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Research Article

Clinical Contrast Sensitivity Function in Patients with Infantile Nystagmus Syndrome Before and After Eye Muscle Surgery

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Abstract

Purpose: To test the hypothesis that eye muscle surgery in patients with infantile nystagmus syndrome improves contrast sensitivity function.

Methods: This is a prospective, interventional case series analysis of clinical data before and after eye muscle surgery in 113 patients who had no previous surgical treatment. Outcome measures included: 1) Routine demography and clinical characteristics, 2) Binocular best-corrected visual acuity in the null position and 3) Contrast sensitivity function. All patients data was collected for this study immediately pre-surgery and 2 to 6 months after surgery. Parametric and non-parametric statistical analysis of outcome measure data collected for this study were performed using standard software on grouped data using computerized software.

Results: Age ranged from 4-43 years (average 14 years), in which 63% were male. After surgery Follow-up the patient with an average of 13.1 months, although the study data was collected as described above, 61% had associated afferent visual system disease, 71% had significant refractive error, 71% had strabismus, 62% had an associated anomalous head posture and 21% had associated (a) periodicity Cumulative data from 113 patients and separate data from patients with either best binocular visual acuity < 20/80 or > 20/100 showed significant improved CS across all spatial frequencies tested.

Conclusion: Infantile nystagmus patients have deficient constrast sensitivity which may proved a measure of visual system dysfunction.This report supports the hypothesis that contrast sensitivity improves after eye muscle surgery in patients with infantile nystagmus and may be a useful outcome measure for future interventional clinical trials.

Keywords: Contrast sensitivity; Eye muscle surgery; Nystagmus

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Introduction

Infantile Nystagmus Syndrome (INS) is an ocular motor disorder of unknown etiology that presents in early infancy. Nystagmus has been classified in many ways, resulting in some confusion and disagreement among clinicians and scientists. The National Eye Institute sponsored workshop, Classification of Eye Movement Abnormalities and Strabismus (CEMAS), has attempted to resolve some of the confusion with a publication that defines the various types of nystagmus [1]. The published definition of INS by the CEMAS working group is used in this study [1]. The major clinical characteristics of INS with variable association include: Increased intensity with fixation, decreased intensity with sleep, variable intensity due to eye position in orbit or gaze (eccentric null position), changing direction in different positions of gaze (neutral positions), decreased intensity with convergence (damping), changing direction and/or intensity with monocular occlusion ("latent component"), anomalous head posturing, strabismus and dissociated horizontal and vertical deviations [1].

In addition to the above characteristics from 17% to 33% of patients with INS will have an inherent, rhythmic, periodic or (a) periodically changing nystagmus intensity and/or direction over time [2,3]. Most clinicians are familiar with this oscillation as acquired Periodic Alternating Nystagmus (PAN). Acquired PAN has a specific pattern identified by the presence of spontaneous nystagmus in the primary position, which beats horizontally in one direction for 1 or 2 minutes, followed by a quiet period, and then reappearance of the nystagmus in the opposite direction for a similar length of time. Infantile Aperiodic Alternating Nystagmus (IAPAN) has all the characteristics of INS except that the nystagmus direction and/or intensity changes in an irregular pattern over time. IAPAN also has the clinical characteristics of a dynamic, anomalous head posture and dynamically changing visual functions both over time and as a function of gaze [2,4].

Two broad areas of visual system treatment in infants and children with nystagmus and include treating their ametropia and ocular motor dysfunctions [5,6]. Common standard visual system treatment includes correction of refractive errors with spectacles, treatment of amblyopia, eye muscle surgery for strabismus, low vision devices, and sunglasses. Although treatment of refractive error is standard of care, the use of devices such as specialized contact lenses is often not included. Likewise, treatment of strabismus and amblyopia is common, but associated treatment of nystagmus and its consequences are rare.

Previous studies have shown that results for letter acuity, vernier acuity and contrast sensitivity in some, but not all, subjects with INS is poorer than in normal observers under conditions of comparable retinal image motion [7-10]. This implies that contrast sensitivity

may not be limited by the motion of the retinal image in some subjects with infantile nystagmus syndrome. There is psychophysical evidence that retinal motion may contribute to vision loss via an amblyopic component in patients with INS separate from ammetropic and strabismic components [10]. High spatial frequency vision, i.e., Snellen acuity, may not be the best subjective measure of visual function in patients with disorders of the ocular motor system such as INS. Other subjective measures such as Contrast Sensitivity (CS), motion detection, gaze dependent visual acuity, visual reaction time, stereopsis, eye-hand and visual-vestibular coordination may more accurately represent measures that was affected by ocular motor disease and thus can be used as outcome variables in interventional clinical trials. This report details the outcome on contrast sensitivity after eye muscle surgery in the treatment of patients with INS after baseline spectacle correction.

