THE ASSOCIATION BETWEEN FOURTH CRANIAL NERVE PALSY AND CONVERGENCE INSUFFICIENCY

by

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ABSTRACT

The purpose of this prospective study was to investigate the association between convergence insufficiency (CI) and fourth cranial nerve palsy (SOP) in patients presenting at 4 clinics within Nationwide Children's Hospital. A patient obtaining a new diagnosis of CI or SOP was then screened for the other diagnosis. The study consisted of a primary and revised analysis. The primary analysis included sixty subjects between the ages of 6 and 80 years of age were recruited with a new diagnosis of CI or SOP. Fifty-four patients were identified to have CI and 18 patients were identified to have SOP. SOP patients were split up into congenital (9) and acquired (9) groups. The primary analysis supported the association between SOP and CI ($P<0.001$). Revised analysis that included ALL inclusion criteria resulted in 18 subjects, 9 CI and 9 SOP. The revised analysis did not show anyone with a SOP and CI together.

LIST OF ABBREVIATIONS USED

AC/A	accommodation convergence/accommodation
CI	convergence insufficiency
DNA	deoxyribonucleic acid
INO	internuclear ophthalmoplegia
MLF	medial longitudinal fasciculus
MRI	magnetic resonance imaging
NATP	not able to perform
NPC	near point of convergence
PD	prism diopter
PI	principal investigator
SOP	fourth cranial nerve palsy

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CHAPTER 1: INTRODUCTION

1.1. Background

Binocularity is a broad term that refers to the use of the two eyes together, and normal binocularity results in three-dimensional vision, or stereopsis. Normal binocular vision is the simultaneous perception of two images, one from each eye. Requirements to achieve require an intact efferent visual system consisting of normal extra-ocular muscle structure and central and peripheral innervation.

Normal binocular vision can be disrupted in the setting of efferent system dysfunction. The most common example is ocular misalignment, known as strabismus. It is one of the primary reasons patients present to Neuro-ophthalmology and/or Pediatric Ophthalmology services (Hatt et al., 2007). Abnormal binocular vision resulting from strabismus can have implications that include; manifestations of systemic problems, loss of employment, poor vision or double vision, financial stress and cause loss of employment. Adults with strabismus have also been reported to suffer low self-esteem and have problems with inter-personal relationships and social anxiety (Hatt et al., 2007).

A binocular vision specialist, such as an Orthoptist or Strabismologist play an important role in these patients by conducting proper clinical assessments in order to make accurate diagnoses and develop appropriate management plans. This includes recognizing the need for additional medical investigations, e.g. radiological studies, and surgical intervention. It is important that binocular vision dysfunctions are diagnosed in a timely manner that if delayed can lead to permanent vision loss or severe medical complications.

1.2. Specific Disorders of Binocular Vision

Strabismus can be classified several ways. The most common means is by direction of misalignment between the visual axes, comitance, age at onset, and etiological mechanism. Table 1A provides a breakdown of these categories and their descriptions. This research project involves two complex forms of strabismus, fourth cranial nerve palsy and convergence insufficiency. Each condition falls into a different etiological category.

Table 1A. Strabismus classification

Category	Term	Description
By direction	Eso deviation	Inward deviation of one eye
	Exo deviation	Outward deviation of one eye
	Hyper deviation	Upward deviation of one eye
	Hypo deviation	Downward deviation of one eye
	Incyclo deviation	Inward rotation of one eye
	Excyclo deviation	Outward rotation of one eye
	Combination	Any combination of the above
By comitancy	Comitant	Eye deviation remains the same in every direction of gaze
	Incomitant	Eye deviation whose amount varies in different positions of gaze
By age at onset	Congenital	Onset at birth or by 6 months of age
	Acquired	Onset after 6 months of age
By etiological mechanism	Innervational disturbance	Third nerve palsy **Fourth nerve palsy** Sixth nerve palsy
	Restrictive processes	Brown's syndrome, Blowout Fracture, Duane's syndrome, Grave's Disease
	Myopathic disorders	Orbital myositis, Ophthalmoplegia, Myokymia, Neuromuscular Disease
	Disorder of the neuromuscular junction	Myasthenia Gravis, Botulism

	Central or sensory issues	Basic or simple strabismus
		• Etiology uncertain
		• Examples:
		  o X(T)
		  o Non-accom ET
		  o Accom ET
		Sensory
		• Due to poor VA
		• Examples: Sensory ET or XT
		
		Central or unspecified
		• Dysfunction of the Ocular Motor System – possible brainstem or cerebellum could be affected
		• Examples:
		  o Disorders of vergence
		  ▪ Convergence paralysis
		  ▪ **Convergence insufficiency**

A patient with strabismus will fall into at least one section of each 'category'. Elucidation of each category occurs in large part by the orthoptic evaluation.

Fourth cranial nerve palsy, otherwise known as fourth nerve palsy, trochlear nerve palsy or superior oblique palsy (hereafter referred to as SOP) falls into the category of innervational strabismus, which also includes 3rd and 6th cranial nerve palsies. Here the superior oblique muscle receives reduced (or absent) innervational input from the fourth cranial nerve. The reasons for this are numerous, but all cases result in an incomitant strabismic pattern. Onset can be congenital or acquired. Patient's with acquired forms typically present with complaints of vertical and torsional diplopia (Ansons & Davis, 2001).

Convergence insufficiency (hereafter to be known as CI), falls within the category of a central mechanism. Ocular movements are full i.e. no innervational, restrictive, or myopathic anomalies present and there is typically no overt strabismus in distance positions of gaze. The main feature is the inability to maintain adequate convergence of the eyes for sustained comfortable near binocular single vision (Cassin, 2006). Patients frequently present with asthenopic symptoms associated with near work. Symptoms can be mild or marked depending on the severity of the CI and the frequency of the individual to perform near work throughout the day.

These two conditions are frequently encountered in the Pediatric ophthalmology practice I am working in. It has been our team's experience there seems to be a greater than expected number of patients that have both conditions. The reasons for this were unclear. It was this anecdotal observation that led to my interest in studying the potential

association. Confirming this association could have a significant impact in how we assess and management these individuals.

The following sections provide an overview of the anatomical and clinical features of each condition.

1.2.1. Fourth Nerve Palsy (SOP)

Anatomy/Pathway

The nucleus of the fourth cranial nerve is located within the midbrain at the level of the inferior colliculus, inferior and posterior to the oculomotor nuclear complex and dorsal to the medial longitudinal fasciculus (MLF). The fascicular portion of the nerve is short and is the only cranial nerve to arise from the dorsal aspect of the brainstem. It travels around the midbrain running contralateral to its nucleus and because of this a lesion to the trochlear nucleus affects the opposite eye, while all other cranial nuclei lesions affect the same eye. Jeong et al., in 2016, reported caution should be taken when trying to localize the lesion site in unilateral SOP. They determined that a fascicular lesion may cause either an ipsilesional or contralesional SOP depending on where in the fascicular pathway the lesion occurs. Additionally, Gold et al., in 2012 reported SOP accompanied by ipsilesional brainstem signs such as INO, Horner Syndrome or cerebellar ataxia. This combination of neurological signs is due to the proximity of the fourth nerve nucleus to the MLF and descending oculosympathetic pathways.

Within the arachnoid space it passes between the posterior cerebral artery and the superior cerebellar artery, and then pierces the dura just under the tentorium cerebelli, close to the crossing of the attached margin of the tentorium and within millimeters of the posterior clinoid process (Bisaria, 1988). The nerve then travels through the cavernous

sinus where it is in close relationship with cranial nerves 3, 5 and 6, along with the internal carotid artery. It crosses over cranial nerve 3 before exiting the cavernous sinus to then enter the posterior aspect of the orbit by passing through the superior orbital fissure but outside the annulus of Zinn.

The superior oblique muscle has several fibers that make up its composition and are divided into medial and lateral compartments. The muscle fibers in these compartments act relatively independently and are responsible for the torsional and vertical movement of the eye (Demer, 2015). Dissection of the human orbit revealed that the medial superior oblique fibers insert near the equator of the globe, which generates mostly torsional rotation in central gaze. The lateral superior oblique fibers insert posterior to the equator which generates mostly vertical rotation in central gaze (Clark & Demer, 2015). The superior oblique muscle ends in a tendon that passes through the cartilaginous trochlea (which means "pulley" in Latin), and the fourth cranial nerve is named after this structure. The following diagrams show the superior oblique pathway referred to above.

Figure 1A. Superior oblique pathway from the nerve to the orbit (Ruchalski & Hathout, 2012)

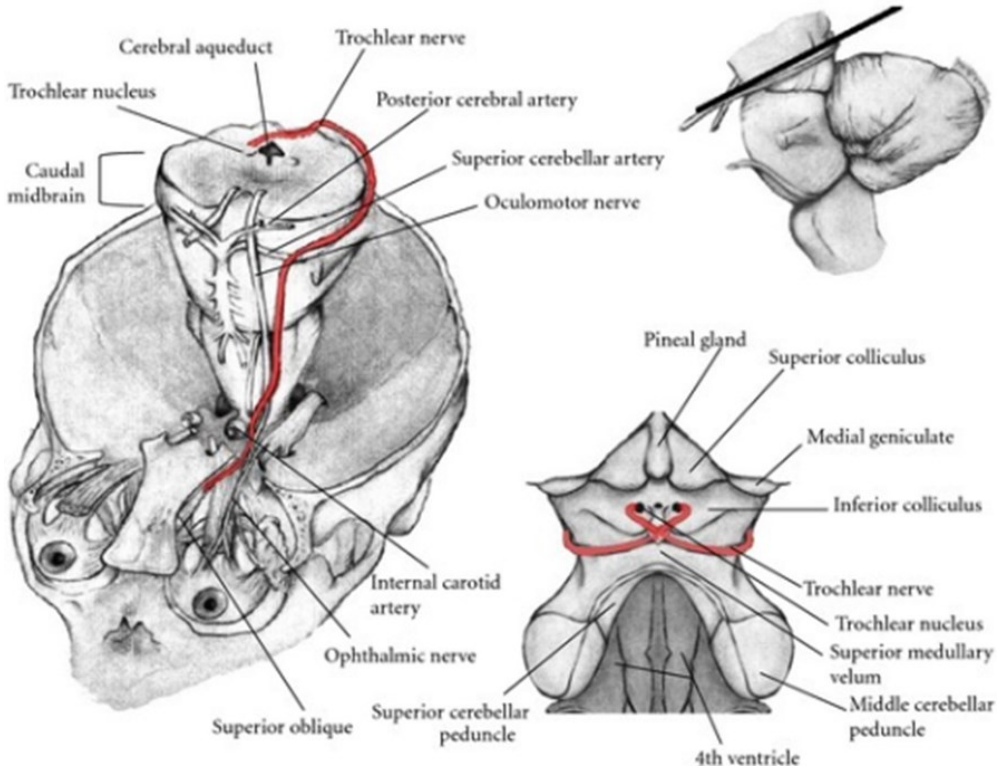
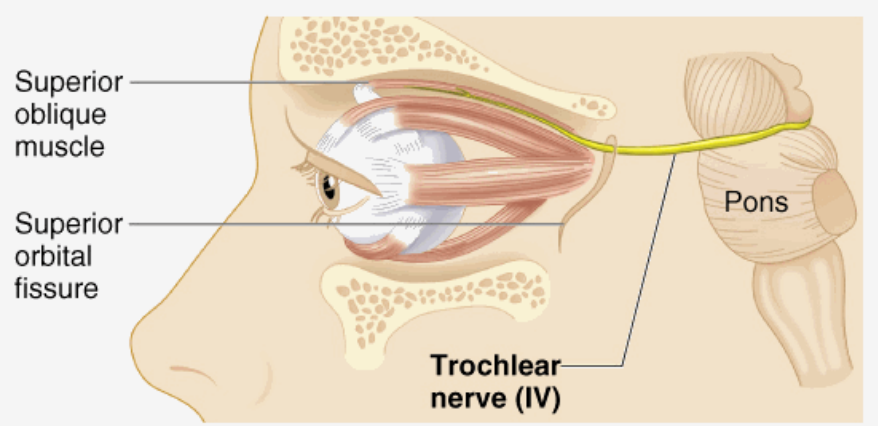


Figure 1B. Superior oblique muscle passing through the superior orbital fissure (Cummings, 2001)



Causes of Congenital SOP

The underlying etiology of congenital SOP remains unknown. There is a debate as to whether it is a result of dysgenesis of fourth nerve nucleus or from abnormal development of peripheral nerve, muscle or even the tendon (Shiek, 2012).

Helveston et al., in 1992, looked at 36 patients with congenital SOP and found 33 had abnormal superior oblique tendons. The tendons were evaluated at the time of surgery and they classified the anomalous tendons as being lax, having abnormal insertions, or absent all together.

Abnormalities of the superior oblique muscle have also been confirmed with neuro-imaging studies reporting an absent muscle (Gore & Malik, 2006) or a hypoplastic muscle (Ozkan et al., 1997 & Sato et al., 1998). A large neuro-imaging study by Yang et al., in 2012 compared the MRI findings to the clinical features of 97 patients with congenital SOP. They reported 73% of patients had absence of the nerve and a hypoplastic superior oblique muscle. This group manifested a head tilt at an earlier age. Twenty-seven percent of patients had a normal nerve with the main clinical distinction being prominent over elevation in adduction and frequently had a dissociated vertical deviation.

Lee et al., in 2014, reviewed the medical records of 125 patients that were diagnosed with unilateral congenital SOP. All patients had MRI testing performed and the following features were analyzed: presence of the trochlear nerve, nerve diameter, and superior oblique muscle volume. A total of 87 patients had absence of the trochlear nerve. The study concluded patients without a trochlear nerve had a reduced trochlear

nerve diameter on the non-paretic side. This suggests different underlying pathogenic mechanisms could cause congenital SOP.

Reports of congenital trochlear nerve anomalies has led some to consider that at least some forms of congenital SOP should be considered as a congenital cranial dysinnervation disorder (Kim & Hwang, 2010). It has been suggested that it may be inherited or as of yet undetermined de novo mutations (Bhola et al. 2001, Botelho & Giangiacoma 1996, Harris et al. 1986, Astle & Rosenbaum 1985). Jiang et al., in 2005, performed genetic sequencing on two genes thought to be related to SOP, *ARIX* and *PHOX2B*. They did this on 31 patients with congenital SOP and compared them to 54 normal subjects (i.e. did not have SOP or strabismus of any kind). All patients and normal individuals were ethnic Japanese. Fifteen out of 31 patients with SOP had heterozygous nucleotide changes in the *ARIX* gene while no changes were found in all 54 normal individuals. *PHOX2B* polymorphisms were also present in 6 patients with SOP and in none of the normal group. This study concluded polymorphisms of the either gene may contribute to the development of congenital SOP. This finding has not yet been confirmed in other studies therefore the genetics of congenital SOP remain elusive.

Suh et al., in 2016a, also used MRI to investigate whether rectus pulleys are significantly displaced in patients with either congenital or acquired SOP. The study evaluated 24 cases of SOP based on atrophy of one or both superior oblique muscles and compared them to 19 healthy age-matched orthotropic control subjects. 19 patients had unilateral SOP and 5 patients had bilateral SOP. The medial rectus pulley, superior rectus pulley, and inferior rectus pulley were displaced in both groups. However, the

lateral rectus pulley was not displaced in either group and ocular torsion does not correlate with pulley displacements.

Suh et al., in 2016b, did another study looking at the medial and lateral compartment volumes of the superior oblique muscle compared in patients with isotropic (round shape) versus anisotropic (elongated shape) superior oblique atrophy. As in their previous study, patients with either congenital or acquired forms were included. MRI was obtained in 19 patients with unilateral SOP and 19 age-matched orthotropic control subjects. The medial and lateral compartments were equally atrophic in patients who had isotropic SOP. The patients that were diagnosed with anisotropic SOP had a significantly smaller lateral compartment in comparison to the medial compartment. There were no differential compartmental volume changes in any of the rectus extraocular muscles. This study concluded that some patients with SOP can have atrophy of the lateral compartment, which is predominately responsible for vertical movements. Shin & Demer, in 2015, did a similar study and obtained an MRI on 62 subjects with congenital and acquired SOP. They found that clinically patients with isotropic atrophy had greater hypertropia in depression versus primary position and greater excyclotorsion when compared to anisotropic atrophy group. They also found that different clinical features are noticed depending on whether the pathology problem is found in the medial or lateral compartment of the superior oblique.

