Full Title:

Visual functioning in adults with Idiopathic Infantile Nystagmus Syndrome (IINS)

Short Title:

Visual functioning in nystagmus

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Introduction

Infantile Nystagmus Syndrome (INS) consists of an involuntary, predominantly horizontal oscillation of the eyes that develops at birth or shortly afterwards and persists throughout life[1-4]. INS may be associated with visual afferent abnormalities, such as albinism, congenital cataract or optic atrophy, but can also be idiopathic, whereby no visual or neurological impairment is detected[4].

The prevalence of Infantile Nystagmus Syndrome in the UK is thought to be around 14 in 10,000 people, with a prevalence of 1.9 in 10000 for Idiopathic INS, IINS[5]. Children & adults with IINS often have associated mild/moderate visual impairment, and their visual function may be worse than that in age-related macular degeneration[6]. Many have associated manifest strabismus and may adopt a Compensatory Head Posture (CHP) to dampen the nystagmus and improve visual function[4,7,8]. The CHPs may be compared to cervical dystonia, with a similar additional detrimental impact on an individual's ability to work and perform everyday tasks[7].

Clinicians have traditionally focussed on using objective measures such as high contrast visual acuity to understand visual functioning in nystagmus[9]. Emerging evidence suggests that subjective assessment of a condition's impact on Quality of Life (QoL) may be equally, if not more, important than objective tests in the case of IINS. The effect of strabismus on quality of life is well known[10-16], but the impact of nystagmus has been investigated less frequently[6,17,18]. Co-existence of nystagmus and strabismus may have a synergistic negative impact on QoL.

Several vision-specific QoL questionnaires have been used to ascertain the impact of ophthalmic conditions on QoL, such as the National Eye Institute Visual Function Questionnaire (VFQ-25) and the Low Vision QoL questionnaire[19,20]. Recently, McLean et al (2016) developed the Adult Nystagmus Questionnaire (NYS-29)[18], a disease-specific QoL tool for patients with nystagmus. The NYS-29 assesses six domains of every-day life important to patients with nystagmus, allowing for a more holistic understanding of the long-term implications of nystagmus.

However, to date, the VFQ-25 remains the most widely used instrument for the assessment of vision-related QoL [19]. It has been used in many large-scale studies to assess the psychological effect of chronic conditions and is thought to be more

sensitive to decreased functioning due to vision loss than more generic health-related tools[20-23]. The original goal of the VFQ-25 was to create a tool to measure the dimensions of self-reported vision-targeted health status in people with chronic eye diseases. As a result, it has been designed to measure the influence of visual disability on generic health domains, as well as task-orientated domains. The original patient VFQ-25 focus groups did not involve adults with nystagmus but included adults with other chronic eye disease, including age related macular degeneration and diabetic retinopathy. [24.]

The aim of this work is to explore the impact of IINS on QoL in adults, measured by the VFQ-25.

Methods:

Study Design

The self-administered VFQ-25 formed part of the baseline clinical data in an unmasked pilot parallel-randomised control trial assessing the use of contact lenses to optimise vision in adults with IINS[25]. All participants were required to complete the VFQ-25 questionnaire at the baseline study visit prior to randomisation. The study was performed in accordance with the Declaration of Helsinki and was approved by the City Road and Hampstead Ethics Committee. Written informed consent was obtained from participants.

Participants

Eligible participants were identified from the ophthalmology clinics at Moorfields Eye Hospital, London and its outreach clinics; from electronic consultation letters and the Contact Lens Clinic database. Inclusion and exclusion criteria are summarised in table 1.

Author MT took a detailed history and carried out a full ophthalmic assessment on all participants, including slit lamp examination of the anterior and posterior segments. Where appropriate, patients underwent further investigations (including macula Optical Coherence Tomography (OCT) and/or Electro-Diagnostic Testing (EDT)) to confirm a clinical diagnosis of IINS. Genetic testing was not routinely available at the time of the study. Distance binocular best corrected LogMAR visual acuity (BCVA) was recorded, as measured by Early Treatment Diabetic Retinopathy Study chart at 4 metres and at near using the Maclure in a well-lit room.

Data collection

All participants were given a paper copy of the self-administered VFQ-25 (https://nei.nih.gov/sites/default/files/nei-pdfs/vfq_sa.pdf) by author MT to complete after clinical assessment, but prior to randomisation. They were given the opportunity to ask any questions/clarifications with author MT. Data was collected on paper case report forms and transferred to an electronic database for analysis.