Methods

All testing, data collection, analysis and reporting were approved by the Institutional Review Board of Akron Children's Hospital, Akron, OH, USA and The Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, USA and Nationwide Children's Hospital, Columbus, Ohio. All procedures observed the declaration of Helsinki and informed consent/assent was obtained from all patients/parents. Inclusion criteria included; INS (diagnosed by clinical evaluation and eye movement recordings), no prior treatment other than spectacles and not taking any medications known to affect the ocular motor system. Exclusion criteria included those patients with syndromic INS or patients in whom there were incomplete data or follow up less than 12 months.

The first step was to prescribe spectacle optical correction. Many patients presented either for the first time or for another treatment opinion who were not already in spectacles. The spectacles prescribed fully corrected myopia ≥ 0.75 diopters, astigmatism ≥ 1.50 diopters and anisometropia ≥ 1.00 diopters and either fully corrected or symmetrically under-corrected (by up to 1.50 D) hyperopia of ≥ +3.50 D (spherical equivalent). Spectacle-corrected distance visual acuity was measured at 3 meters in the patient's habitual head position using the Amblyopia Treatment Study (ATS) HOTV protocol for patients ≤ 7 years and the ATS ETDRS protocol for patients > 7 years of age at least every 4 (± 1) weeks after spectacle wear until acuity remained at within 1 line from the prior visit [11]. This testing was accomplished in the patient's eccentric null position if they did not have IAPAN and in primary position during the patient's time of least intense nystagmus if they had IAPAN using the acuity testing protocols mentioned above [12-20]. The visit at which visual acuity remained stable became the baseline for all further measurements. All subsequent measures of visual acuity described below were obtained using the age-appropriate ATS protocol [11-20].

The goals of eye muscle surgery were to; simultaneously treat combinations of the patient's strabismus, anomalous head posture and nystagmus with one operation. Standard methods of preoperative evaluation, anesthesia and fornix based eye muscle surgery were employed in the surgical treatment of all patients. The exact surgical procedure for each patient was based on the surgeon's clinical experience and published reports detailing those used in the treatment of strabismus, anomalous head posture and nystagmus. The surgical procedures are outlined in table 1.

Operation type (113 patients)	# (%)
Operation 1 - Horizontal head posture alone *Horizontal rectus recess and resect or recess and renotomy + Reattach*	25 (22)
Operation 2 - Chin down head posture (+/- Strabismus) Superior rectus recess 5.0 mm + Inferior oblique myectomy	22 (20)
Operation 3 - Strabismus alone Primary position deviation using at least two recti each eye	15 (13)
Operation 4 - Horizontal head posture + Strabismus Fixing eye straightens head + Non-fixing eye straightens eyes	14 (12)
Operation 5 - Chin up head posture (+/- Strabismus) Inferior rectus recess 5.0 mm + Superior oblique tenectomy 5.0 mm	8 (7)
Operation 6 - No head posture, strabismus or vergence bamping Horizontal rectus tenotomy + Reattach	8 (7)
Operation 7 - Multiplanar head posture (+/- Strabismus) Transposition of recti + Combinations of oblique or recti recess	8 (7)
Operation 8 - Vergence damping alone (Artificial divergence) Medical rectus recess 3.0 mm + Lateral rectus tenotomy + Reattach	7 (6)
Operation 9 - Torsional head posture alone Horizontal transposition of vertical recti 1 tendon width	6 (5)

Table 1: Percentage of patients who had each one of operations 1-9.

These 9 operations describe a methodological approach to eye muscle surgery on patients with infantile nystagmus syndrome and are based on multiple previous publications. # - Number of patients; (%) - Percentage of patients; mm - Millimeters; reattach - Reattachment of muscle at original insertion with no recession or resection

Outcome variables

Measures prospectively analyzed for this study was done immediately pre-surgery and 2 to 6 months after surgery and included: 1) Routine demography and clinical characteristics, 2) Binocular best-corrected visual acuity in the null position (BVA) and 3) Contrast Sensitivity Function (CS). Standard clinical monitoring of surgical complications and side effects were performed. While all clinical measures were obtained after each treatment modality, the reported baseline measures were being those measured immediately after adaptation to spectacle treatment and immediately prior to surgery. Post-treatment measures were obtained ≥ 2 to ≤6 months after the patient's surgery.

Clinical and ocular motor evaluation

Demographic and clinical data reported in this series includes: Age, sex, AHP, ocular alignment, presence of IAPAN and refractive error. Ocular motor examination included a determination of heterophoria/tropia at distance (> 3 m) and near (33 cm) in all diagnostic positions of gaze. Cycloplegic refraction, tonometry, and examination of the anterior and posterior segments were performed on all patients. Clinical evaluation of the ocular motor oscillations included changes in the oscillation in primary position, at near, in all nine diagnostic positions of gaze, under monocular and binocular conditions and over time (~5 minutes) (Table 2).