None of the above reports looking at superior oblique dysfunction arising from nerve, muscle or pulley anomalies resulted in clinical features similar to convergence insufficiency.

Causes of Acquired SOP

The common causes of acquired isolated SOP are idiopathic and then traumatic (Brazis, 1993; Keane, 1993; Robb, 1990). If SOP is detected only after minor trauma one must suspect an underlying structural abnormality as the cause and not the trauma. Microvasculopathy secondary to diabetes, atherosclerosis, or hypertension is another cause of isolated SOP (Rush & Younge, 1981). Thyroid ophthalmopathy and myasthenia gravis rarely present as isolated SOP (Sheik, 2012). On occasion, congenital SOP may present as an acquired form following cataract surgery. After restoration of vision in both eyes a previously asymptomatic patient might now appreciates diplopia (Nayak et al., 2008). Tumor, aneurysm, multiple sclerosis, or iatrogenic injury may present with an isolated SOP that may evolve over time and include other palsies or neurological symptoms (Son et al., 2010).

The long course of the trochlear nerve makes it susceptible to injury resulting in an acquired SOP. Injury to the nerve can occur anywhere along the course from the midbrain to the orbit. Lesions at the nucleus will cause a contralateral fourth cranial nerve palsy. This happens because the nerve decussates in the dorsal midbrain near the inferior colliculus. A bilateral fourth cranial nerve palsy is not uncommon with midbrain, compression or ischemia in this area (Sheik, 2012). Christoff, in 2015, published a retrospective chart review looking at the most common clinical characteristics of adult neuro-ophthalmology and oculo-plastics patients seen over a 9-year period. Of the 575 patients included, 82 had a SOP of which 59 were acquired, 20 were longstanding and 3 it was impossible to determine. Trauma was the commonest cause accounting for 19 cases. 2 of the patients, one acquired and one congenital, reported migraines but none of the SOP patients were listed as having associated CI.

A fascicular lesion should be suspected in patient's presenting with a contralateral Horner Syndrome or an ipsilateral afferent pupillary defect. This happens because of the close proximity of the sympathetic pathways in the dorsolateral tegmentum of the midbrain and the pupillomotor fibers that run through the superior colliculus (Sheik, 2012).

Injury to the peripheral nerve can result from compressive injury from tumors or aneurysms within the subarachnoid. Other causes can include high intracranial nerve pressure, such as pseudotumor cerebri or meningitis, which causes nerve inflammation. (Sheik, 2012).

Frequency of SOP

Estimating the true frequency of congenital SOP is difficult because many patients compensate with the use of a head tilt or large fusional amplitudes. It is when their fusional control begins to deteriorate that the patient starts noticing symptoms and present to an ophthalmologist.

Frequency citied information regarding on the incidence and etiology of acquired and congenital SOP comes from the The Mayo Clinic studies. In this report SOP was less common than abducens or oculomotor palsies (Richards et al., 1992). In a series of 4,373 acquired cases of extraocular muscle palsy in adults, 657 cases were isolated fourth nerve disease, or about 1 in 7 (Richards et al., 1992). SOP was also reported to be the least common ocular motor palsy in the pediatric population. In another study of 160 children with an ocular motor nerve palsy 19 cases (about 1 in 8) were an isolated SOP (Holmes et al., 1999; Kodsi & Younge, 1992).

Clinical Presentation

Dr. Alfred Bielschowsky, a German Ophthalmologist, wrote that SOP, was the most common cause of vertical double vision. It was in 1935 that he introduced his classic head-tilt test, which would diagnose a cyclo-vertical muscle weakness (Von Noorden, 1996). This head tilt test was later incorporated into the Parks 3-Step test as the third step to confirm an isolated cyclo-vertical muscle palsy (Parks, 1958).

Patients presenting with vertical diplopia or signs of vertical strabismus must always be evaluated for SOP as this is the most frequent cause (Von Noorden, 1996). However, the clinician must be aware of the various types to accurately make the diagnosis. Figure 1C illustrates the various types of SOP while Table 1B outlines the main clinical features for each.

Figure 1C. Flowchart for vertical strabismus and types of SOP

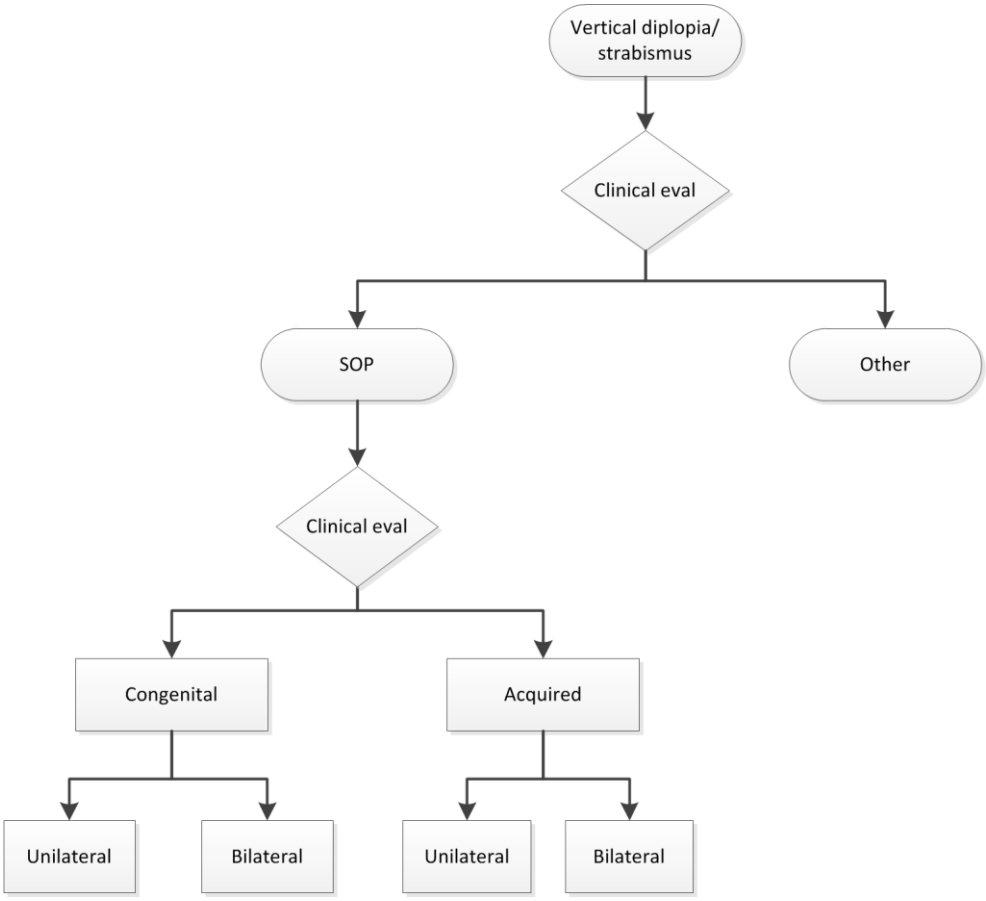


Table 1B. Main clinical features of SOP

Feature	Presenting feature	AHP	OM	PCT	FA	Tor
Type						
Unilateral acquired	Vertical/ torsional diplopia	Contralateral head tilt; slight ipsilateral head turn; chin down	IOOA affected eye; (+) 3 step head tilt test	HT increasing contralateral gaze and ipsilateral head tilt	No enlarged vertical fusional amplitudes	Sympto matic Excyclot orsion
Unilateral congenital (decompe nsating)	No or intermittent diplopia; AHP; facial asymmetry	Contralateral head tilt; slight ipsilateral head turn; chin down	IOOA affected eye, (+) 3 step head tilt test	Same as above or have spread of comitance	Enlarged vertical fusional amplitudes	No Sympto matic excyclot orsion
Bilateral acquired	Vertical/tors ional diplopia	Chin down	IOOA of affected eye, (+) 3-step head tilt test to either side	V-pattern esotropia	No enlarged vertical fusional amplitudes	Sympto matic Excyclot orsion
Bilateral congenital	None or intermittent diplopia; AHP	Chin down	IOOA can be 1 eye or both, (+) 3-step head tilt test to either side	V-pattern esotropia	Enlarged vertical fusional amplitudes	No Sympto matic excyclot orsion
Masked bilateral	Vertical/tors ional diplopia	Contralateral head tilt; slight ipsilateral head turn; chin down	IOOA affected eye; (+) 3 step head tilt test	HT increasing contralateral gaze and ipsilateral head tilt	No enlarged vertical fusional amplitudes	Sympto matic Excyclot orsion

AHP = abnormal head posture; OM = ocular motility features; PCT = prism and cover test; FA = fusional amplitudes; Tor = torsion findings

Congenital SOP can be unilateral or bilateral. Unilateral congenital SOP frequently presents with an abnormal head posture with the head tilting to the shoulder opposite the affected superior oblique. Some children have undergone unnecessary orthopedic treatment for a head posture that only later was determined to be due a SOP (Ansons & Davis, 2001). Facial asymmetry is another feature that can occur. It consists of a smaller distance between the lateral canthus and the corner of the mouth on contralateral side of the affected superior oblique. Bagheri et al., reported this was

present in 6.8% of patients with SOP. Diplopia is uncommon but can occur in cases when control of the vertical strabismus begins to decompensate. Individuals will frequently have large vertical fusional amplitudes often exceeding 20 prism diopters in cases of moderate to severe palsy (Ansons & Davis, 2001). An important clinical test to perform in patients with a suspected SOP is the Parks 3 Step-test. A positive response is considered when the degree of vertical misalignment of the higher eye increases in contralateral gaze and ipsilateral head tilt. This is generally used to confirm a SOP, however the degree of incomitancy in congenital/long-standing SOP reduces over time and can sometimes limit the effectiveness of this test. (Parks, 1958; Ansons & Davis, 2001).

Bilateral congenital SOP show a V-pattern esotropia and large excyclotropia, with hypertropia of the nonfixing eye (Hermann, 1981). Bilateral paralysis typically will clinically present with a right hypertropia in left gaze and a left hypertropia in right gaze and a positive Bielschowsky test on tilting the head toward either shoulder (von Noorden et al., 1986). Any compensatory head posture is likely to be a chin depression and these patients often have associated inferior oblique muscle over action that can be unilateral or bilateral. These patients generally do not have symptomatic torsion like the acquired group.

Acquired SOP can unilateral or bilateral. Most patients with acquired SOP have associated symptoms of vertical diplopia, awareness of a head posture, no evidence of enlarged vertical fusional amplitudes, and commonly a history of recent head trauma (Ansons & Davis, 2001). Patients are also commonly aware of cyclotorsion. The 3 Step-

Test is also key in the clinical evaluation to help distinguish vertical strabismus due to SOP from other isolated cyclo-vertical muscle imbalance. (Ansons & Davis, 2001).

Bilateral acquired SOP present with a main symptom of torsional diplopia. The typical head posture in these cases is a chin down posture to avoid diplopia. The 3 Step-Test in bilateral cases consists of reversing hypertropia on right sides and head tilts helping distinguish it from unilateral cases. (Ansons & Davis, 2001). V-pattern with esotropia in downgaze and excyclotorsion measuring greater than 10 degrees in the primary position are other common features (Sydnor et al., 1982). Bilateral acquired SOP is not as common as unilateral cases. Von Noorden et al., in 1986, reviewed 270 cases of SOP. In this series only 1 case was bilateral.

Some patients present to clinic with apparent unilateral SOP but in fact have a masked bilateral SOP (Kushner, 1998). Kraft and Scott, in 1986, did a study that looked at 92 patients that had been surgically treated between 1972 and 1983 that were initially diagnosed as having a unilateral SOP. Follow up showed that 8 (8.7%) of the patients developed a SOP of the other eye confirming the presence of a masked bilateral SOP. All 8 patients had a unilateral inferior oblique weakening and some also had a recession of the contralateral inferior rectus at the initial surgery. 7 of the 8 cases came back to clinic and had an over action of the contralateral inferior oblique that manifested itself on average 9.8 weeks after the first surgery.

After a thorough review of the various clinical manifestation of all forms of SOP, no reports were identified to overlap this condition with features of convergence insufficiency.

Treatment

Treatment options vary depending on the type of SOP present. There is a high probability of recovery within 6 months in isolated acquired unilateral palsies without neurological disease (Ansons & Davis, 2001). Ischemic SOP normally resolves within 3 months. Non-ischemic palsies have variable resolution time depending on cause and degree of damage. Recovery after 12 months is rare and bilateral palsies rarely fully recover (Ansons & Davis, 2001). SOP due to trauma has a poor prognosis for recover and often requires surgical treatment.

Patients often adopt an abnormal (compensatory) head posture to obtain binocular single vision, however depending on the degree of weakness this may not always be possible. Fresnel prisms are another means to eliminate the associated vertical diplopia. This is especially helpful in mild superior oblique weakness or longstanding cases where a spread concomitance has developed. They are mainly used pre-operatively to temporarily relieve diplopia or in cases where resolution is expected to occur. The goal of Fresnel prism use is to achieve binocular single vision in primary position and if possible also reading position. Patients with a torsional component will not find relief from Fresnel prisms. These patients may be advised to patch one eye.

Extraocular muscle surgery is generally successful in providing a sufficient zone of single binocular vision. Eye muscle surgery should only be considered when the size of the deviation has become outside fusion range. Single muscle surgery is considered for vertical deviations less than 15PD. Overaction of the ipsilateral antagonist (ipsilateral inferior oblique) is generally addressed by weakening the inferior oblique by myectomy or recession (Ansons & Davis, 2001). Deviations greater than 15PD require surgery on

multiple eye muscles and/or require multiple procedures (Plager, 1999). Von Noorden et al., in 1986, reported that surgical treatment in 112 patients with SOP resulted in an 85% cure rate with an average of 1.45 operations per patient. In the case of a large excyclotorsional deviation, often associated with bilateral SOP, a modified Harada-Ito procedure is useful (Mitchell & Parks, 1982). The Harada-Ito procedure was introduced in the 1960's. In the 1970's, Knapp developed a surgical approach based on a classification system identifying the most affected fields of gaze (Knapp, 1974).

Botulinum toxin also has been studied in the treatment of SOP. Botulinum toxin is a neuromuscular agent that blocks the release of the neurotransmitter acetylcholine that results in temporary muscle paralysis. Use of this agent as a primary treatment for SOP has been discouraging. However, it may be used best to correct residual deviation after strabismus surgery to delay or avoid further surgery (Garnham et al, 1997).

1.2.2. Convergence Insufficiency (CI)

Anatomy/Pathway

Most CIs present without a known psychological or systemic etiology. Acquired CI has been associated with brain injury from closed head trauma and lesions in the pretectal area of the midbrain. Midbrain lesions that are dorsal to the third cranial nerve nuclei could also cause CI with a normal third nerve function (Bartiss, 2013).

CI is a common condition characterized by the inability to maintain proper convergence of the visual axis on near objects (Von Noorden, 1996). This disruption of convergence may be primary or secondary. Primary CI is present when neurological, innervational, mechanical, accommodative, or refractive mechanisms have been ruled out. Secondary CI may occur in the setting of any of the above problems.

There are six different types of convergence (Cassin, 2006). Accommodative convergence occurs in response to an increase in optical power for focusing by the eyes' lenses. Fusional convergence is the amount of convergence the eyes can undergo while maintaining single vision. Proximal convergence is the portion of convergence that happens by awareness of an objects nearness. Relative convergence is the amount of prism power that can be overcome while single clear binocular vision is maintained. Tonic convergence is the portion of convergence ability that results from changing from sleeping to the awake state. Voluntary convergence is the amount the eyes can voluntarily converge without regard to clarity or single image (Cassin, 2006). Dysfunction of any of these convergence functions can cause a near visual disturbance.

Causes

Von Graefe first described this condition in 1855 and believed CI was due to myogenic mechanisms. This theory has since been disproved by electromyographic work (Bartiss, 2013). Other theories involve a central innervational imbalance of convergence and the often-achievable reduction of symptoms with appropriate therapy supports this theory (Von Noorden, 1996). CI can also occur in cases of a primary loss of accommodation (Harrison, 1987). In the past, Ophthalmologists believed that CI was associated with neurotic manifestations of non-related psychological problems and that such cases would best be dealt with by a psychiatrist (Brown, 1990). However, over time, it is now clear that CI is a legitimate dysfunction of binocular cooperation.

