocular vision, all below the resolution of current imaging techniques. Comitant strabismus is

the most common etiologic group of all ocular misalignments and occurs in approximately 3% of otherwise healthy, neurologically intact children.[11] This same type of strabismus also occurs in a much higher frequency in children with other neurologic impairments, such as Down syndrome and cerebral palsy.[12] Onset is usually between 3 months of age to 6 years.[13,14] The most common sub-types of strabismus falling into this etiologic group include accommodative esotropia, congenital/infantile esotropia, and intermittent exotropia.[13,14]

3. Paralytic strabismus: Ocular misalignments resulting from a lesion anywhere along the pathway of cranial nerves (CN) III, IV and VI from the lower motor nuclei in the midbrain to the neuromuscular junction with their corresponding extraocular muscles. Among a cohort of 627 pediatric patients with any type of strabismus, paralytic strabismus secondary to CN III palsy was observed in 11 (1.8%) of the patients, CN IV palsy in 13 (2.1%) and CN VI palsy in 25 (4.0%).[11] Paralytic strabismus can occur congenitally or develop secondarily due to intracranial neoplasms, trauma, inflammations, infarctions, demyelination, elevated intracranial pressure, aneurysms and myasthenia gravis.[15-18] The principal ophthalmic findings of paralytic strabismus are an ocular misalignment and impaired ocular rotation(s). Ptosis and pupillary dysfunction may occur with CN III palsy. An anomalous head tilt or a head turn in any direction may be present to compensate for the limited ocular motility.[19] These patients will often require pediatric neurology consultation, as well as magnetic resonance imaging (MRI) imaging of the brain and orbits with contrast.

4. Sensory strabismus: An ocular misalignment that develops secondary to poor vision in one or both eyes, due to any ocular sensory pathology or unilateral amblyopia.[20] Properly aligned eyes are not just a matter of anatomy or healthy extraocular muscles. Rather, there is a very active CNS process of checks and balances that maintains normal ocular alignment, referred to as fusional amplitudes. This process has a variety of requirements and inputs, one of which is a clear visual image from both eyes received by the CNS visual centers. With a loss of vision, the fusional amplitude process fails, and a secondary ocular misalignment may ensue, either in the form of an esotropia or an exotropia.[21] Sensory esotropia occurs in 6.7% of all strabismus cases in children younger than 19 years of age.[14] Underlying causes include retinal dystrophies, foveal hypoplasia, optic nerve disease, intraocular tumors, cataracts, glaucoma, and corneal opacification.[20] The presence of an abnormal red reflex, nystagmus and sluggish pupillary reflexes often point out the sensory nature of strabismus. This type of strabismus is also the second most common presentation of retinoblastoma.

When a young child presents with a unilateral loss of vision and strabismus, the ophthalmologist must distinguish if the loss of vision occurred first with a subsequent sensory strabismus, versus a child who develops a strabismus first and secondarily develops a strabismic amblyopia. These children may require ancillary testing for those cases in which a suspected primary loss of vision is not readily evident.

5. Syndromic strabismus: Specific forms of strabismus that have stereotypic and unique misalignment patterns, and are distinguishable from the other etiologic groups on an ophthalmologic exam. These strabismic "syndromes" are mostly isolated to the ocular motility system, but can also be a feature of systemic syndromes. Examples that fall within this group include Duane syndrome, Brown syndrome, Mobius syndrome, monocular elevation deficiency (double elevator palsy) congenital fibrosis of the extraocular muscles (CFEOM) and chronic progressive external ophthalmoplegia.[22] A key feature common to this group is a limitation of some ocular rotation. The specific entities within this group have a variety of etiologies, which include aplasia of cranial nerves, intra-uterine anomalous innervation and dysinnervation, tendon dysfunction, and CNS lesions, amongst others.[22] Some of these forms are strictly congenital, some

are strictly acquired, and some can be either. These patients may warrant limited, directed work-ups, such as an audiogram for patients with Duane syndrome, or genetics work-up for Duane syndrome and CFEOM.[23]

6. Orbital strabismus: Ocular misalignments that result from structural changes within one or both bony orbits. These changes can result from birth anomalies, trauma, inflammations, infections or masses.[24] Proptosis with or without limited ocular rotations often accompany this type of misalignment. Examples include the craniosynostoses, blow-out fractures, thyroid eye disease, orbital cellulitis and orbital neoplasms.[24-26] Additional testing, such as orbital computed tomography or MRI with ensuing surgical treatment of the underlying lesion is often required.[27]