Visual acuity testing at the null position

Best visual acuity was measured by a technician trained to perform the ATS visual acuity protocols and they were also masked to treatment status [11]. Visual Acuity (VA) testing was performed with the patient's full optical correction in place using the electronic ATS protocol

PT#	Age	STRAB	(A)PAN	EYE DX	Refractive Error
1	43.1	XT-HT	No	Amblyopia	(+3.00 +2.50 x 90 OU)
2	17	None	No	None	(+4.00+0.75 x 75OD, x 100 OS)
3	6	ET	Yes	Amblyopia	(+3.00 +4.50 x 90 OU)
4	8.1	ET	No	OCA	(+0.50 +3.75 x 90 OU)
5	6.7	None	No	None	(+2.00 +4.00 x 120 OD and x 60 OS)
6	8.5	ET	No	DVM	(+2.00 OD, +2.75 OS)
7	7.5	ET	No	OCA	(+2.25 +2.75 x 90 OU)
8	16.6	ET	No	RD	(+2.00 +2.00 x 45 OD, x 135 OS)
9	42.3	None	No	None	(+75 +1.75 x 90 OU)
10	25.1	ET	No	OCA	(-3.00 +1.50 x 90 OU)
11	41.2	None	No	None	(+3.00+3.50 x 90 OD, +2.00+2.75 x 90 OS)
12	11.2	ET	No	OCA	(+3.00 OU)
13	17	ET	No	None	(+3.00 +4.50 x 90 OU)
14	12.1	None	No	None	(+1.50 +2.50 x 90 OU)
15	59.2	XT	No	RD	(-4.00 +2.50 x 150 OD, -4.00 +1.25 x 65 OS)
16	27.4	None	No	None	(-5.00 +.75 x 90 OD)
17	34.7	None	No	None	(-4.00 +0.75 x 180 OD, -4.75 +1.00 x 180 OS)
18	31.5	XT	Yes	None	(PL +4.50 x 90 OD, PL +5.00 x 90 OS)
19	38	ET	No	Amblyopia	(-1.00 +4.50 x 45, -0.75 +3.00 x 135 OS)
20	42.7	None	No	None	(-1.00 +2.00 x 90 OU)
21	31	ET	Yes	OCA	(+3.00 +6.50 x 45 OD, x 135 OS)
22	6.5	ET	No	None	(PL +5.50 x90 OU)
23	27.2	None	No	OCA	(-5.00 + 1.00 x 135 OD, x 45 OS)
24	3.1	ET	Yes	None	(+2.50 +4.50 x 125 OD, x 60 OS)
25	16.8	None	No	None	(-7.50 +2.25 x 90 OU)
26	38.6	ET	Yes	RD	(+1.00 +3.75 x 60 OD, x 120 OS)
27	7.2	None	No	None	(+4.50 +1.25 x 90 OD, x 135 OS)
28	18	ET	No	FOV HYP	(+3.00 +3.00 x 90 OD, +3.75 +4.00 x 135 OS)
29	4.3	XT	No	None	(-4.75 OU)
30	10.2	None	Yes	RD	(-7.50 +1.00 x 90 OU)
31	4.1	None	No	None	(+5.75 OD, +5.00 OS)
32	13	XT	No	OCA	(-8.50 +2.50 x 90 OU)
33	5.7	XT	No	Amblyopia	(-3.50 +4.50 x 110 OD, x 70 OS)
34	33	None	No	None	(+1.25 +4.25 x 90 OU)
35	4.5	ET	No	None	(-2.00 +4.00 x 45 OD, -2.25 +3.25 x 110 OS)
36	13	ET	No	None	(+2.25 OU)
37	15	ET	Yes	Aphakia	(+11.50 +4.00 x 90 OD, x 120 OS)
38	6	ET	No	OCA	(-5.00 +3.50 x120 OD, -4.00 +4.00 x 60 OS)
39	17	None	No	None	(+2.75 OU)
40	4	ET-HT	Yes	Amblyopia	(-0.50 +1.75 x 175 OD, x 10 OS)
41	5	None	No	None	(-0.75 +2.50 x 140 OD, -1.00 +3.00 x100 OS)
42	11	ET	Yes	FOVE HYO	(+5.50 +2.00 x 90 OD, +5.75 +2.00 x 10 OS)
43	8.5	None	No	OCA	(+2.00 +1.00 x 90 OU)
44	15	ET	No	OCA	(-5.00 +4.00 x 135 OD, x 85 OS)
45	10	None	No	CVI	(-3.00 +0.75 x 85 OD, -4.50 +1.00 x 100 OS)
46	6.5	ET	No	None	(+2.00+2.50 x 90 OU)
47	7	ET	Yes	Amblyopia	(+.75 +2.75 x 90 OU)
48	9.5	ET	No	None	(+4.00 +1.00 x 90 OD, +3.00 +0.50 x 90 OS)
49	5	ET-HT	No	OCA	(-4.00 +3.00 x 90 OU)
50	8.3	None	Yes	DVM,CVI	(-0.75 +.75 x 160 OD, x 20 OS)
51	12.5	None	No	None	(-0.50 +2.50 x 90 OU)
52	8.5	ET	Yes	RD	(+6.50 OD, +1.75 +1.75 x 140 OS)
53	8.5	XT-HT	No	FOV HYP	(+6.25 +1.25 x 90 OD, x 100 OS)
54	8.5	ET	No	OCA	(-2.00 +4.50 x 45 OD, x 135 OS)