Visual disorders following a brain injury are relatively common. The type of visual disturbance will depend on what part of the visual system is involved. Afferent system defects can affect visual acuity, visual fields, color vision, contrast sensitivity, and

even higher level of visual processing, including recording of visual memory and comprehension of visual stimuli (Singman, 2010). Efferent system defects include reduction of the ability to track moving targets, maintain fixation on stationary targets, or maintain binocular alignment (Singman, 2010).

The past two decades has produced several clinical studies looking at the association between the vergence eye movement system and traumatic brain injuries. One study by Cohen et al., investigated convergence abnormalities in two groups of patients with traumatic brain injuries. The first group included 26 patients that had a clinical investigation of vergence function less than 3 months post injury. They found that over a third of the examinees revealed visual disturbances with convergence. The second group included 72 patients 3 years post brain injury. Forty-two percent were found to have vergence insufficiency, either of the convergence or divergence type. This study showed that for both groups there was an association of CI with longer periods of coma, cognitive disturbances and patients failing to gain employment (Cohen et al., 1989). Ciuffreda et al., in 2007, found similar results in their retrospective analysis of 160 patients with traumatic brain injury. 56.3% of the patients were diagnosed with a vergence abnormality, with CI being the most common type (36.7%).

Two case series have also reported vergence dysfunction following traumatic brain injury. Berne, in 1990, reported three cases of young adults all exhibiting vergence dysfunction. All had features suggestive of CI that included a reduced NPC, decreased convergence amplitudes, and abnormally high exophoria at near. Scheiman and Gallaway, in 2001, reported nine patients. Five (55%) were diagnosed with CI and four were diagnosed with unspecified vergence problems.

Schlageter et al., in 1993, conducted a hospital based study of 51 patients with traumatic brain injury. They reported three different abnormalities of vergence they described as an abnormal horizontal phoria at near (38%), abnormal vertical phoria at near (18%), and an abnormal horizontal phoria at a distance (26%). None of these cases suggested the co-existence of SOP.

Researchers in Vancouver looked at the medical records of 557 brain injury patients and reviewed the visual acuity, oculomotor function, binocular vision function, accommodation, visual fields, ocular health and vestibular function for each patient. Only 9% of the patients had an isolated case of CI, while most of the patients had CI with other vision problems. Photophobia and CI was observed in 16.3% of patients. Vestibular dysfunction and CI was seen in 18.5% of the patients. SOP and CI was present in 4.4% of the patients, while SOP alone was noted in 11.7% of the patients. Accommodation dysfunction and visual field defects were also common (Alvarez et al., 2012). However, the authors applied weak diagnostic criteria for a CI and did not define criteria for a SOP.

Lastly, Hellerstein et al., in 1995, compared the binocular vision function of 16 patients with traumatic brain injury to 16 age-matched control subjects. Significant abnormalities were found in regard to near phoria, distance base-in prism break point, NPC break and recovery points, and randot stereoacuity.

These studies provide clear evidence that traumatic brain injuries can have a substantial adverse effect on a person's vergence function. Apart from the one study by Alverez 2012.

Frequency and Symptomatology of CI

CI disorder interferes with a person's ability to maintain comfortable near vision. As a result, it can impact an individual's ability to function at school and work.

It is estimated that CI has a reported prevalence among children and adults in the United States of 2.5 to 13% with no racial predilection (Letourneau & Ducic, 1988; Rouse et al., 1999; Scheiman et al., 2005). The prevalence of this condition is the same internationally (Bartiss, 2013). The symptoms associated with CI vary from mild to severe, but patients typically present as teenagers or in early adulthood, complaining of gradually worsening eyestrain, periocular headache, blurred vision after brief periods of reading and double vision with near work (Bartiss, 2013). High school or college students present with CI most commonly because of excessive demands with near work during extended periods of studying. Lack of sleep, illness, and anxiety are known to aggravate the problem (Bartiss, 2013).

Clinical Presentation

To achieve near binocular single vision both eyes must converge equally and be maintained at that position. Individuals with CI have difficulty maintaining sustained convergence effort leading to eyestrain, blurred vision, double vision, lines of print running into each other, and headaches (Cooper & Copper, 2005). It is not unusual for a person to cover or close one eye while reading to relieve the blurring or double vision.

Criteria varies for a CI diagnosis but commonly accepted criteria for CI includes: a reduced near point of convergence that is greater than or equal to 10 cm or can only be maintained at this level with effort; reduced convergence amplitudes (around <15PD); associated with asthenopic symptoms at near; and generally, a small near exophoria.

Monocular near point of accommodation should be normal for age of the patient (Ansons & Davis, 2001).

Clinical evaluation of convergence ability is by assessing NPC and convergence fusional amplitudes. The NPC point is where convergence (and therefore binocular single vision) can no longer be maintained as an object approaches the eye. This end point is recorded in centimeters. Convergence amplitudes are a measurement of the amount the eyes simultaneously convergence while maintaining fusion before double vision occurs. This test is measured in prism diopters using base out prism bar (Ansons & Davis, 2001).

Treatment

There are many treatment modalities for CI. First and foremost, correction of refractive error is required that generally includes the need for a cycloplegic refraction. Following this orthoptic exercises are generally the first treatment initiated, followed by base in prisms in reading glasses and in certain severe cases eye muscle surgery may be required (Ansons & Davis, 2001).

Resolution of symptoms can generally be relieved with orthoptic exercises when applied to appropriately selected patients. They tend to work best on patients who are symptomatic thereby having sufficient motivation to treat, those with near and distance exo-deviations (under 20PD) with appreciation of diplopia when NPC is exceeded. According to Ansons & Davis, there are four stages in orthoptic treatment. First, the patient must overcome suppression and obtain spontaneous recognition of diplopia on failure to converge. This step is usually easily achieved by using colored filters. Secondly, improve convergence and extension of convergence (positive) fusional

amplitudes. This is achieved with simple convergence exercises using pen pushups and/or base out prisms. Third, the patient must appreciate physiological diplopia, which can then be used in the uncrossed position to improve relative convergence and in the crossed position to ensure that relaxation of convergence is easy to obtain. Stereograms and the dot card are useful methods based on physiological diplopia. Last step is voluntary convergence where the patient is able to stimulate convergence and maintain without a near stimulus. Success of orthoptic therapy is best achieved by working closely with patients in the clinic on a regular basis and providing detailed instruction on home exercises.

In 2002, the Convergence Insufficiency Treatment Trial study group survey a group of ophthalmologists and optometrists that indicated that home-based pencil-pushups therapy is the most common treatment despite evidence suggesting treatment may be ineffective at eliminating symptoms (Scheiman et al., 2005). However, other studies have shown good response to orthoptic exercises with an estimated cure rate of 72% lasting at least 2 years (Grisham, 1988). The convergence insufficiency treatment trial study group also found that office-based vergence accommodative therapy is an effective treatment for children with symptomatic convergence insufficiency (Scheiman et al., 2005).

Elderly patients and patients whose convergence has not been sufficiently improved with orthoptic exercises may benefit from prisms. Trial Fresnel prisms are placed on reading glasses in order to assess the correct strength and ensure that symptoms are relieved. Once the correct prism power is obtained it can then be incorporated into the spectacles.

1.3. Purpose of the Study

The intent of this study is to investigate the anecdotal association between SOP and CI at a major strabismus clinic in a large US city.

An association between these conditions would have several implications to our practice:

- It would warrant a change in our current practice patterns where patients receiving one diagnosis would then be screened carefully for the other. This would be easy to enact since the screening tests for both conditions are well established, quick and reliable. It would also ensure earlier recognition of patients with dual underlying mechanisms accounting for their symptomatology.
- Facilitate a more targeted, and a potentially staged, management approach.
- Lead to further research.
    - If CI is found to occur more commonly with a particular subtype of SOP additional investigations as to why this may occur would be warranted.
    - Investigations to determine the best management strategy in the setting of combined diagnoses, e.g. what effect does surgical correction of SOP have on conventional CI treatment?

1.4. Research Questions

This study will answer the following questions:

Is there an association between CI and SOP in our patient population?

If there is an association:

- Does CI have a stronger association with a particular subtype of SOP?

If there is no association:

- What factors led to our preliminary conclusions?
- What changes will need to be made to our current practice patterns?

Hypothesis

The hypothesis of this study is that there is an association between SOP and CI.

The Null Hypothesis

The null hypothesis of this study is that no association exists between SOP and CI.

CHAPTER 2: LITERATURE REVIEW

2.1. Critical Analysis of Literature

A diagnosis of SOP or CI is common within strabismus clinics, but these generally occur independently. To the best of my knowledge an association between these has not been reported adequately proven in the literature. A Pubmed search (March 2017) using the Mesh heading 'Trochlear nerve diseases' revealed 407 publications. A search using 'convergence insufficiency' revealed 329 articles. A search combining both terms as [Text Word] revealed a single publication, "Sensorimotor Characteristics of Neuro-Ophthalmology and Oculo-Plastics Patients" by Alex Christoff. However, no patient from this large retrospective cohort had both diagnoses.

This lack of association is in contrast to my clinical training in a tertiary care pediatric ophthalmology & strabismus center that sees over 34,000 patients annually. It has been our team's impression that we have several patients with both diagnoses. This led to the question of whether a true association exists between these seemingly unrelated disorders. A positive correlation between the two disorders would have implications for patient investigation and management, while a negative correlation would force us to re-evaluate our clinical evaluations of patients presenting to our facility with complex strabismus patterns.

2.2. Clinical Findings of Intermittent Exotropia and Superior Oblique Palsy

Cho and Kim, in 2007, did a retrospective chart review looking at 93 patients that that had an intermittent exotropia with a hypertropia of more than 2 prism diopters. These patients showed oblique dysfuntion and a positive Bielschowsky head tilt test prior to having horizontal eye muscle surgery. Postoperative alignment was analyzed at 1 day,

6 months and 1 year. This study concluded that a hypertropia of up to 14 prism diopters with an intermittent exotropia could disappear after having horizontal eye muscle surgery alone.

Lee et al., in 2016, retrospectively reviewed 118 patients with intermittent exotropia. Patients were divided into 2 groups based whether they had a positive or negative Bielschowsky head tilt test. Fifty patients had a positive head tilt test and 68 had a negative head tilt test. Their conclusions were that a positive head tilt test was associated with patients with a large deviation intermittent exotropia, had the deviation for longer and worse stereoacuity. Surgery on the horizontal muscles alone in these cases eliminated the positive head tilt test.

Hata et al., in 2013, investigated the causes of isolated SOP and the association of other ocular deviations. The study consisted of 126 cases of isolated SOP that were split into five groups based on etiology: microvascular, congenital, decompensation of congenital, traumatic and others. Vertical and horizontal deviations were measured in primary position for all patients included. Microvascular (47%) and decompensated (33%) cases made up the majority of the patients included and the rate of recovery was significantly different, 92% for the microvascular and 55% for the decompensated. There were no significant differences amongst the age of onset or mean vertical deviations but what was different was the horizontal deviation. The microvascular group consisted of more exodeviations while the decompensated group included more cases of esodeviation. This study concluded that the differentiation of the horizontal deviation could be crucial in determining the recovery of these isolated SOP's.

While the association of vertical misalignment with exodeviations is well established none of the above studies specifically mentioned CI. This highlighted the need to carefully assess current clinical practice at my institution.

CHAPTER 3: METHODS

3.1. Study Design

3.1.1. General Study Design

This prospective study examined a geographically defined cohort of subjects referred to our strabismus testing centers (see section 3.2.1.). All subjects underwent an orthoptic evaluation that included specific clinical tests used to determine a diagnosis of SOP, CI or both. Subjects having one or both diagnoses were included if they then met inclusion and exclusion criteria. Clinical testing was performed by any member of the research team (see section 3.4.3.). Subjects were identified for a 6-month time period from May 1st 2011 through October 31st 2011.

3.1.2. Participants

A chart review conducted 6 months prior to initiating the project identified a prevalence of a new diagnoses of SOP or CI was approximately 4 per week. Based on this it was felt a 6-month study period would provide approximately 96 participants. Consultation with the initial supervisor and statistician determined this was adequate to determine coincidence with sufficient accuracy.

3.1.3. Data Analysis

Data analysis was performed after collection of all subject data. However, this study includes two sets of results based on two different analyses of the clinical data. The first analysis is referred to as the 'primary analysis' and the second analysis is referred to as the 'revised analysis'. The reasons for this are explained in the study.

Primary analysis included a cross tabulation, Fisher's Exact test and p values to assess the association of CI and SOP. Data was analyzed using Excel and SPSS software

and was stored under the secure login of the principal investigator on the hospital's secure database. Revised data analysis was done using descriptive statistics.

3.2. Recruitment

3.2.1. Study Population & Testing sites

All subjects were patients attending his/her regularly scheduled appointment in the Pediatric Ophthalmology and Strabismus service at Nationwide Children's Hospital in Columbus, Ohio. This included 4 different clinical sites in the Columbus Ohio area (see Appendix A). Only subjects given a new diagnosis of SOP or CI were considered for inclusion.

3.2.2. Social / Cultural / Safety Considerations

The entire diverse population of patients were eligible to participate free from discrimination based on gender, race, religion, language or mental or physical disability (with the exceptions identified in inclusion/exclusion criteria).

3.2.3. Permissions

No site permissions were required for this study. All subjects were under the care of ophthalmologists who were part of the research team.

3.3. Ethics and Study Information

The Children's Hospital Research Ethics Board approved all material and methods necessary for this study (Appendix B – Ethics Approval Form). All subjects (or parent/guardian) found to have one or both diagnoses were required to be given a study information form informing them certain data from his or her records may be used in a research study (Appendix D – Study information sheet).

3.4. Detailed Methodology

3.4.1. Testing Procedure

Prior to subject recruitment all members of the research team performing the clinical assessment of patients participated in a training session coordinated by the principal investigator (PI). The session identified the clinical tests that were required to be performed in the examination, standardizing the method for performing and documentation of the results, and the required diagnostic criteria to make a diagnosis of SOP and/or CI. The CI criteria that was applied was based off of the Convergence Insufficiency Treatment Trial Group research and the SOP criteria applied was based off of our standards we apply at the clinic (Scheiman et al., 2005).

Diagnostic criteria for SOP:

1. Positive 3 step-test: This was determined by performing a Prism Cover Test with the patient viewing a distance target at eye level. A 'positive' result required the presence of a vertical misalignment in primary position that increased on contralateral gaze and on ipsilateral head tilt with respect to the higher eye.
2. Presence of an ipsilateral Inferior oblique over action. This was determined by performing horizontal ocular versions. In the setting of vertical misalignment an observed increase in elevation of the higher eye on contralateral gaze (or alternatively an increase of depression of the lower eye if fixing with the higher eye) was considered positive for an inferior oblique over action.
3. Presence of excyclotorsion. A double Maddox rod test was performed on patients to evaluate torsion. A red cylinder and clear cylinder is aligned vertically in a trial frame that patient looks through. When a light is shined the patient views 2

horizontal lines that run horizontal to one another. If one is tilted or slanted the patient moves the cylinders to make the lines perfectly horizontal to one another.

Diagnostic criteria for CI:

1. Any exophoria at near with minimal or no distance deviation as determined with Prism Cover Test.
2. Insufficient positive fusional vergence: less than 15PD break point. This was tested using a base-out prism bar that was held before one eye as the investigator slowly increased the magnitude of prism. The subject was instructed to look at a 20/30 size letter ("H" on a near fixation stick) and report when diplopia occurred. The prism strength at this break point was taken as their fusional convergence amplitudes.
3. Reduced NPC: 6 cm or greater as measured with the RAF Near Point Rule. The subject was instructed to look at the dot and line target on the carriage that slides along the ruler. The subject was to report when the target split into two (diplopia) and the RAF Near point rule measured the distance. This was taken as the NPC break point. The distance at which this occurred was read directly from the ruler.

If a patient was given a diagnosis of SOP, CI or both the research staff member conducting the assessment would then be required to provide a study information sheet (see Appendix D) and discuss the form with the patient (or parent/guardian). Patient (or parent/guardian) was offered the option to opt out of the study at that time or at any future time prior to a specified date that was listed on the form.

On a daily basis, the PI would review the charts of all patients seen at all 4 clinics to determine who received a diagnosis of SOP, CI or both. The PI would then ensure all

inclusion/exclusion criteria were met before the patient would be considered a subject in this project.