7. Supranuclear strabismus: Ocular misalignments that develop secondary to lesions above the level of the midbrain lower motor nuclei.[28] The ocular motor system is complex and diffuse, with many diverse inputs such as from proprioceptors throughout the body and the vestibular system, and control centers such as those to maintain a steady gaze, to coordinate horizontal and vertical gaze, and for fast or slow eye movements.[29] The pathways from these control centers to the lower motor nuclei of CN III, IV and VI are also complex and indirect. Lesions anywhere along the various inputs, centers or pathways may result in ocular misalignments or eye movement abnormalities.[30] Sometimes, discrete lesions may produce localizing ocular motility abnormalities, such as an internuclear ophthalmoplegia from lesions of the medial longitudinal fasciculus.[31] Other times, lesions result in ocular motility abnormalities that are non-specific and non-localizing, such as those observed in the setting of fetal alcohol syndrome.[32] According to two previous US studies, 17.2% of childhood esotropias and 21.3% of childhood exotropias have been found to be associated with congenital or acquired abnormalities of the CNS.[13-14] Given the common association of childhood strabismus with CNS abnormalities, it is important to have a lower threshold for neurologic workup of childhood strabismus if the strabismus cannot be easily identified as "comitant" by a pediatric ophthalmologist. These supranuclear patients are often the most complex to diagnose, and may require hospitalization, imaging and various consultations in consideration of possible tumors, vascular and inflammatory processes, infections and neurodegenerations.

8. Pseudostrabismus: The false appearance of misaligned eyes in a patient with normal ocular alignment and no evidence of strabismus with the cover-uncover test.[19] Often, this appearance is due to normal morphological features of the child's face such as epicanthal folds, flat nasal bridge and wide-set or narrow-set eyes, creating an illusion of misalignment. Pseudostrabismus can also arise from pathological ocular or facial changes such as alterations of the visual axis from retinal dystopias (so called positive or negative angle kappas), blepharophimosis or facial dysmorphisms.[8,33] Pseudostrabismus can be a common diagnosis in a pediatrician's office but the true prevalence of the condition is unknown. As a caveat, studies suggest an increased incidence of true strabismus ranging between 10-12% in patients who had been diagnosed previously with pseudostrabismus.[33-35] True strabismus should be ruled out prior to diagnosing pseudostrabismus, and these patients may need to be followed at 4 to 6-month intervals to monitor for the development of true strabismus.[33,34]

It is not the intention of this paper to provide an in-depth literature survey of the individual types of strabismus conditions discussed here. Thus, the reader is encouraged to review relevant publications for a more comprehensive evaluation of these medical conditions. The preliminary survey was limited to one academic center; it is possible that pediatricians in other clinical settings may have different levels of competencies regarding strabismus evaluation. However, it is the authors' opinion that the results of the survey conducted are representative of academic centers where

Pediatrics residency programs are being implemented.

Strabismus is a fairly common ocular condition in children, and may be the presenting sign of a serious underlying medical condition. Pediatricians are often the first physicians to diagnose strabismus in their patients, and so, having a clear understanding of the underlying causes, the nomenclature and a classification scheme for strabismus is imperative. Certain ocular misalignments such as physiologic strabismus and comitant strabismus are benign in nature. However, other types of strabismus such as paralytic and supranuclear may be associated with life-threatening disorders and need a more expedited approach.

The classification scheme of strabismus presented in this paper is specifically developed for Pediatricians in light of an unmet need observed in our survey of our university's Department of Pediatrics. The classification scheme uses mostly familiar nomenclature, and emphasizes the underlying etiology of the strabismus in order to present a clearer understanding of strabismus to the Pediatrician. It is anticipated that this scheme can assist Pediatricians with improving their triaging skills when faced with various strabismic conditions in the outpatient setting. By providing non-ophthalmic medical terminology, this classification scheme can familiarize Pediatricians with various strabismic conditions and help identify which patients need to be promptly referred to the Ophthalmologist (i.e. non-alternating comitant, sensory, orbital) or urgently to the emergency room for urgent care (i.e. acute paralytic strabismus), thus expediting the work up and improving the overall care of children with strabismus.

Ethical approval

No patient data was extracted and therefore an IRB approval was not required for this survey.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: LK, MCM; data collection: AP, MCM; analysis and interpretation of results: MCM, AP, LK; draft manuscript preparation: MCM, AP. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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