55	3.5	None	Yes	None	(-2.50 +2.50 x 90 OD, PL +1.00 x 90 OS)
56	5.4	ET	No	None	(-1.25 +2.75 x 45 OD, -2.50 +1.00 x 135 OS)
57	30.4	ET	No	OCA	(+6.00 +1.75 x 105 OD, +5.75+1.75 x 90 OS)
58	7	None	No	None	(-5.50 +1.75 80 OD, -4.75 +1.00 x 180 OS)
59	4	XT	Yes	ONH	(-5.00 +2.00 x90 OU)
60	3.4	None	No	OCA	(+2.50 +4.50 x 90 OU)
61	57	None	No	None	(+1.00 +4.00 x 45 OD, x 135 OS)
62	4.5	None	No	ONH	(-5.00 +2.00 x 80 OD, -8.00 +3.00 x 75 OS)
63	47	ET	Yes	Aphakia	(+14.50 +2.75 x120 OD, +15.25 +3.25 x60 OD)
64	35	ET	No	RD	(-3.25 +2.50 x 115 OD, -4.50 +1.75 x 110 OS)
65	16	None	No	OCA	(+4.50, OD +3.25 OS)
66	8.5	ET	No	FOV HYP	(-4.00 +3.50 x 80 OD, -4.00 +4.00 x 90 OS)
67	14	ET	Yes	Amblyopia	(+6.75 +2.25 x 90 OU)
68	44	None	No	OCA	(-3.00 +1.00 x 185 OD, -3.50 +1.50 x 170 OS)
69	4	None	No	None	(-4.25 +3.25 x 60 OD, +2.75 +3.50 x 120 OS)
70	8	XT-HT	No	RD	(-2.50 +5.75 x 15 OD, -1.50 +6.00 x 125 OS)
71	42	XT	No	Amblyopia	(-3.00 +3.25 x 45 OD, -3.50 +2.75 x 135 OS)
72	6.6	XT	No	Amblyopia	(-1.00 +2.25 x 115 OD, -,25 +4.25 x 90 OS)
73	35	ET	Yes	OCA	(-4.00 +3.00 x 120 OD, -2.50 +3.25 x 60 OS)
74	23	None	No	None	(-3.75 +4.00 x 90 OD, -3.25 +4.00 x 90 OS)
75	7.1	ET	Yes	DVM,CVI	(+3.50 +4.75 x 70 OD, +3.75 +5.00 x 110 OS)
76	33.5	ET-HT	No	None	(-12.00 +3.00 x 60OD, -16.00 +4.25 x 120 OS)
77	11	ET	Yes	Amblyopia	(+6.50 +2.00 x 90 OD, +5.75 +1.75 x 90 OS)
78	8	ET	No	OCA	(-8.50 +4.25 x 115 OD, -7.75 +3.50 x 110 OS)
79	4.5	None	No	OCA	(-4.00 +0.75 x 180 OD, -4.75 +1.00 x 180 OS)
80	7	ET	No	Amblyopia	(+0.75 +2.75 x 90 OU)
81	9.5	ET	Yes	OCA	(+4.00 +1.00 x 90 OD, +3.00 +.50 x 90 OS)
82	5	ET	No	None	(-4.00 +3.00 x 90 OU)
83	8.3	None	No	CVI. DVM	(-0.75 +0.75 x 160 OD, x 20 OS)
84	12.5	None	No	OCA	(-0.50 +2.50 x 90 OU)
85	8.5	ET	Yes	FOV HYP	(+6.50 OD, +1.75 +1.75 x 140 OS)
86	8.5	XT-HT	No	OCA	(+6.25 +1.25 x 90 OD, x 100 OS)
87	3.6	XT	No	RD	(+3.50 +4.75 x 70OD,+3.75 +5.00 x110 OS)
88	5.8	XT	No	None	(-3.00 +2.00 x 90 OU)
89	26	ET	No	Amblyopia	(PL +3.50 x 90 OD, +1.75 +3.00 x 90 OS)
90	13	ET	No	None	(+5.25 +1.25 x 90 OU)
91	11	ET-HT	No	OCA	(-6.50 +1.00 x 45 OD, x 135 OS)
92	6.3	XT-HT	No	FOV HYP	(+2.00 +4.00 x 90 OU)
93	6.3	XT-HT	Yes	FOV HYP	(+2.00 +4.00 x 90 OU)
94	7	None	No	OCA	(+0.75 +2.75 x 90 OU)
95	9.5	ET	No	Amblyopia	(+4.00 +1.00 x 90 OD, +3.00 +.50 x 90 OS)
96	5	None	No	OCA	(-4.00 +3.00 x 90 OU)
97	8.3	ET	Yes	ONH	(-0.75 +.75 x 160 OD, x 20 OS)
98	12.5	None	No	None	(-0.50 +2.50 x 90 OU)
99	8.5	None	Yes	None	(+6.50 OD, +1.75 +1.75 x 140 OS)
100	8.5	XT-HT	No	RD	(+6.25 +1.25 x 90 OD, x 100 OS)
101	31.5	XT	No	OCA	(PL +4.50 x 90 OD, PL +5.00 x 90 OS)
102	38	ET	No	Amlbyopia	(-1.00 +4.50 x 45, -0.75 +3.00 x 135 OS)
103	42.7	XT	No	OCA	(-1.00 +2.00 x 90 OU)
104	31	ET	Yes	ONH	(+3.00 +6.50 x 45 OD, x 135 OS)
105	6.5	ET	No	OCA	(PL +5.50 x 90 OU)
106	27.2	None	No	None	(-5.00 + 1.00 x 135 OD, x 45 OS)
107	3.1	ET	No	ONH	(+2.50 +4.50 x 125 OD, x 60 OS)
108	16.8	None	No	OCA	(-7.50 +2.25 x 90 OU)
109	8.6	ET	No	Aphakia	(+18.00 +3.75 x 60 OD, x 120 OS)