Inclusion criteria:

1. Age 6 and above
2. Best corrected visual acuity of 20/30 or better OU at distance & near.
3. Have a diagnosis of SOP and/or CI

Exclusion criteria:

1. Previous treatment for CI
2. History of strabismus surgery
3. History of amblyopia
4. Monocular accommodation reduced for age
5. Presence of Nystagmus
6. Diagnosis of ADHD, developmental delay, learning disability or behavioral disorder.
7. Diagnosis of any disease that would affect accommodation, vergence or motility, i.e. multiple sclerosis, myasthenia gravis, Grave's disease, Parkinson's disease, etc.
8. Any medications known to affect accommodation: i.e. pain medication.

Following this, clinical details of appropriate subjects would be entered directly into an electronic database by the PI.

3.4.2. Recorded Data

Chart review was conducted over a six-month time period from all 4 locations and patients with a new diagnosis of SOP or CI were entered as study subjects. A database was created for each study subject that included investigator, location of appointment, age, gender, diagnosis given, 3-step head tilt test, inferior oblique function, torsion, fusional amplitudes, NPC, near vision, and near and distance Prism cover test.

3.4.3. Research Team

During attendance at his/her regularly scheduled appointment, every patient was evaluated by one member of the research team. This team consisted of 2 certified orthoptists and 7 pediatric ophthalmologists. All members were employees of Pediatric Ophthalmology Associates within Nationwide Children's Hospital in Columbus, Ohio but were located at any one of 4 different clinical sites (see section 3.2.2.). The evaluation was done as part of a patient's normal examination. The principal investigator (MT) examined subjects, but was also responsible for conducting the training session with the research team, reviewing all charts to identify subjects that had been given one or both diagnoses by a member of the research team, entering of clinical data into a database, and analyzing the results. The original supervisor of the project oversaw progress of the study and provided feedback throughout collection of the data.

3.4.4. Subject Study Duration

Data was collected at the initial subject visit. The investigation did not vary from the normal standard of care. There was no additional time or follow up needed by the study subject. All patients with a new diagnosis of SOP or CI were included in this study, thus there was to be no randomization, blinding or placebos.

3.5. Risk Analysis

3.5.1. Confidentiality & Anonymity

Breach of confidentiality was a potential risk identified by the researcher's due to access of clinic records. All study subjects were identified by medical record number and not by name. Health Insurance Portability and Accountability Act (HIPAA) guidelines were strictly followed and ethical approval was obtained from Dalhousie University and Nationwide Children's Hospital in Columbus Ohio. There were no printed charts and all charts remained secure on the Nationwide Children's Hospital/Pediatric Ophthalmology Associates database. No personal identifiers were used for this study.

The data was stored and saved under the secure login of the PI at Pediatric Ophthalmology Associates within Nationwide Children's Hospital. All pertinent information was entered into Excel software that was only accessible through the same secure login.

In accordance with Dalhousie University *Policy on Scholarly Integrity* the data will be held securely under my login for 5 years, post publication. After the appropriate time has elapsed the data will be erased from my login and become inaccessible.

3.5.2. Conflict of Interest

There was no conflict of interest or financial interest for any member of the research team in relation to the study. The PI and all co-investigators are involved in the provision of health care to the participants.

3.6. Statistical Tests

The association of SOP and CI in subjects obtained during a 6-month time period was split into a *primary analysis* and *revised analysis*. The primary analysis used cross tabulation and Fisher's exact test to describe the association. The revised analysis used descriptive statistics to describe the collection of information collected.

According to a University of Toronto Political Science class, cross tabulation, also known as crosstabs for short, brings together two variables and displays the relationship between them in a single table. They provide a basic picture of the relationship between two variables by tabulating the results of one variable against the other variable. Crosstabs were used to show how SOP and CI inter-relate. Appendix F has a picture of the table that was used.

Fisher's exact test was used, instead of Pearson Chi-Square, to show statistical significance of the data because the N value was less than 5 in at least one cell of each of the crosstabs (Armitage, 1994). In practice, Fisher's exact test is used when sample sizes are small, but it is valid for all sample sizes. Using this test can calculate the p-value exactly, rather than relying on an approximation. The p-value in statistics is the probability of obtaining the observed sample results when the null hypothesis is actually true (Nuzzo, 2014).

The number alpha is the threshold value that we measure the p-values against, and for this study the alpha value used was 0.05 because historically it has been accepted as the standard (Taylor, 2014). If the p-value is less than or equal to the alpha then we reject the null hypothesis and say that the result is statistically significant. If the p-value is

greater than the alpha then we fail to reject the null hypothesis and the result is not statistically significant.

Measures of association provide a way to calculate the size of the association between two variables. Most measures of association range in numerical value from 0 to 1. A maximum numerical value of 1 is when the two variables have a perfect relationship with each other and a value of 0 is when there is no relationship at all between the two variables. Phi and Cramer's V are used in the statistical analysis to measure the strength of the association. A chart was used from a University of Toronto Political Science class to interpret the value of the level of association. This chart gave a verbal description of the association based off the numerical value.

Descriptive statistics are statistics that quantitatively describe features of a collection of information. They provide simple summaries about the sample and about observations that have been made. The secondary analysis uses descriptive statistics to describe the sample.

CHAPTER 4: RESULTS

4.1. Statistical Analysis

In this chapter, the results of the data analysis are presented. The data was collected and subsequently analyzed in response to the hypothesis and questions posed in chapter 1 of this thesis. Both groups were investigated with appropriate statistical tests. Means, ranges and standard deviation were calculated for descriptive purposes.

4.2. Primary Analysis

A total of 68 participants were recruited for this study over the 6-month time period. Once reviewing the data 7 subjects that had a SOP were removed from the data analysis because they were not binocular and therefore could not participate in all the clinical testing to identify CI. One other SOP subject was also removed because the testing for CI was omitted in error by the co-investigator. Once these participants were omitted, the total analyzed subjects were determined to be 60 for this group.

These 60 subjects ranged in age from 6 to 80 with a mean age of 19.88 and a standard deviation of 18.40. There were 26 males and 34 females enrolled in the study. Of these 42 subjects had a diagnosis of isolated CI, 6 subjects were identified to have only SOP, and 12 subjects were found to have both diagnoses. All subjects collected had the same clinical testing done whether they were primarily diagnosed with CI or SOP, however the testing procedure order was left up to the investigators discretion, thus not standardized for all study participants. All subjects underwent measurement in the 9 diagnostic positions of gaze, extraocular motility testing, convergence fusional amplitudes testing and NPC assessment. Figures 4A-C below reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of

all subjects that were analyzed. It should be noted that category "H" is the total patient's that the Orthoptist's recruited for the study.

Figure 4A. Subject examination locations

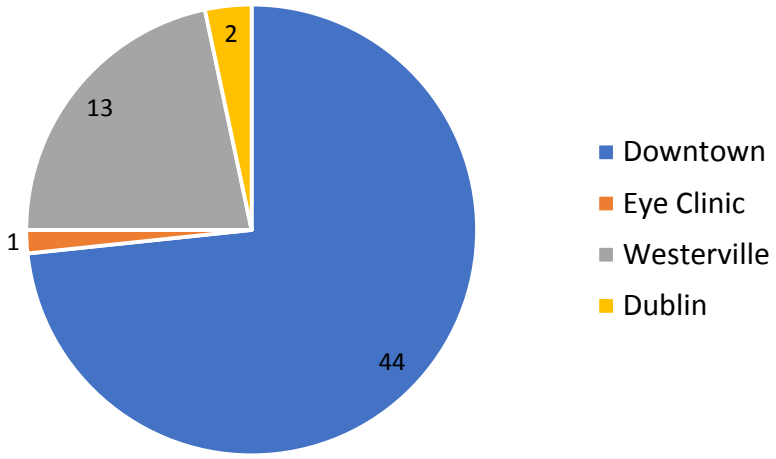


Figure 4B. Examiner distribution

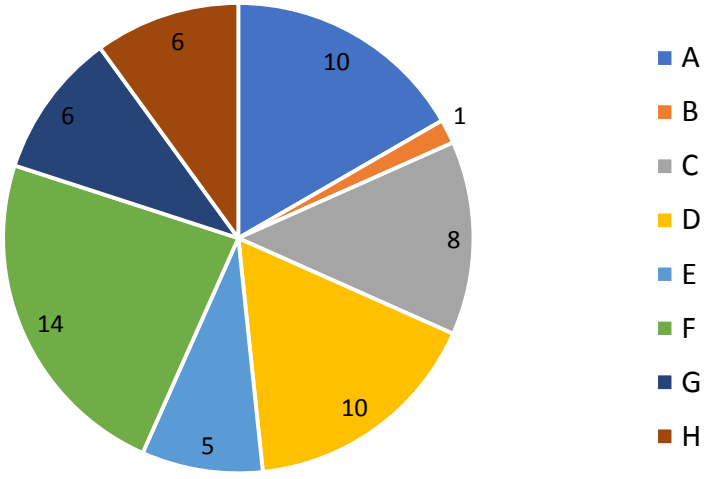
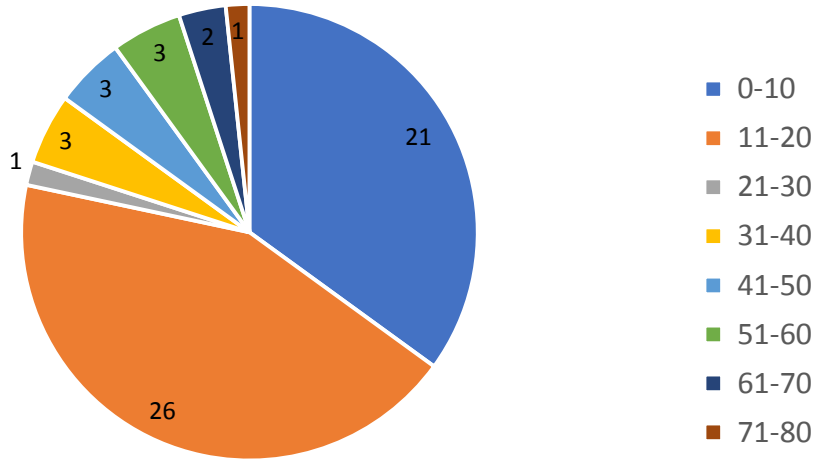


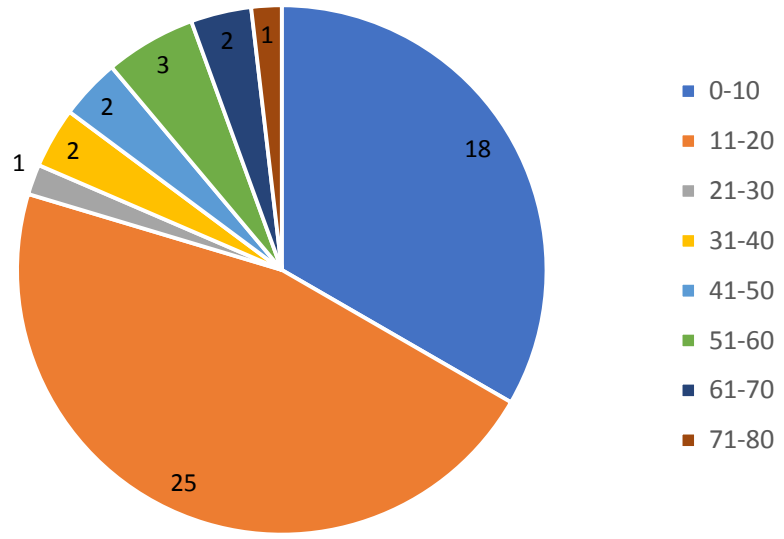
Figure 4C. Age distribution of all subjects



4.2.1. Convergence Insufficiency Subjects

The age range of the 54 subjects identified to have the diagnosis of CI was 6 to 80 years of age with a mean age of 19.91 and a standard deviation of 18.81. There were 22 males and 32 females in this group. Figure 4D shows the age distribution of the CI subjects that were analyzed.

Figure 4D. Age distribution of CI subjects



4.2.2. SOP Subjects

The SOP group analyzed consisted of 18 subjects, 9 congenital SOP subjects and 9 acquired SOP subjects. The 18 SOP subjects analyzed ranged in age from 6 to 80 with a mean age of 36.44 and a standard deviation of 26.13. The total SOP group consisted of 10 females and 8 males. The 9 congenital SOP subjects analyzed ranged in age from 8 to 78 with a mean age of 24.11 and a standard deviation of 24.17. The congenital SOP group consisted of 5 females and 4 males. The 9 acquired SOP subjects analyzed ranged in age from 6 to 80 with a mean age of 48.78 and a standard deviation of 22.9. The acquired SOP group consisted of 5 females and 4 males. There were no bilateral cases, 7 had a right SOP and 11 had a left SOP. Figures 4E-G show the age distributions of all the SOP subjects analyzed.

Figure 4E. Age distribution of all SOP subjects

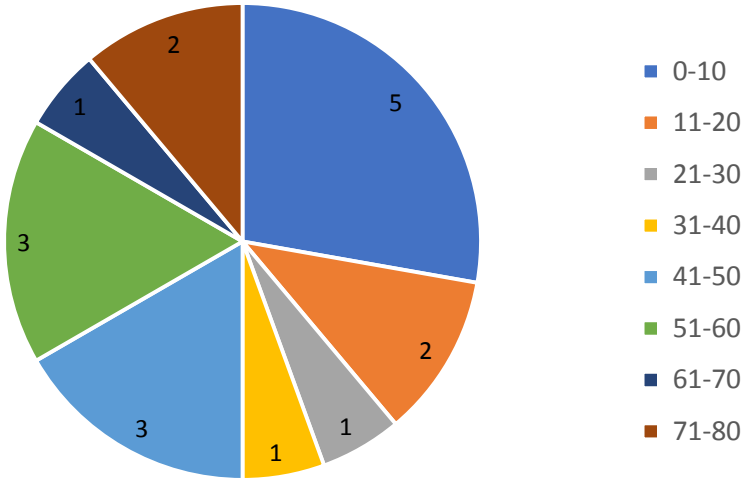


Figure 4F. Age distribution of congenital SOP subjects

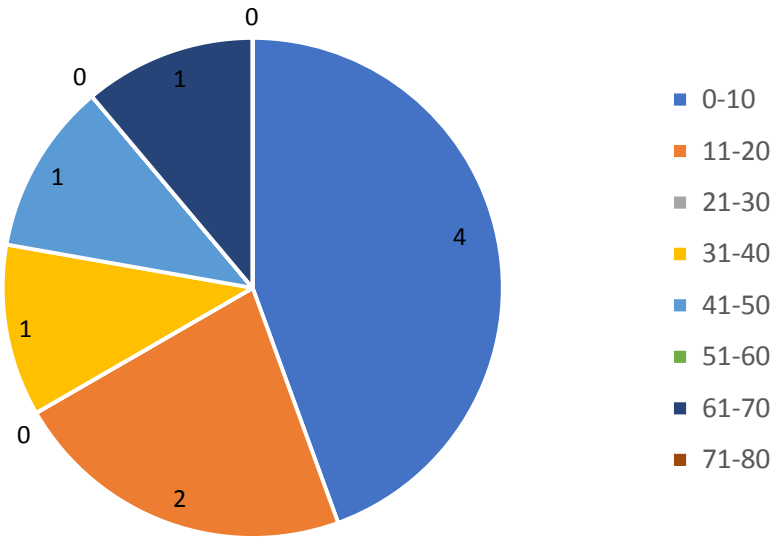
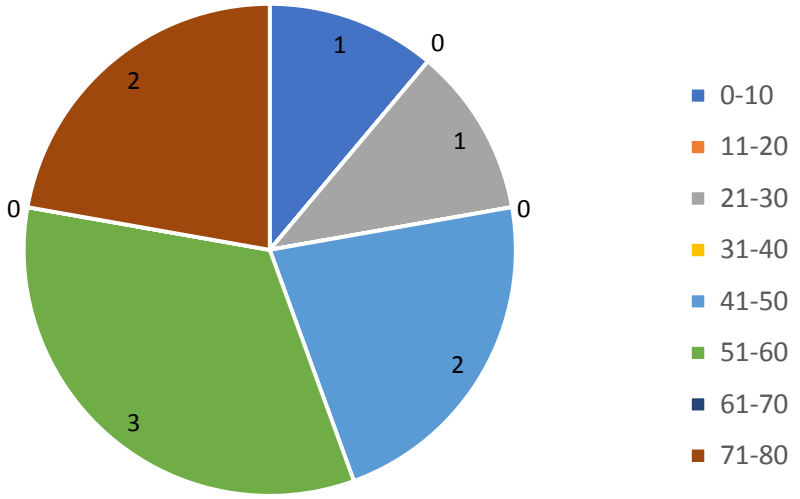


Figure 4G. Age distribution of acquired SOP subjects



4.2.3. Data Analysis

Descriptive statistics, cross tabulation, Fisher's exact test was used to analyze the association between SOP and CI in the primary analysis group. Fisher's exact test was used, instead of Pearson Chi-Square, to show statistical significance of the data, because the frequencies were less than 5 in at least one cell of the crosstabs. Using Fisher's exact test the p-values that were obtained are exact rather than approximation. The p-value gives us the probability of whether the null hypothesis is actually true or not, and Cramer's V was used to measure the strength of the relationship.