110	7.2	ET	No	OCA	(+4.50 +1.25 x 90 OD, x 135 OS)
111	18	ET	No	None	(+3.00 +3.00 x 90OD, +3.75 +4.00 x135OS)
112	18	None	No	OCA	(+3.00 +3.00 x 90OD,+3.75+4.00x 135 OS)
113	3.3	XT	No	None	(-4.75 OU)

Table 2: Clinical characteristics of 113 patients with INS.

Clinical characteristics of 113 patients with INS. PT - Patient age (in years); STRAB - Strabismus; (A) PAN - (a) Periodic Alternating infantile Nystagmus; EYE DX - Eye Diagnosis; XT - Exotropia; ET - Esotropia; HT - Hypertropia; OCA - Oculocutaneous Albinism; DVM - Delayed Visual Development; RF - Retinal Dystrophy; FOV HYP - Foveal Hypoplasia; CVI - Cortical Vision Impairment; ONH - Optic Nerve Hypoplasia; OD - Right eye; OS - Left eye; OU - Both eyes

[21]. Measurements of Best Visual Acuity (BVA) were obtained both binocularly and monocularly in the patient's habitual head position (using either their static null position or during the patient's least nystagmus intensity if diagnosed clinically or using eye movement recordings with IAPAN) [12-21].

Eye movement recordings

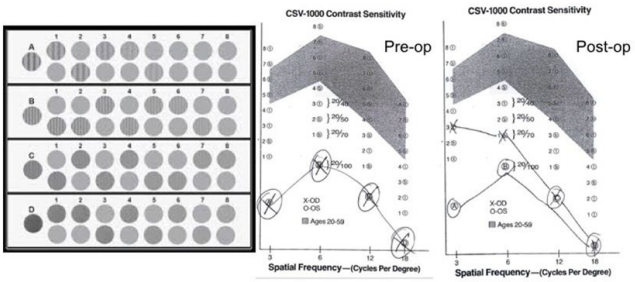
All patients had eye movement recordings using the Eyelink^{R} remote video eye movement system (Eyelink^{R}, SR Research Ltd., Mississauga, Ontario, Canada) with a data-sampling rate of 500-1000 Hz. The presentation of stimuli and the acquisition, display and storage of data were controlled by a series of computers using standard Microsoft^{R} and Matlab^{R} software. The types of waveforms present were classified according the previously described waveforms associated with INS.

Contrast Sensitivity testing (CS)

CS was measured using the CSV-1000E^{R} sine wave grating test face (Vector Vision^{R}) with the patient seated 2.5 meters from the chart (Figure 1). This test provides for four rows of sine wave gratings. At the recommended test distance, these gratings test spatial frequencies of 3, 6, 12 and 18 cycles/degree (cpd). Testing at all spatial frequencies was administered under monocular and binocular conditions after the patient had adapted to room luminance (85.0 candelas/meter^{2}) for 5 minutes. The patient's refractive correction was in place while allowing use of any anomalous head posture necessary to position their gaze in their null zone. CS values were documented in Log Units (LU). Sensitivity levels at each frequency ranged from 0.70 to 2.08 LU for 3 cpd, 0.91 to 2.29 LU for 6 cpd, 0.61 to 1.99 LU for 12 cpd and 0.17 to 1.55 LU for 18 cpd. The console of the contrast sensitivity-measuring unit provides internal fluorescent luminance calibrated to 85 cd/m^{2} for 0.1-log unit instrument light level. The luminance levels were measured with a luminance meter. While reading across the row, the patient was asked to indicate whether the gratings were visible on the top row or the bottom row at each frequency. If the grating was not visible in either patch, the patient's response was recorded as "both blank". The results of the patient's first attempt were considered a trial and the values recorded at the second attempt were used as the CS measurement. The contrast level of the last correct response was taken as the CS threshold.

Statistical analyses

A Wilcoxon signed-rank test was used to analyze BVA pre-operatively to post-operatively. A Friedman test was used to test CS pre-operatively to post-operatively with the Bonferroni method used prior for pair wise comparison. The impact of BVA on CS pre-operatively to post-operatively was tested in three groups, (the entire cohort of 113 patients, those with BVA



	S	1	2	3	4	5	6	7	8
Row (CPD)									
A (3.0)	.70	1	1.17	1.34	1.49	1.63	1.78	1.93	2.08
B (6.0)	.91	1.21	1.38	1.55	1.70	1.84	1.99	2.14	2.29
C (12.0)	.61	.91	1.08	1.25	1.40	1.54	1.69	1.84	1.99
D (18.0)	.17	.47	.64	.81	.96	1.10	1.25	1.4	1.55

Figure 1: Measurement of contrast sensitivity using the CSV 1000^{R}.

Fundus photographs shows retinal hemorrhages, dilatation with tortuosity. A photograph of the CSV 1000 light box with stimuli is shown on the upper left. Either the patient is asked to identify, for each of the gratings 1-8, the location of the stripes, top, bottom or both gratings are blank. As an example, the plot of patient # 51's contrast sensitivity curve before and after treatment is shown on the right with marks for each stimulus checked and a line connecting the results, creating the contrast sensitivity curve. The table below shows the log units of each of the eight stimuli at the four spatial frequencies presented in rows A through D.

≥ 20/80; logMar 0.60 and those with BVA ≤ 20/100; logMar 0.70) using repeated measures of P value of the Friedman test. Separate analysis in two additional acuity groups were accomplished to test for the possibility of a "celling-floor" effect in improvement, e.g., lower acuity patients have more potential for improvement than those patients with better acuity. The absolute change in CS against BVA preoperatively to post-operatively was accomplished using the Spearman correlation coefficient (r). All analyses were conducted using GB-STAT version 10 (Dynamic Microsystems, Inc^{R}, 2004).

Results

From 2006-14, 113 patients were recruited and are the subjects of this study. They ranged in age from 4-43 years (average 14 years), 63% were male. Follow-up, after surgery, ranged from 9-48 mos (average 13.1 mos), 61% had associated afferent visual system disease (22% with visual pathway, optic nerve or retinal disease, 43% with amblyopia and 27% with albinism), 71% had significant refractive error, 71% had strabismus, 62% had an associated anomalous head posture and 21% had associated (a) periodicity (Table 2).

Surgical procedure

The method used to approach surgery on the extra ocular muscles of both eyes is represented in table 2. 22% had operation 1, 20 % had operation 2, 13% had operation 3, 12% had operation

4, 7% had operation 5, 7% had operation 6, 7% had operation 7, 6% had operation 8 and 5% had operation 9. The goals of surgery were to treat combinations of the patient's strabismus, anomalous head posture and nystagmus. No patients with fusion prior to surgery lost fusion after surgery. 15 patients (13%) had another operation for re-current strabismus or treatment of a new or recurrent head posture. Of these 15 patients, 12 were re-operated on within the first year and 3 more than one year after the initial procedure. There were no serious surgical complications.

Visual acuity

Visual acuity outcome data reported in this study included baseline and ≥ 2 and ≤ 6 months after surgery. We used 2-6 months post-surgery data to allow for complete healing from surgery and to avoid natural age related changes in the younger age group due to visual system maturation. The average group mean BVA improved significantly ($p<0.05$) after treatment (baseline BVA = 0.68, post-treatment BVA log Mar 0.45) (Figure 2). Five percent of patients had no change in BVA while 18%, had an increase of 0.1 logMar, 30% an increase of 0.2 logMar and 47% an increase of 0.3 logMar. 89% of patients had a final BVA of better than or equal to 0.70 logMar, making them eligible for a restricted driver's license in most US States. Although group means showed improvement in visual acuity, individual patient acuity may have varied +/- 0.1 logMar based on chance alone. This is inherent in the testing methodology and age of the patients involved in this report and the reason we chose to perform group mean analysis.

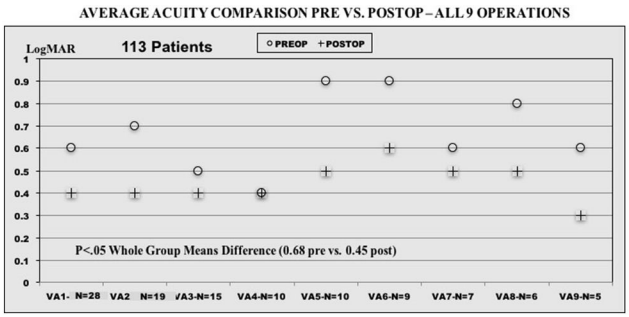


Figure 2: Visual acuity at baseline and after treatment.