The number alpha is the threshold value that we measure the p-values against, and for this study the alpha value was 0.05. If the p-value is less than or equal to 0.05 then we reject the null hypothesis and say that the result is statistically significant. If the p-value is greater than the alpha number then we fail to reject the null hypothesis and the

result is not statistically significant. The tables below show the key data to validate or not validate the particular associations being analyzed.

SOP & CI

The following tables represent the primary analysis looking at SOP characteristics against the presence or absence of CI.

Table 4A. SOP characteristics versus presence of CI

	CI present	**CI Absent**
Congenital SOP	4	5
Acquired SOP	8	1

	CI present	**CI Absent**
Right eye	6	1
Left eye	6	5

	CI present	**CI Absent**
Male	4	4
Female	8	2

Appendix E contains all statistics performed for the primary analysis. Appendix E-1 shows the cross-tabulated frequencies of subjects that were diagnosed with SOP and also had CI. The cross tabulation shows that 42 subjects out of 60 (70%) did not have SOP, leaving 18 (30%) that did have SOP either of the congenital or acquired type. Of those 18 subjects, 12 (66.7%) were concluded to also have a diagnosis of CI. The cross tabulation shows that 6 out of 60 (10%) did not have a diagnosis of CI and 54 out of 60 (90%) did have a diagnosis of CI. Of the 54 subjects that have CI, 12 (22.2%) also have a diagnosis of SOP. The expected counts refer to the frequencies that are expected based off of the sample sizes in the cross tabulation.

Appendix E-2 shows the Chi-Square testing that was completed showing the frequency of subjects with a SOP and CI. Fisher's Exact Test was used in this table to

calculate the $p < 0.001$. This p-value is less than the alpha number of 0.05, which indicates significance. Appendix E-3 indicates the significance of the effect estimate of the Chi-Square tests. Cramer's V reports a value of .509 in the statistical results ran. This test supports the association.

Congenital Superior Oblique Palsy and Convergence Insufficiency

Appendix E-4 shows the cross-tabulated frequencies of subjects that were diagnosed with congenital SOP and also had CI. The cross tabulation shows that 5 subjects out of 9 (55.6%) did not have CI, leaving 4 (44.4%) that did have CI and congenital SOP.

Appendix E-5 shows the Chi-Square testing that was completed showing the frequency of subjects with a congenital SOP and CI. Fisher's Exact Test was used in this table to calculate the $p = .131$. This p value is more than the alpha number of 0.05, which does not indicate significance. Appendix E-6 indicates the significance of the effect estimate of the Chi-Square tests. Cramer's V reports a value of .471 in the statistical results ran. Cramer's V test supports the lack of association.

Acquired Superior Oblique Palsy and Convergence Insufficiency

Appendix E-7 shows the cross-tabulated frequencies of subjects that were diagnosed with acquired SOP and also had CI. The cross tabulation shows that 1 subject out of 9 (11.1%) did not have CI, leaving 8 (88.9%) that did have CI and acquired SOP.

Appendix E-8 shows the Chi-Square testing that was completed showing the frequency of subjects with an acquired SOP and CI. Fisher's Exact Test was used in this table to calculate the $p = .131$. This p value is more than the alpha number of 0.05, which does not indicate significance. Appendix E-9 indicates the significance of the effect

estimate of the Chi-Square tests. Cramer's V reports a value of .471 in the statistical results ran. This test supports the lack of association.

Right Superior Oblique Palsy versus Left Superior Oblique Palsy

Appendix E-10 shows the cross-tabulated frequencies of subjects that were diagnosed with right SOP and also had CI. The cross tabulation shows that 1 subject out of 7 (14.3%) did not have CI, leaving 6 (85.7%) that did have CI and right SOP.

Appendix E-11 shows the Chi-Square testing that was completed showing the frequency of subjects with a right SOP and CI. Fisher's Exact Test was used in this table to calculate the p = .316. This p value is more than the alpha number of 0.05, which does not indicate significance. Appendix E-12 indicates the significance of the effect estimate of the Chi-Square tests. Cramer's V reports a value of .322 in the statistical results ran. This test supports the lack of association.

Appendix E-13 shows the cross-tabulated frequencies of subjects that were diagnosed with left SOP and also had CI. The cross tabulation shows that 5 subjects out of 11 (45.5%) did not have CI, leaving 6 (54.5%) that did have CI and left SOP.

Appendix E-14 shows the Chi-Square testing that was completed showing the frequency of subjects with a left SOP and CI. Fisher's Exact Test was used in this table to calculate the p = .316. This p value is more than the alpha number of 0.05, which does not indicate significance. Appendix E-15 indicates the significance of the effect estimate of the Chi-Square tests. Cramer's V reports a value of .322 in the statistical results ran. This test supports the lack of association.

4.3. Revised Analysis

A change in supervisors prompted a review and then subsequent revised analysis of the data. The outcome of this re-analysis determined only 18 of the original 60 subjects met all of the inclusion criteria. Within this group there was no association between these diagnoses. The only statistics possible with this revised sample size are descriptive.

All patients in both the original and revised cohort were given the opportunity to withdraw consent if they did not want their data to be used in this research. No participant withdrew their consent, therefore, this cohort can be considered to represent a population-based study.

Of these 18 subjects, there were 6 males and 12 females ranging in age from 8 to 80 with a mean age of 24.78 and a standard deviation of 20.45. Nine subjects were identified to have CI and 9 subjects were identified to have SOP. Below the figures reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of all subjects that were analyzed.

Figure 4H. Revised analysis - subject examination location

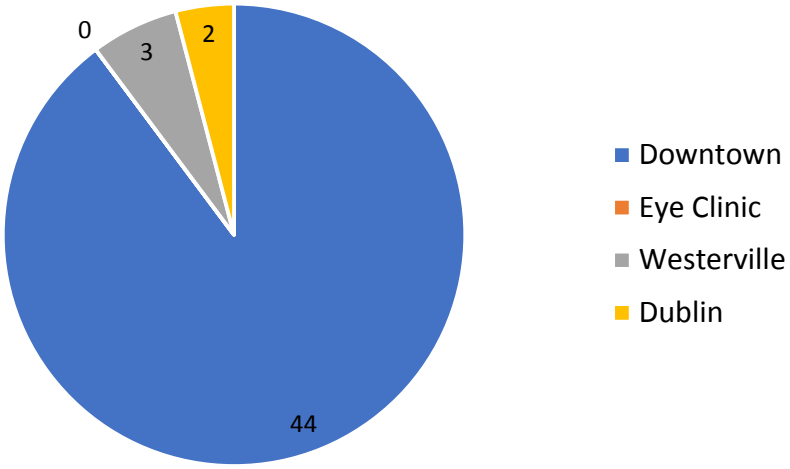


Figure 4I. Revised analysis - examiner distribution of recruitment

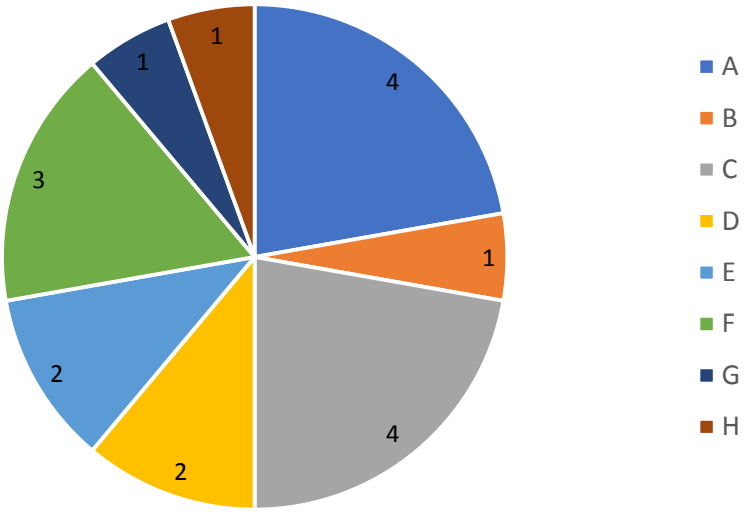
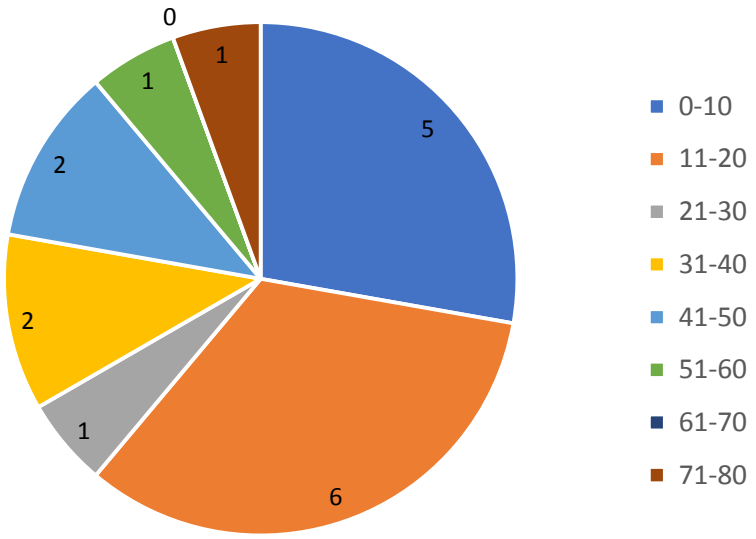


Figure 4J. Revised analysis - age distribution of subjects



4.3.1. Convergence Insufficiency Subjects

The CI group consisted of 9 subjects that ranged in age from 8 to 80 with a mean age of 22.11 and a standard deviation of 23.27. There were 2 males and 7 females. Below the figures reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of all subjects that were analyzed.

Figure 4K. Revised analysis - examination location for CI subjects

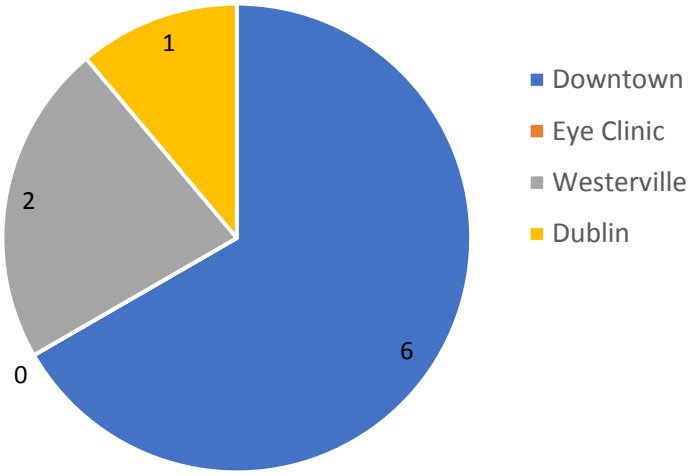


Figure 4L. Revised analysis - examiner distribution of recruitment for CI subjects

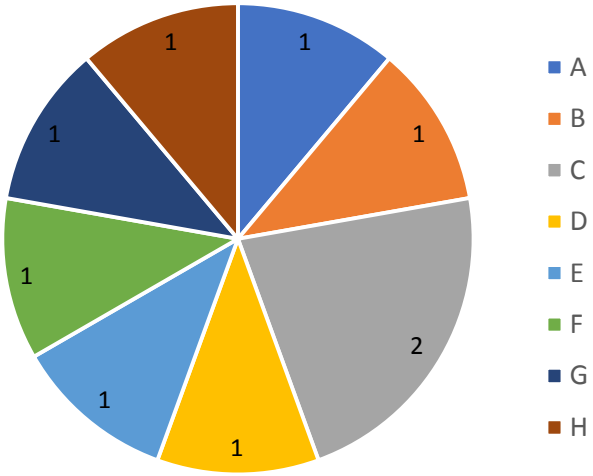
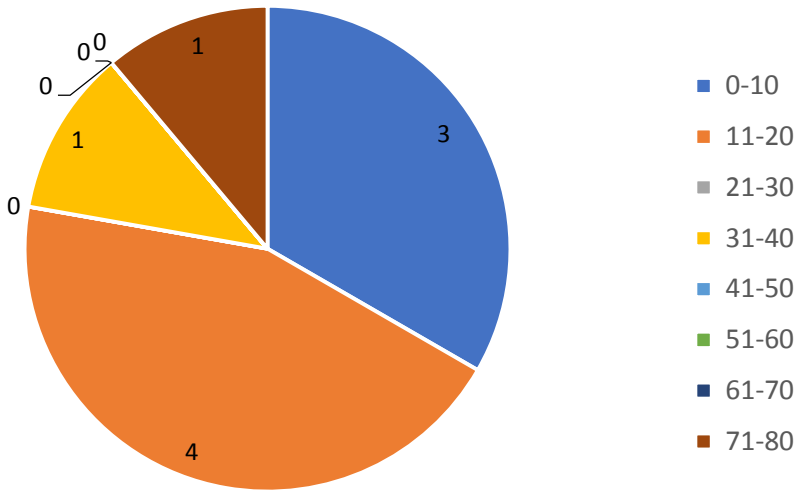


Figure 4M. Revised analysis - age distribution of CI subjects



4.3.2. SOP Subjects

The SOP group consisted of 9 patients that ranged in age from 8 to 58 with a mean age of 27.44 and a standard deviation of 18.20. There were 4 males and 5 females enrolled in the study. Below the figures reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of all subjects that were analyzed.

Figure 4N. Revised analysis - examination location for SOP subjects

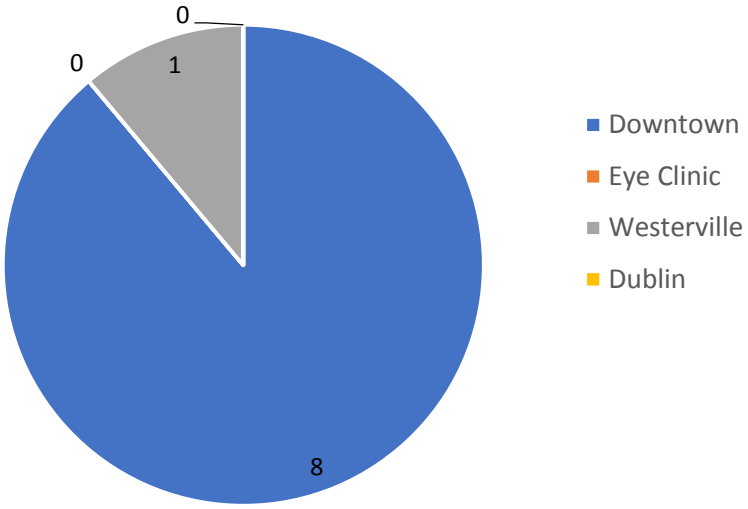


Figure 4O. Revised analysis - examiner distribution of recruitment for SOP subjects

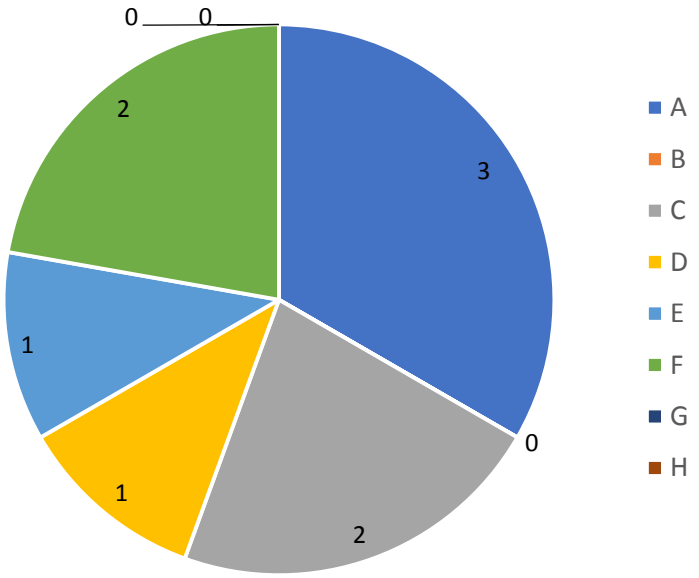
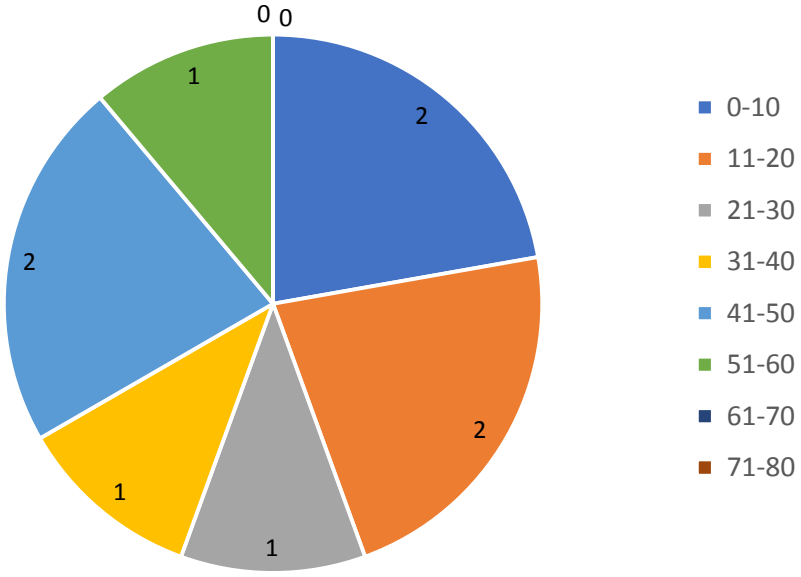


Figure 4P. Revised analysis - age distribution of SOP subjects



Congenital SOP

The congenital SOP group consisted of 6 patients that ranged in age from 8 to 43 with a mean age of 20.33 and a standard deviation of 15.46. There were 3 males and 3 females enrolled in the study. Below the figures reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of all subjects that were analyzed.

Figure 4Q. Revised analysis - examination location for congenital SOP subjects

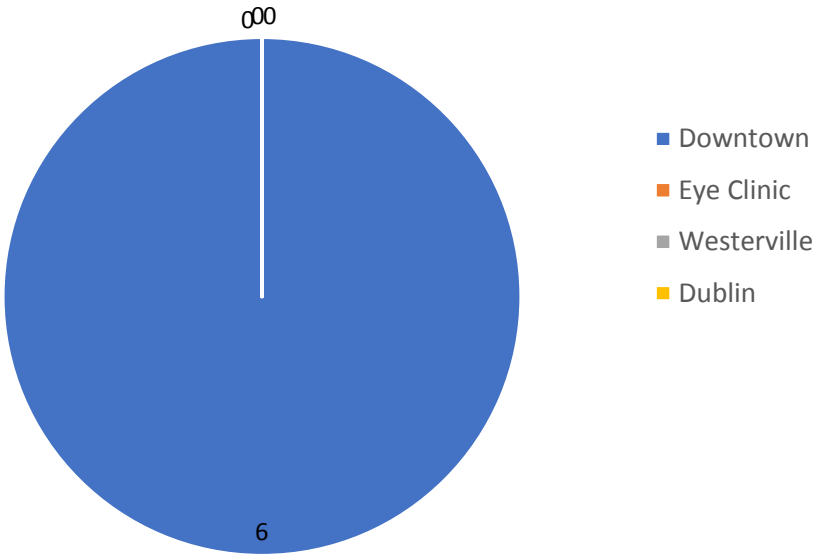


Figure 4R. Revised analysis - examiner distribution of recruitment for congenital SOP subjects

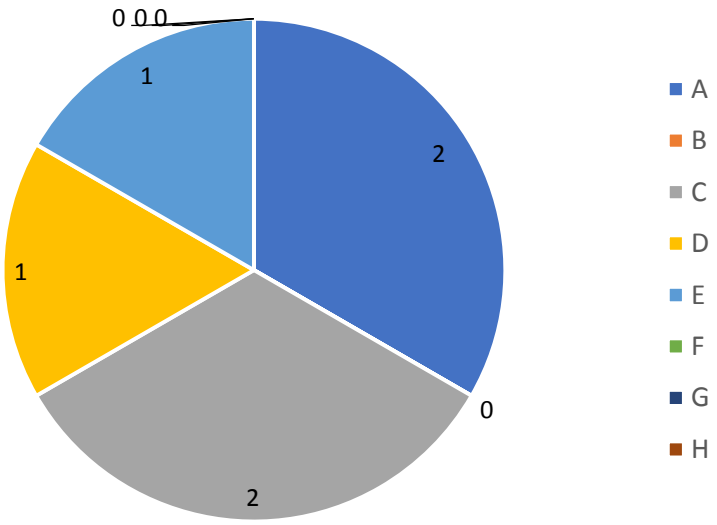
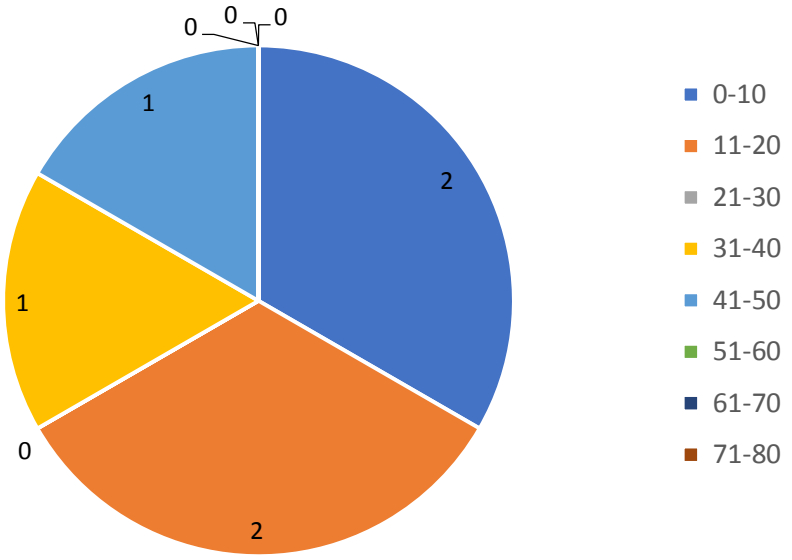


Figure 4S. Revised analysis - age distribution of congenital SOP subjects



Acquired SOP

The acquired SOP group consisted of 3 patients that ranged in age from 25 to 58 with a mean age of 41.67 and a standard deviation of 16.50. There was 1 male and 2 females enrolled in the study. Below the figures reveal the location of where the patients were seen, each investigator's recruitment and the age distribution of all subjects that were analyzed.

Figure 4T. Revised analysis - examination location for acquired SOP subjects

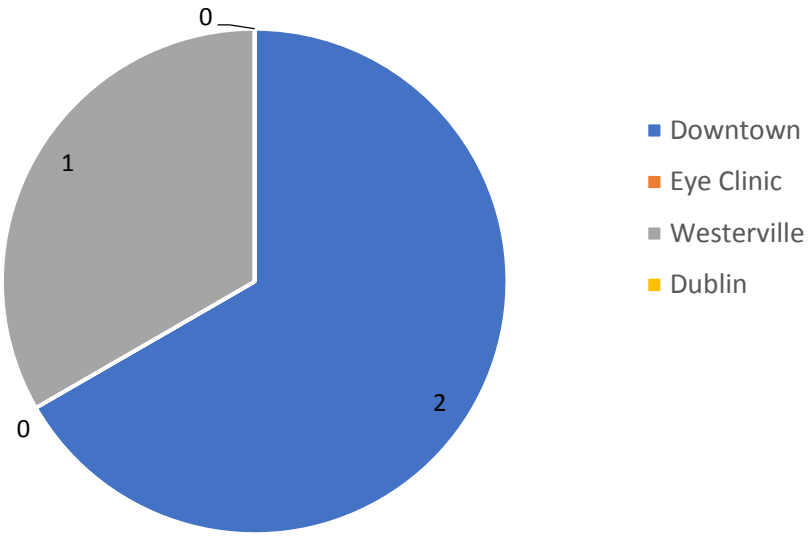


Figure 4U. Revised analysis - examiner distribution of recruitment for acquired SOP subjects

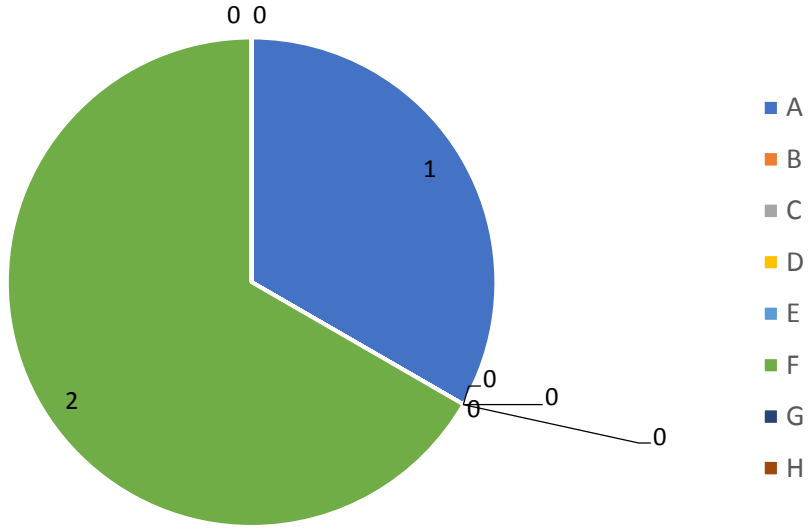
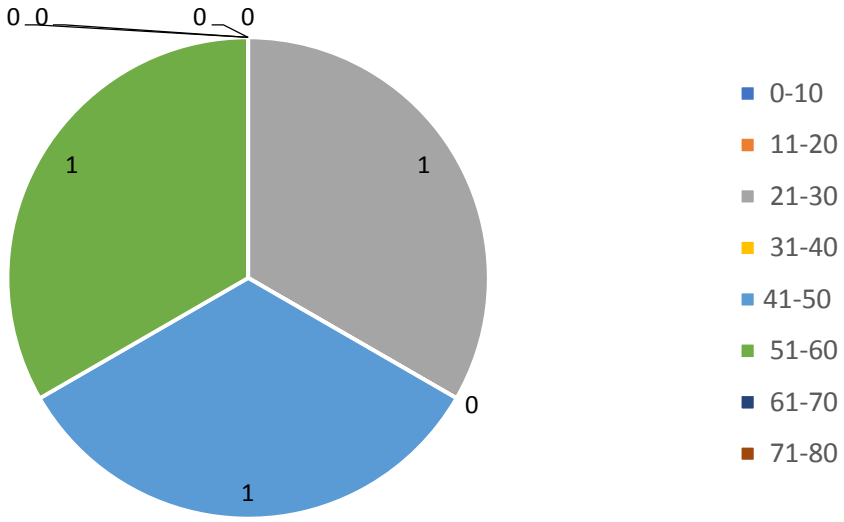


Figure 4V. Revised analysis - age distribution of acquired SOP subjects



CHAPTER 5: DISCUSSION

Prior to commencement of this research, there was the perception within the Nationwide Children's Hospital ophthalmology department that convergence insufficiency (CI) coexists with fourth cranial nerve paresis (SOP). As clinicians, we questioned the possibility that patients with CI were not responding to therapy had an additional underlying diagnosis of SOP. Despite the lack of evidence in the literature, the purpose of this study was to conduct a prospective study to determine if there is an association between CI and SOP in our patient population. Knowledge of any correlation between these two ocular disorders has important clinical implications, not just in terms of therapeutic management, but to gain a more comprehensive understanding of our patient population.

Subjects were collected from multiple pediatric ophthalmology offices in the Columbus Ohio area, and all subjects included in the study had a new diagnosis of SOP or CI. Initially 68 subject's with a diagnosis of CI or SOP, aged 6 and above were included in this research. All subjects underwent standardized orthoptic assessment which included; near point of convergence, fusional convergence amplitudes, extraocular motility testing and a 3-step head tilt test.

5.1. Summary of Primary Analysis

This research study was completed to examine the relationship between SOP and CI. Providing evidence-based research as to whether this association does exist will enhance our clinical knowledge transfer.

By hypothesis I predicted that there was an association between these two ocular motility disorders. Additional queries were posed to address whether this association

correlated to a specific etiology. Initially, the cross-tabulated frequencies of subjects that were diagnosed with SOP and CI showed that 42 subjects out of 60 (70%) had an isolated diagnosis of CI, 6 (10%) had a SOP, and 12 (20%) had a combined diagnosis of CI and SOP. Of those 18 subjects with a diagnosis of SOP, 12 (66.7%) were concluded to have CI. Fisher's Exact Test was used to calculate the $p < 0.001$. This p-value is less than the alpha number of 0.05, which indicates significance. Cramer's V reports a value of .509 in the statistical results ran and supports the association. Those who have CI or SOP are more likely to have the other diagnosis based off of the initial statistics.

The attending physician or orthoptist were responsible for determining the primary diagnosis. This was determined by a comprehensive ophthalmological examination. Each clinician used his or her own clinical judgment to determine the direction of investigation. The order of the subject's exam was generated based upon the subject's chief complaint and presenting symptoms to the office. For example, a subject that presents complaining of reading problems would be assessed for CI before their torsion would be assessed. Another example, a subject presenting with diplopia and a tilting image at distance would have their distance motility assessed and a double Maddox rod before assessing their convergence.

The second question the study aimed to answer was whether the frequency of associated CI was higher among acquired or congenital fourth nerve palsies. The cross-tabulated frequencies of subjects that were diagnosed with congenital SOP and also had CI showed that 9 subjects out of 18 (50%) had a congenital SOP, leaving 9 (50%) that were an acquired fourth nerve palsy. Of those 9 subjects with congenital fourth nerve palsy, 4 (44.4%) were concluded to have CI. Fisher's Exact Test was used to calculate the

p = .131. This p-value is more than the alpha number of 0.05, which does not indicate a significance. Cramer's V reports a value of .471 in the statistical results ran and supports the lack of association. Those who have a congenital SOP are no more likely to have CI versus the acquired SOP subjects.

The cross-tabulated frequencies of subjects that were diagnosed with acquired SOP and also had CI showed that 9 subjects out of 18 (50%) had an acquired SOP, leaving 9 (50%) that were congenital fourth nerve palsies. Of those 9 subjects with acquired fourth nerve palsy, 8 (88.9%) were concluded to have CI. Fisher's Exact Test was used to calculate the p = 0.131. This p value is more than the alpha number of 0.05, which does not indicate significance. Cramer's V reports a value of .471 in the statistical results ran, which supports the lack of an association. Those who have an acquired fourth cranial nerve palsy are no more likely to have CI versus the congenital SOP subjects.

Before the study started it was approximated that 96 subjects would be included in the study providing data was collected over a 6-month time frame. Based upon a report that was ran prior to starting the study it was approximated that 2 SOP patients and 2 CI patients per week would be included. An over estimation of the variability of the study subjects was made by the study's author when the studies inclusion and exclusion criteria was not factored into the sample size calculation. If the inclusion/exclusion criteria were taken into consideration then the author would have realized that many of these patients were not new diagnoses to the office, which was one of the inclusion criteria for this study. There were also patients included in this report that were coming back for a follow up visit after eye muscle surgery or orthoptic treatment was prescribed and these patients would be excluded from the study also.

Despite an inability to obtain 95+ participants within the collection period there is statistical significance to confidently suggest an association between SOP and CI. The p-values do not suggest that the association is more significant amongst the congenital group of fourth cranial nerve palsy vs. the acquired group, although the percentages would suggest otherwise. It should be discussed that 6 (40%) patients in the acquired group could not clinically be tested for CI because of a constant strabismus at near. Although clinically their convergence ability could not be quantified, it should be noted that these patients complained of CI symptoms when doing near work. They were not added to the CI group because there were strict inclusion and exclusion guidelines that needed to be met in order to be diagnosed with CI.