This figure shows a comparison plot of group mean best corrected binocular logMar acuity at pre-op and post-op based on the 9 operation subtypes. There was a significant difference for the entire 113 patients. ($p < 0.05$ group means 0.68 logMar baseline vs 0.45 logMar post-treatment) VA# - Visual Acuity operation number, N - Number of patients having operation #. Standard deviations for all operations were within +/- 0.15 logMar.

Contrast Sensitivity (CS)

Tables 3-5 shows changes in CS at all cycles per degree (cpd) stimuli for baseline and post-surgery. CS was statistically significantly better at all cpd stimuli after treatment cumulatively and also when analyzed as a function of better (> 20/80; logMar 0.60) or worse (< 20/100; logMar 0.70) BVA (p=0.001).

Discussion

Visual function in patients with INS is affected by unpredictable combinations of ocular motor (eccentric null zones, damping with convergence, monocular intensity changes, periodicity, strabismus, poor smooth pursuit, OKN and attentional changes) and sensory system defects (ammetropia, amblyopia, photosensitivity, loss of contrast sensitivity, poor motion perception, decreased temporal luminance, impaired contour interaction, light interference and pre-chiasmal, chiasmal, post-chiasmal and maldevelopment) [22-27]. Visual functions directly affected include high spatial acuity vision, contrast sensitivity, motion detection, visual recognition time, gaze and time dependent vision, depth, stereopsis, smooth pursuit, vestibular and proprioceptive functions [23,28-32]. Tests of these visual based functions are usually not part of routine eye evaluations and are more commonly used in research settings but may be important measures of visual function outside the office. It may be that some of all of these visual functions contribute to the subjective improvement in visual "well-being" described by these patients and their families after treatment.

Frequency/ Exam	Mean +/- SD	Median	Minimum	Maximum	P value <
Postop	1.53 + 0.38	1.24	0.7	1.95	
6 cpd					0.003
Preop	0.87 + 0.56	0.68	0.68	1.77	
Postop	1.66 + 0.29	1.44	1.01	2.11	
12 cpd					0.01
Preop	0.62 + .026	0.33	0.23	1.01	
Postop	0.96 + 0.24	0.87	0.88	1.47	
18 cpd					0.01
Preop	0.23 + 0.22	0.11	0.11	0.91	
Postop	0.92 + 0.27	0.89	0.89	1.55	

Table 3: 113 Cumulative data CS pre and post-operatively.

*= cycles/degree > = Friedman test

This table summarized the group mean response to CS testing with the CSV 1000R chart at each of the four testing stimuli for the entire cohort. There were significant group mean improvements in all four spatial frequency targets after treatment. Frequency - Cycles/degree test pattern, Exam - Baseline or final, +/- SD - Standard deviation, cpd*- Cycles per degree. CS values were documented in Log Units (LU). Sensitivity levels at each frequency ranged from 0.70 to 2.08 LU for 3 cpd, 0.91 to 2.29 LU for 6 cpd, 0.61 to 1.99 LU for 12 cpd and 0.17 to 1.55 LU for 18 cpd.

Frequency/Exam	Mean +/- SD	Minimum	Maximum	P Value <
3 cpd*				0.001
Preop	0.82 + .50	0.4	1.55	
Postop	1.66 + .65	0.98	1.95	
6 cpd				0.001
Preop	0.99 + 0.47	0.68	1.84	
Postop	1.77+ 0.48	1.31	2.18	
12 cpd				0.002
Preop	0.70 + 0.39	0.3	1.31	
Postop	1.16 + 0.24	0.91	1.71	
18 cpd				0.01
Preop	0.19 + 0.22	0.13	0.21	
Postop	0.68 + 0.27	0.61	1.31	

Table 4: 69 Patients acuity ≥ 20/80 (logMar 0.60) CS pre and post-operatively.

* - cycles/degree > - Friedman test

This table summarized the group mean response to CS testing with the CSV 1000R chart at each of the four testing stimuli of those 69 patients with acuity ≥ 20/80 (LogMar 0.60). There were significant group mean improvements in all four spatial frequency targets after treatment. Frequency - cycles/degree test pattern, Exam - Baseline or final, +/- SD - Standard deviation, cpd* - Cycles per degree. CS values were documented in log units (LU). Sensitivity levels at each frequency ranged from 0.70 to 2.08 LU for 3 cpd, 0.91 to 2.29 LU for 6cpd, 0.61 to 1.99 LU for 12 cpd and 0.17 to 1.55 LU for 18 cpd.