Based on this primary analysis, the high association between a fourth cranial nerve palsy and CI, would make it imperative for clinicians practicing within this patient population to screen all patients with a CI for a fourth nerve palsy.

5.2. Summary of Revised Analysis

Two major errors occurred within this study. First, on several occasions subjects were given a diagnosis who had not met ALL diagnostic criteria. Next, this error was further compounded when the PI and original supervisor did not recognize this had occurred prior to running the initial statistical analyses. This came to light after "new eyes" were put on the study with new supervisors looked at the data. This led to a review of the database to exclude those subjects in which all criteria were not met. The outcome was a reduction in the number of subjects found to have SOP, CI, or both. When the data was re-analyzed with new numbers there was no longer an association.

5.3. Practical Implications for our Department

This research was designed to answer clinical questions using scientific methodology that would be clinically transferable, in order to apply the findings as directly as possible to everyday clinical practice. Maintaining transferability was important as the findings could directly impact clinical procedures. Although this research is in agreement with the current literature, it contradicts our pre-study clinical impressions. Perhaps the most likely explanation for our original mistaken conviction of a correlation between SOP and CI rest solely in flawed convergence testing in the presence of a vertical or torsional ocular misalignment. It is possible patients with a complex strabismus are not able to accurately perform convergence assessment as the other deviation is a barrier to fusion (or the maintenance of binocularity). Correction of the ocular misalignment (with synoptophore for example) prior to convergence testing would be necessary in order to achieve a true and accurate evaluation of convergence ability.

5.4. Potential Limitations

This study has several limitations, which may have influenced the findings and limited the generalizability. The limitation of recruitment from a geographically defined region of Columbus, Ohio, over a 6-month period limits the generalizability of this study's findings. Continued enrollment from multicenter sites would increase the number of subjects and may overcome this limitation. The results of this study cannot be transferred to other populations outside the set inclusion criteria.

Furthermore, this study was limited by having the research team of seven pediatric ophthalmologists and 2 orthoptists recruiting subjects utilized in the study. The

testing procedures for each subject was not standardized as it was up to the clinicians' discretion as to which clinical tests were performed first. If motor fusion was assessed following strabismic measurements they could possible appear to be falsely reduced due to pre-testing dissociation. Although all research staff responsible for application of clinical testing were provided with an educational session, there was some discrepancy in the testing protocol for convergence fusional amplitude. Allowing the endpoint to be either 'blur' or 'break' point could alone result in protocol violation and variability. A more detailed and standardized testing protocol for all subjects, regardless of the potential clinical diagnosis would reduce this inconsistency and strengthen the study results.

In addition, another limitation is that the research team was not blinded and there may be a potential bias to the belief that CI may be associated with SOP or vice versa. Inclusion criteria for the study were based on the ophthalmologist or orthoptists assessment of the subject. Tester bias may cause the tester to accept that a NPC is reduced much faster on a subject and not adequately encourage the subject to exert some effort to converge to an approaching near target or potentially may influence their measurement of a vertical deviation. In order to reduce this limitation, all examiners were highly qualified board certified pediatric ophthalmologists or certified orthoptists with many years of clinical experience and are familiar with the clinical signs both conditions have. Prior to the study starting all investigators were reminded of the protocol and instructed on the proper way all testing should be completed. All study personal knew to encourage subjects to put forth as much effort as possible so accurate testing results could be obtained. Although the investigators were not masked, they did

perform all of the clinical tests on individual subjects reducing the potential inter-rater variability. Each examiner should be internally consistent in their testing.

Another potential limitation was recruiting subjects with a new diagnosis of SOP and CI that came in during the 6-month time period. Historically in our group an average of 4 new diagnoses of SOP or CI were made each week, of these SOP's I believed that 75% would have CI. This percentage was obtained by doing a brief chart review prior to starting the study and noticing that approximately 75% of the patients diagnosed with SOP also had CI. In an ideal world, it would have been nice to have had an equal age matched number of subjects in each category. To try to overcome this limitation subjects were recruited from multiple testing sites. If the average of new diagnoses were to decrease then my sample size would also decrease.

The study population was gathered from pediatric ophthalmology offices and consisted of mostly children, and is not an accurate representation of the general population. The study subjects that I was looking for had a specific pathology and would potentially end up going to the doctor once becoming symptomatic. There is the possibility that these patients would visit an adult general ophthalmologist's office, neuro-ophthalmologist's office or the CI patients end up in an optometry office.

The large age range accepted for inclusion could also have played a limiting factor when looking at convergence ability. Although convergence ability should not alter with age, accommodative amplitudes change dramatically with age. Accommodative amplitude testing should also have been performed with the subject's distance correction in place to ensure accuracy, however this was not part of the testing protocol and in future should be. Since convergence is part of a near triad which

includes accommodation and miosis, in hindsight, a complete pupillary examination should also have been included to rule out pupillary anomalies which could play a contributing role in accommodative convergence.

A strict inclusion criterion in this study was designed to reduce the influence of tester bias, however initially all inclusion criteria were not applied, resulting in the need for a revised analysis. This gave the PI a false impression that the number of subjects was significantly higher than it actually was, resulting in the cessation of recruitment much sooner than it should have been.

CHAPTER 6: CONCLUSIONS & FUTURE DIRECTIONS

Prior to the start of this study, there was a preconceived assumption that, in our clinic patient population, fourth nerve palsy (SOP) and convergence insufficiency (CI) correlated. Initial results indicated that there was an association. Initially, I relied heavily on my supervisor for design methodology and also on my research team that the application of all diagnostic criteria was being completed as we had discussed prior to the study starting. At the end of each clinic day I completed a chart review and entered the data into the secure database, but focused first on whether a diagnosis was made of either SOP or CI. During the initial analysis, it turned out that not all the criteria were being met, and I should have reviewed the data closer. It was not until after the initial statistics were performed it was noticed all the inclusion criteria were not met for each diagnosis resulting in the initial finding of a high association.

A new light was brought to my study when I was assigned a new supervisory committee. When the data was re-evaluated looking for adherence to study protocol the association dissolved completely. For example, on my initial evaluation of the convergence amplitudes for the study subjects, I only looked at the convergence reserves, failing to include the free space control of the exodeviation, for the total fusional convergence amplitude threshold. This error resulted in the initial false over-diagnosis of CI in many of the patients included. Once errors, such as this one, were brought to my attention, a revised analysis was completed.

No definitive statement can be made about no association between SOP and CI because after the exclusion of our population in the revised analysis this sample is too

low to perform adequate analysis. A future direction would be to reassess with a sample size that would permit this.

Knowledge was gained through this research in terms of testing procedures as well as interpretation of the clinical results. I never realized how difficult doing a thesis project was, from the beginning literature review, to learning how to use Ref Works, to meeting with a statistician and running stats through SPSS. Through mistakes you gain knowledge and that knowledge will help me in future studies that I am to endeavor in. As an Orthoptist, I plan to continue doing research to make our profession the best that it can be. The whole research process has been extremely enlightening and something that I am glad I got to experience.

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APPENDICES

APPENDIX A – Site Locations

Pediatric Ophthalmology and Associates sites within Nationwide Children's Hospital in Columbus, Ohio area.

Pediatric Ophthalmology Associates
555 S. 18th St., Ste 4C
Columbus, OH 43205

Pediatric Ophthalmology Associates
5665 Venture Dr., Ste 1C
Dublin, OH 43017

Pediatric Ophthalmology Associates
433 N. Cleveland Ave., Ste 2B
Westerville, OH 43081

Nationwide Children's Hospital Eye Clinic
555 S. 18th St., Ste 4B
Columbus, OH 43205

APPENDIX B – Ethic Approval Nationwide Children's Hospital

NATIONWIDE CHILDREN'S HOSPITAL

March 4, 2011

Meghan McMillin
Ophthalmology

Study ID: IRB11-00131
Study Name: The Frequency of Association between Fourth Cranial Nerve Palsies and Convergence Insufficiency: A Cross-sectional study.

Dear Dr. McMillin,

The response to modifications requested, submitted on 3/1/2011, for the above study has been reviewed by the Institutional Review Board on 3/4/2011 - **STUDY APPROVED**.

Date of Approval: 3/1/2011
Date of Expiration: 2/29/2012

This approval is for one year only. A Continuing Review Report must be approved before this study can proceed beyond the date of expiration. Please be aware that all changes to the research protocol consent form, or any other aspect of this study must receive prospective IRB approval. IRB policy requires that provisions are made for assent of subjects age nine and older.

The Federalwide Assurance number assigned to the IRB at Nationwide Children's Hospital, Inc. is FWA00002860.

If we can provide additional assistance, please do not hesitate to call this office at ext. 22708.

Sincerely,

Grant Morrow III, MD, Vice-Chair
Institutional Review Board

APPENDIX C – Ethic Approval Dalhousie University

DALHOUSIE UNIVERSITY
Inspiring Minds

Health Sciences Human Research Ethics Board
Letter of Approval

Date: April 14,2011.

To: Meghan McMillin, Clinical Vision Science
Karen McMain, Clinical Vision Science

The Health Sciences Research Ethics Board has examined the following application for research involving human subjects:

Project # 2010-2331 (version 3)

Title: The Frequency of Association Between Fourth Cranial Nerve Palsies and Convergence Insufficiency: A cross-Sectional Study

and found the proposed research involving human subjects to be in accordance with Dalhousie Guidelines and the Tricouncil Policy Statement on *Ethical Conduct in Research Using Human Subjects.* This approval will be in effect for 12 months from the date indicated below and is subject to the following conditions:

1. Prior to the expiry date of this approval an annual report must be submitted and approved.
2. Any significant changes to either the research methodology, or the consent form used, must be submitted for ethics review and approval *prior to their implementation.*
3. You must also notify Research Ethics when the project is completed or terminated, at which time a final report should be completed.
4. Any adverse events involving study participants are reported immediately to the REB

Effective Date: April 12,2011. signed:
Expiry Date: April 12,2012.

IMPORTANT FUNDING INFORMATION - *Do not ignore*

To ensure that funding for this project is available for use, you must provide the following information and FAX this page to RESEARCH SERVICES at 494-1595

Name of grant /contract holder _____ _____ Dept. _____ _ _____
Signature of grant / contract holder _____ _____ _____ _____
Funding agency _____ _____ _____ _____ _____
Award Number _____ _____ Dal Account # (if known) _____ _____

Dalhousie Research Services • Research Ethics • 6299 South Street,2nd Floor, Suite 231 • Halifax, NS, Canada • B3H 4H6
Tel: 902-494-1462 • Fax: 902-494-1595 • Email: Patricia.Lindley@dal.ca • www.dal.ca/~research

APPENDIX D – Subject information sheet

The Association Between Fourth Cranial Nerve Palsy and Convergence Insufficiency

At Nationwide Children's Hospital and Pediatric Ophthalmology Inc we are participating in a research study to look at the possible association between Fourth Cranial Nerve Palsy and Convergence Insufficiency. The principal investigator of this study is a student and the research study is being done in partial fulfillment of a Master's Degree at Dalhousie University. We will be reviewing charts over a 6 month time period and collecting data from each chart to find out whether an association exists amongst these two medical conditions. The new diagnosis today of fourth cranial nerve palsy **and/or** convergence insufficiency has made you/your child eligible for this study. These conditions are different, but both involve a problem with eye alignment. Your doctor has explained the information specific to you or your child.

It is important to remember that this study only looks at information in your/your child's medical chart and will NOT change the standard of care or treatment that you will receive at Nationwide Children's Hospital or Pediatric Ophthalmology.

Important clinical information from your chart will be gathered and kept under your medical record number for the 6 month time period of the study. All information will be secured under a password-protected database and no personal information will be recorded. At the end of the 6 month time period all information will be scanned for duplicate medical record numbers. Once duplicates have been removed, medical record numbers will be deleted, making the data de-identified. This means there will be no way to link the information to you or your child.

Participating in this study will help us better understand and treat these two conditions. If you have any further questions regarding this ongoing study or would like to remove your/your child's information from the study, please call Meghan McMillin at Pediatric Ophthalmology, 614-224-6222. You may also contact Patricia Lindley (Director Research Ethics, Dalhousie University) at 1-902-494-3423 or by e-mail at Patricia.Lindley@Dal.ca, or Nationwide Children's Hospital Institutional Review Board at 614-722-2708 if you have further questions regarding this study.

Please note that the deadline for having your data removed from the study is October 31, 2011. After that date the data will be anonymous and we won't know which data is yours.

APPENDIX E – Statistics for Primary analysis

Appendix E-1. SOP & CI Cross Tabulation

			Dx CI		
			no	yes	Total
Dx SOP	no	Count	0	42	42
		Expected Count	4.2	37.8	42.0
		% within Dx 4CNP	0.0%	100.0%	100.0%
		% within Dx CI	0.0%	77.8%	70.0%
		% of Total	0.0%	70.0%	70.0%
	yes	Count	6	12	18
		Expected Count	1.8	16.2	18.0
		% within Dx 4CNP	33.3%	66.7%	100.0%
		% within Dx CI	100.0%	22.2%	30.0%
		% of Total	10.0%	20.0%	30.0%
Total		Count	6	54	60
		Expected Count	6.0	54.0	60.0
		% within Dx 4CNP	10.0%	90.0%	100.0%
		% within Dx CI	100.0%	100.0%	100.0%
		% of Total	10.0%	90.0%	100.0%

Appendix E-2. SOP & CI Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	15.556[a]	1	.000		
Continuity Correction[b]	12.072	1	.001		
Likelihood Ratio	16.095	1	.000		
Fisher's Exact Test				.000	.000
N of Valid Cases	60				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.80.

b. Computed only for a 2x2 table

Appendix E-3. SOP & CI Symmetric Measures

		Value	Approx. Sig.
Nominal by Nominal	Phi	-.509	.000
	Cramer's V	.509	.000
	Contingency Coefficient	.454	.000
N of Valid Cases		60	

Appendix E-4. Congenital SOP & CI Cross Tabulation

			C 4CNP		Total
			no	yes	
Dx CI	no	Count	1	5	6
		Expected Count	3.0	3.0	6.0
		% within Dx CI	16.7%	83.3%	100.0%
		% within C SOP	11.1%	55.6%	33.3%
		% of Total	5.6%	27.8%	33.3%
	yes	Count	8	4	12
		Expected Count	6.0	6.0	12.0
		% within Dx CI	66.7%	33.3%	100.0%
		% within C SOP	88.9%	44.4%	66.7%
		% of Total	44.4%	22.2%	66.7%
Total		Count	9	9	18
		Expected Count	9.0	9.0	18.0
		% within Dx CI	50.0%	50.0%	100.0%
		% within C SOP	100.0%	100.0%	100.0%
		% of Total	50.0%	50.0%	100.0%

Appendix E-5. Congenital SOP & CI Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.000[a]	1	.046	.131	.066
Continuity Correction[b]	2.250	1	.134		
Likelihood Ratio	4.270	1	.039	.131	.066
Fisher's Exact Test				.131	.066
N of Valid Cases	18				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.00.
b. Computed only for a 2x2 table

Appendix E-6. Congenital SOP & CI Symmetric Measures

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	-.471	.046	.131
	Cramer's V	.471	.046	.131
	Contingency Coefficient	.426	.046	.131
N of Valid Cases		18		

Appendix E-7. Acquired SOP & CI Cross Tabulation

		A 4CNP		Total
		no	yes	
Dx CI	Count	5	1	6
	Expected Count	3.0	3.0	6.0
no	% within Dx CI	83.3%	16.7%	100.0%
	% within A SOP	55.6%	11.1%	33.3%
	% of Total	27.8%	5.6%	33.3%
	Count	4	8	12
	Expected Count	6.0	6.0	12.0
yes	% within Dx CI	33.3%	66.7%	100.0%
	% within A SOP	44.4%	88.9%	66.7%
	% of Total	22.2%	44.4%	66.7%
Total	Count	9	9	18
	Expected Count	9.0	9.0	18.0
	% within Dx CI	50.0%	50.0%	100.0%
	% within A SOP	100.0%	100.0%	100.0%
	% of Total	50.0%	50.0%	100.0%

Appendix E-8. Acquired SOP & CI Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.000[a]	1	.046	.131	.066
Continuity Correction[b]	2.250	1	.134		
Likelihood Ratio	4.270	1	.039	.131	.066
Fisher's Exact Test				.131	.066
N of Valid Cases	18				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 3.00.
b. Computed only for a 2x2 table

Appendix E-9. Acquired SOP & CI Symmetric Measures

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	.471	.046	.131
	Cramer's V	.471	.046	.131
	Contingency Coefficient	.426	.046	.131
N of Valid Cases		18		

Appendix E-10. Right SOP & CI Cross Tabulation

			Right Eye		Total
			no	yes	
Dx CI	no	Count	5	1	6
		Expected Count	3.7	2.3	6.0
		% within Dx CI	83.3%	16.7%	100.0%
		% within Right Eye	45.5%	14.3%	33.3%
		% of Total	27.8%	5.6%	33.3%
	yes	Count	6	6	12
		Expected Count	7.3	4.7	12.0
		% within Dx CI	50.0%	50.0%	100.0%
		% within Right Eye	54.5%	85.7%	66.7%
		% of Total	33.3%	33.3%	66.7%
Total		Count	11	7	18
		Expected Count	11.0	7.0	18.0
		% within Dx CI	61.1%	38.9%	100.0%
		% within Right Eye	100.0%	100.0%	100.0%
		% of Total	61.1%	38.9%	100.0%

Appendix E-11. Right SOP & CI Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.870[a]	1	.171	.316	.199
Continuity Correction[b]	.731	1	.393		
Likelihood Ratio	2.015	1	.156	.316	.199
Fisher's Exact Test				.316	.199
N of Valid Cases	18				

a. 3 cells (75.0%) have expected count less than 5. The minimum expected count is 2.33.
b. Computed only for a 2x2 table

Appendix E-12. Right SOP & CI Symmetric Measures

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	.322	.171	.316
	Cramer's V	.322	.171	.316
	Contingency Coefficient	.307	.171	.316
N of Valid Cases		18		

Appendix E-13. Left SOP & CI Cross Tabulation

			Left Eye		Total
			no	yes	
Dx CI	no	Count	1	5	6
		Expected Count	2.3	3.7	6.0
		% within Dx CI	16.7%	83.3%	100.0%
		% within Left Eye	14.3%	45.5%	33.3%
		% of Total	5.6%	27.8%	33.3%
	yes	Count	6	6	12
		Expected Count	4.7	7.3	12.0
		% within Dx CI	50.0%	50.0%	100.0%
		% within Left Eye	85.7%	54.5%	66.7%
		% of Total	33.3%	33.3%	66.7%
Total		Count	7	11	18
		Expected Count	7.0	11.0	18.0
		% within Dx CI	38.9%	61.1%	100.0%
		% within Left Eye	100.0%	100.0%	100.0%
		% of Total	38.9%	61.1%	100.0%

Appendix E-14 Left SOP & CI Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.870[a]	1	.171	.316	.199
Continuity Correction[b]	.731	1	.393		
Likelihood Ratio	2.015	1	.156	.316	.199
Fisher's Exact Test				.316	.199
N of Valid Cases	18				

a. 3 cells (75.0%) have expected count less than 5. The minimum expected count is 2.33.

b. Computed only for a 2x2 table

Appendix E-15 Left SOP & CI Symmetric Measures

		Value	Approx. Sig.	Exact Sig.
Nominal by Nominal	Phi	-.322	.171	.316
	Cramer's V	.322	.171	.316
	Contingency Coefficient	.307	.171	.316
N of Valid Cases		18		

APPENDIX F – Cross Tabulation Interpretation Table

LEVEL OF ASSOCIATION	Verbal Description	COMMENTS
0.00	No Relationship	Knowing the independent variable does not help in predicting the dependent variable.
.00 to .15	Very Weak	Not generally acceptable
.15 to .20	Weak	Minimally acceptable
.20 to .25	Moderate	Acceptable
.25 to .30	Moderately Strong	Desirable
.30 to .35	Strong	Very Desirable
.35 to .40	Very Strong	Extremely Desirable
.40 to .50	Worrisomely Strong	Either an extremely good relationship or the two variables are measuring the same concept
.50 to .99	Redundant	The two variables are probably measuring the same concept.
1.00	Perfect Relationship.	If we the know the independent variable, we can perfectly predict the dependent variable.

Taken from POL242 Lab Manual, Department of Political Science 2013, University of Toronto.

APPENDIX G – Raw Data

Pt#	Inv	Loc	Age	Sex	Int. Dx	CI	SOP	3ST	IOOA	Tor	BOB	BOR	TTL	NPC	Both	NVA	NH#	HDev	Near V#	VDev	Dist H	Dist V
1	JML	7	13	1	CI RA SOP	yes	no	*	*	*	6	4	12	30cm	no	J1+	6	X(T)	0	none	Ortho	Ortho
2	GLR	1	64	1	P	NA	yes	(+)	yes	3 ex	NA	NA	NA	NA	NA	drop	*	*	*	*	*	*
3	MLM	1	6	2	CI RA SOP	no	no	(-)	*	*	8	6	20	10cm	no	J1+	12	X(T)	0	none	4X(T)	Ortho
4	MLM	6	80	1	LA SOP	yes	no	(-)	yes	5 ex	6	4	12	12cm	no	J2	6	X(T)	0	none	Ortho	1RHT
5	MLM	1	58	2	RC SOP	no	yes	(+)	yes	5 ex	14	12	29	12cm	no	J2	15	X(T)	6	LH(T)	8X(T)	6LH(T)
6	MLM	1	8	2	P	no	yes	(+)	yes	5 ex	14	12	26	25cm	no	J1+	12	X(T)	2	RH(T)	15XT	20RHT
7	DLR	7	10	2	CI	yes	no	(-)	*	*	Rmt	Rmt	NA	Rmt	no	J1+	10	X(T)	0	none	2X	Ortho
	RPG	7	9	2	CI	no	no	(-)	*	*	12	10	26	15cm	no	J1+	14	X(T)	0	none	2X	Ortho
9	RPG	7	10	2	CI	no	no	(-)	*	*	14	12	22	10cm	no	J1+	8	X	0	none	1X	Ortho
10	DLR	7	25	1	LA SOP	no	yes	(+)	yes	5 ex	16	14	26	10cm	no	J1+	10	X(T)	12	LH(T)	2X(T)	6LH(T)
11	GLR	1	52	2	P	NA	yes	(+)	yes	3 ex	NA	NA	NA	NA	NA	drop	*	*	*	*	*	*
12	MCM	1	16	2	CI	no	no	(-)	*	*	16	14	34	10cm	no	J1+	18	X(T)	0	none	2X	Ortho
13	MCM	1	16	2	CI	no	no	(-)	*	*	18	16	38	10cm	no	J1+	20	X(T)	0	none	Ortho	Ortho
14	GLR	1	37	1	LC SOP	no	yes	(+)	yes	10 ex	25	20	29	6cm	no	J1+	4	X(T)	2	LH(T)	15X(T)	20LH(T)
15	CBC	1	8	1	LC SOP	no	no	(+)	yes	?	25	20	****	2cm	no	J1+	4	E(T)	8	LH(T)	Ortho	Ortho

Pt#	Inv	Loc	Age	Sex	Int. Dx	CI	SOP	3ST	IOOA	Tor	BOB	BOR	TTL	NPC	Both	NVA	N H#	H Dev	Near V#	V Dev	Dist H	Dist V
16	GLR	1	71	1	L A SOP R C SOP	no	yes	(+)	yes	5 ex	12	10	12	10cm	no	J2 *	12	none	8	RH(T)	10E(T)	5LH(T)
17	RPG	1	13	1	SOP	no	yes	(+)	yes	5 ex	25	18	40	5cm	no	J1+	15	X(T)	8	RH(T)	20X(T)	15RH(T)
18	RPG	7	11	1	CI	no	no	(-)	*	*	14	12	24	6cm	no	J1+	10	X(T)	0	none	2X	Ortho
19	RPG	7	14	1	CI	no	no	(-)	*	*	20	18	40	8cm	no	J1+	20	X(T)	0	none	2X	Ortho
20	JML	1	16	2	CI	no	no	(-)	*	*	10	8	16	15cm	no	J1+	6	X(T)	0	none	Ortho	Ortho
21	DLR	1	13	2	CI	yes	no	(-)	*	*	6	4	14	20cm	no	J1+	8	X(T)	0	none	Ortho	Ortho
22	MCM	1	14	2	CI	no	no	(-)	*	*	14	12	18	12cm	no	J1+	4	X	0	none	Ortho	Ortho
23	GLR	1	9	1	CI R A SOP	no	no	(-)	*	*	6	4	26	10cm	no	J1+	20	X(T)	0	none	10X(T)	Ortho
24	GLR	1	57	1	SOP	no	no	(+)	yes	0 ex	4	2	4	12cm	no	J1+	0 prism	none	6	RH(T)	Ortho P	6RH(T)
25	CBC	1	8	2	CI R C SOP	yes	no	(-)	*	*	8	6	12	15cm	no	J2	4	X	0	none	Ortho	Ortho
26	GLR	1	12	2	SOP	no	yes	(+)	yes	2 ex	10	8	18	12cm	no	J1+	8	X(T)	1	RH(T)	4XT	4RHT
27	MCM	1	32	2	CI	no	no	(-)	*	*	8	6	16	12cm	no	J1+	8	X(T)	0	none	4X(T)	Ortho
28	MLM	1	36	2	CI	yes	no	(-)	*	*	4	2	10	30cm	no	J1	6	X(T)	0	none	Ortho	Ortho
29	DLR	1	6	2	CI	no	no	(-)	*	*	14	12	20	12cm	no	J1+	6	X(T)	0	none	Ortho	Ortho
30	MLM	1	11	1	CI	no	no	(-)	*	*	14	12	20	8cm	no	J1+	6	X(T)	0	none	Ortho	Ortho
31	JML	1	16	1	CI	no	no	(-)	*	*	14	12	22	12cm	no	J1+	8	X	0	none	Ortho	Ortho
32	RPG	1	11	2	CI R A SOP	no	no	(-)	*	*	14	8	26	15cm	no	J1+	12	X(T)	0	none	Ortho	Ortho
33	MLM	1a	73	1	SOP	NA	yes	(+)	yes	10 ex	NA	NA	NA	NA	NA	drop	*	*	*	*	*	*
34	RPG	7	14	2	CI	no	no	(-)	*	*	4	2	29	14cm	no	J1+	25	X(T)	0	none	20X(T)	Ortho

Pt#	Inv	Loc	Age	Sex	Int. Dx	Cl	SOP	3ST	IOOA	Tor	BOB	BOR	TTL	NPC	Both	NVA	N	H#	H Dev	Near V#	V Dev	Dist H	Dist V
35	RPG	1	10	2	Cl	yes	no	(-)	*	*	2	1	12	30cm	no	J1+		10	X(T)	0	none	2X	Ortho
36	MCM	1	10	1	Cl	no	no	(-)	*	*	8	6	16	15cm	no	J1+, J1		8	X(T)	0	none	Ortho	Ortho
37	DLR	1	10	1	Cl	no	no	(-)	*	*	8	6	18	15cm	no	J1+		10	X(T)	0	none	Ortho	Ortho
38	MLM	1	44	2	Cl R CSOP	NA	no	(-)	yes	3 ex	NA	NA	NA	NA	NA	drop	*		*	*	*	*	*
39	MCM	1	16	2	Cl	yes	no	(-)	*	*	8	6	14	15cm	no	J1		6	X(T)	0	none	Ortho	Ortho
40	JML	1	10	2	Cl	no	no	(-)	*	*	14	12	20	20cm	no	J1		6	X(T)	0	none	Ortho	Ortho
41	EC	1	14	1	Cl	no	no	(-)	*	*	10	8	18	15cm	no	J1+		8	X(T)	0	none	Ortho	Ortho
42	MLM	6	26	1	Cl LASOP	NA	yes	(+)	yes	15 ex	NA	NA	NA	NA	NA	drop	*		*	*	*	*	*
43	RPG	7	11	2	Cl	no	no	(-)	*	*	8	6	16	12cm	no	J1+		8	X(T)	0	none	Ortho	Ortho
44	GLR	0	42	2	Cl LASOP	NA	yes	(+)	yes	2 ex	NA	NA	NA	NA	NA	drop	*		*	*	*	*	*
45	RPG	7	10	1	Cl	no	no	(-)	*	*	12	8	22	12cm	no	J1+, J1		10	X(T)	0	none	4X	Ortho
46	JML	7	9	1	Cl R ASOP	no	no	(-)	*	*	14	12	34	20cm	no	J1+		20	X(T)	0	none	12X(T)	Ortho
47	GLR	1	58	2	L CSOP	no	yes	(+)	yes	5 ex	12	10	20	12cm	no	J1		8	X(T)	2	RH(T)	Ortho	15RHT
48	CBC	1	9	1	Cl	no	yes	(+)	yes	2 ex	18	16	26	5cm	no	J1+		8	X(T)	20	LH(T)	6X(T)	25LH(T)
49	DLR	1	11	1	Cl	no	no	(-)	*	*	10	8	16	15cm	no	J1		6	X(T)	0	none	Ortho	Ortho
50	DLR	1	15	1	Cl LASOP	no	no	(-)	*	*	12	10	18	10cm	no	J1+		6	X(T)	0	none	Ortho	Ortho
51	DLR	1	42	2	Cl	no	yes	(+)	yes	5 ex	18	16	*	10cm	no	J1+		6	E(T)	6	LH(T)	2E(T)	2LH(T)
52	MCM	6	17	2	Cl	no	no	(-)	*	*	14	0	24	9cm	no	J1+		10	X(T)	0	none	Ortho	Ortho
	DLR	1	10	2	Cl	no	no	(-)	*	*	14	12	16	7cm	no	J2		2	X(T)	0	none	Ortho	Ortho

Pt#	Inv	Loc	Age	Sex	Int. Dx	CI	SOP	3ST	IOOA	Tor	BOB	BOR	TTL	NPC	Both	NVA	N H#	H Dev	Near V#	V Dev	Dist H	Dist V
53																						
54	DLR	1	11	1	CI R CSOP	no	no	(-)	*	*	14	10	22	20cm	no	J1	8	X(T)	0	none	Ortho	Ortho
55	MLM	1	7	1		NA	yes	(+)	yes	3 ex	NA	NA	NA	NA	NA	drop	*	*	*	*	*	*
56	JML	7	11	2	CI	no	no	(-)	*	*	12	10	20	12cm	no	J1+	8	X(T)	0	none	Ortho	Ortho
57	MLM	1	16	1	CI	no	no	(-)	*	*	12	10	20	15cm	no	J1+	8	X(T)	0	none	Ortho	Ortho
58	DLR	1	11	1	CI L CSOP	no	no	(-)	*	*	14	10	22	15cm	no	J1	8	X(T)	0	none	Ortho	Ortho
59	MLM	1	43	2		no	yes	(+)	yes	3 ex	6	4	6	40cm	no	J1	0	none	20	LH(T)	Ortho	15LH(T)
60	DLR	1	15	1	CI	no	no	(-)	*	*	12	10	18	10cm	no	J1+	6	X(T)	0	none	Ortho	Ortho
61	DLR	1	6	1	CI	no	no	(-)	*	*	14	12	24	9cm	no	J1+	10	X(T)	0	none	2X	Ortho
62	DLB	7	14	2	CI L ASOP	yes	no	(-)	*	*	6	2	12	20cm	no	J2	6	X(T)	0	none	Ortho	Ortho
63	GLR	1	6	2	L CSOP	no	yes	(+)	yes	3 ex	10	8	22	11cm	no	J1+	12 prism	X(T)	0	none	15XTP	6LHT
64	GLR	1	78	2		NA	yes	(+)	yes	3 ex	NA	NA	NA	25cm	NA	J1	8 prism	X(T)	0	none	2X(T)P	2LH(T)
65	GLR	1	9	2	CI L CSOP	yes	no	(-)	*	*	12	10	14	6cm	no	J1+	2	X	0	none	Ortho	Ortho
66	GLR	1	9	2	R ASOP	no	no	(+)	yes	NAP	16	12	*	15cm	no	J1+	2	E(T)	8	LH(T)	Ortho	2LH(T)
67	CBC	1	42	2	R ASOP	no	yes	(+)	yes	2 ex	14	12	*	18cm	no	J1	4 prism	E(T)	2	RH(T)	4E(T)P	2RH(T)
68	GLR	1	25	1		NA	yes	(+)	yes	2 ex	*	*	*	*	NA	drop	*	*	*	*	*	*