Frequency/Exam	Mean +/- SD	Minimum	Maximum	P Value >
3 cpd*				0.001
Preop	0.53 + 0.21	0.4	1.01	
Postop	1.46 + 0.43	0.68	1.95	
6 cpd				0.001
Preop	0.71 + 0.27	0.6	1.22	
Postop	1.59 + 0.33	1.11	1.88	
12 cpd				0.002
Preop	0.78 + 0.39	0.3	0.91	
Postop	1.01 + 0.24	0.87	1.61	
18 cpd				0.01
Preop	0.13 + 0.08	0.09	0.2	
Postop	0.98 + 0.29	0.41	1.33	

Table 5: 44 Patients acuity < 20/100 (logMar 0.70) CS pre and post-operatively.

*- cycles/degree > - Friedman test

This table summarized the group mean response to CS testing with the CSV 1000R chart at each of the four testing stimuli of those 69 patients with acuity < 20/100 (Log Mar 0.70). There were significant group mean improvements in all four spatial frequency targets after treatment. Frequency - Cycles/degree test pattern, Exam - Baseline or final, +/- SD - Standard deviation, cpd* - Cycles per degree. CS values were documented in Log Units (LU). Sensitivity levels at each frequency ranged from 0.70 to 2.08 LU for 3 cpd, 0.91 to 2.29 LU for 6 cpd, 0.61 to 1.99 LU for 12 cpd and 0.17 to 1.55 LU for 18 cpd.

Traditional visual system treatment of patients with INS includes spectacles, routine amblyopia and strabismus management. In the classroom, preferential seating, lighting, computer assisted devices and handouts of board written content are helpful aids.

There is no cure for many of the visual sensory system deficits that are associated with INS. Treatment directed specifically at the nystagmus would have as its goal to increase the quality and quantity of foveation periods, thereby, increasing the potential for more time and gaze angles during which best visual function could take place [25,33]. There is a large body of data supporting the hypothesis that foveation periods occurring during each beat of nystagmus can be lengthened or increased by therapeutic interventions (i.e., medicines, surgery, contact lenses, etc.) [12-20]. Quantitating these foveation periods is accomplished with accurate, calibrated, eye movement recordings using various foveation programs. The improvement in INS applies both to patients with and without associated sensory-system defects. Ocular motor and visual system benefits have been shown to be consistently observed in patients who undergo eye muscle surgery for INS, even if the purpose was to decrease torticollis or improve strabismus [12-20].

Several reports suggest it is clinically reasonable to measure CS to assess visual system disability in patients with multisystem vision disease [21,34-37]. Anatomical and electrophysiological anomalies found in human albinos are reflected by reduced contrast sensitivity. Testing of CS in patients with INS has repeatedly shown it to be abnormal [21,34-37]. High astigmatic errors, nystagmus and other retinal/neural anomalies may result in abnormal meridional differences in sensitivity. Previous reports have also shown an increase in peak CS in INS patients while using telescopes and other low vision aids. The data from this report supports deficient CS in INS patients and the potential for subsequent improvement after visual system treatment.

The approach outlined in table 1 to eye muscle surgery in INS1 patients was developed as a result of a need to improve multiple preoperative ocular motor and/or visual system abnormalities in the patient population with INS [14,17,18]. This 9-operation system allows the clinician to maximize surgical intervention by performing one procedure to address all possible indications, e.g., eye position, head/face position and nystagmus characteristics. This surgical algorithm is based on standard eye muscle surgical techniques and is easily applicable in most clinical situations. The data from this study add to others that have shown that INS patient's strabismus and anomalous head posture can be improved after eye muscle surgery in the same way as other populations of patients with strabismus.

Study Limitations

There are several limitations of this case series. This is not a randomized clinical trial comparing an isolated intervention to a known treatment or placebo. There are no randomized clinical trials evaluating surgical treatments of INS thus clear evidenced based guidelines including indications and risks of treating visual system anomalies associated with INS are based on historical face validity and case/cohort series such as this one. Although all patients had INS, we included patients of all ages, varied baseline visual systems and associated eye diseases. There can be, in children, an age and repeated performance related improvement in clinical testing. In order to minimize these effect two things were included in the study protocol; 1) Outcome measure testing was obtained within 6 months of surgery limiting an age related effect and 2) Specific acuity and contrast sensitivity protocols have been demonstrated to have good test re-test reliability.

Although the patients reported here consist one of the largest prospective treatment cohorts of INS patients, this remains level 2-3 evidence at best. The data reported in this study showed significant improvements in BVA and CS from baseline to post surgery, suggesting that these measures of visual function can be improved in patients with INS after surgical treatment. Although group means showed improvement in visual acuity, individual patient acuity may have varied +/- 0.1 logMar based on chance alone. This is inherent in the testing methodology and age of the patients involved in this report and the reason we chose to perform group mean analysis. These surgical procedures are not novel, and also the treatment of the visual system of patients with INS. This study has shown that the use of standard surgical treatments of patients with INS significantly improves their contrast sensitivity function.

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