Data Analysis

The VFQ-25 data was recorded and scored as detailed in the original manual (https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/vfq/vfq25_manual.pdf). In summary: each item is recoded to a score of 0-100, whereby 0 is the lowest possible score (ie. marked effect on QoL) and 100 is a perfect score (ie. no effect on QoL). The outcomes are then grouped together into 2 broad groups with 12 subscales overall: General health (general health, general vision, ocular pain and near activities); Vision specific (social functioning, mental health, role difficulties, dependency, driving, colour vision and peripheral vision). The 'overall' compositive score is an average of the 7 vision specific subscale scores. Sample questions and recoded VFQ-25 scores are shown in supplementary table 4.

Descriptive summary statistics are provided as mean and standard (SD) deviation for continuous approximately normally distributed variables, and median and interquartile ranges (IQR) for non-normally distributed continuous variables. Where correlations were documented, the Pearson correlation coefficient was calculated. A p-value of less than 0.05 was considered statistically significant.

Results

38 participants were recruited. Table 2 summarises participant characteristics including: age; sex; ethnicity; Best Corrected Distance Visual Acuity (both eyes open, with CHP as required); Best Corrected Near Visual Acuity; manifest strabismus; previous treatment for nystagmus and/or strabismus.
35/38 (92%) participants completed the questionnaire. The mean age (± SD) of the population was 35.1 years (±13.0), range 17-64 years at the time the questionnaire was administered. 15/35 (42.8%) of the participants who completed the questionnaire were British Caucasian, and 14/35 (40%) were female. Mean (SD) and range (min-max) VFQ-25 scores as well as vision-specific scores are presented in Table 3, detailed individual 'recoded' scores are presented in Supplementary Table 5.

The overall mean VFQ-25 value was 65, standard deviation (SD) 13, range (min-max) 34-91. Perceived general health (mean 68 (SD 21, range 25-100) scored higher than overall vision (mean 59, SD 15, range 40-80). VFQ scores for near (mean 65, SD 21, range 25-92) and distance activities (mean 63, SD 17, range 25-92) did not differ significantly. There was no evidence of an association of VFQ-25 scores (for near and distance) with the level of near (r=-0.33, p=0.05) or distance visual acuity (r=-0.2,p=0.3) respectively.
Perceived peripheral vision was moderately reduced (mean 66, SD 24, range 25-100). Only 9/35 of the group held a current UK driving license (although 17/35 met the UK driving standard of a visual acuity of 0.3 logMAR)[26], and 2/9 had given up driving. However, the mean VFQ-25 score in the 7/25 that were still driving was high at 73 (SD 16, range 58.3-100).

Ocular pain scored highly (mean 76, SD 23, range 25-100) suggesting that IINS in itself is not often associated with ocular pain, as did perceived colour vision (mean 97, SD 8, range 75-100) and social functioning (mean 75, SD 17, range 37.5-100). However despite the high levels of social functioning, the effects on mental health were low (mean 44, SD 21, range 6.3-87.5). The effect on role

limitations and dependency were also markedly reduced at mean 51 (SD 29, range 0-100) and mean 58 (SD 18, range 25-92) respectively.

Discussion

In the clinical setting, the effects of an eye disorder are typically measured with high contrast visual acuity tests such as the Snellen or LogMAR visual acuity chart. However, this study suggests that eye disorders may have a greater than expected impact on an individual's quality of life, without necessarily causing

markedly reduced visual acuity. Consequently, a measure of health-related quality of life is an important outcome measure. Vision-related QoL questionnaires have been used to ascertain the impact of ophthalmic conditions on quality of life, but are not routinely used in the clinical setting. This will become increasingly important with the financial restrictions on public health services if high contrast visual acuity alone is used as the main outcome measure of a condition such as IINS.

Whilst the psychological impact of strabismus has been well documented[10-16], data on nystagmus are scarce[6,17,18]. In the current study, where subscale scores are compared to visually normal English speaking adults[27], despite a reasonable range of documented high contrast distance and near visual acuity in our group, VFQ-25 scores for near and distance activities were lower in adults with IINS. This was also demonstrated in the peripheral vision assessment, in keeping with worsening of visual function outside of a 'null zone'. The QoL values found in this study do not correspond with the visual acuity measurements seen.

Similar to published data reporting a negative impact of nystagmus on QoL, we found that the effect of nystagmus on visual function is comparable, or even worse, to that seen within low-vision services - mean vision score of 59 in our group compared to 55 in age related macula degeneration[28], 80 in diabetic retinopathy[29], and 79 in optic neuritis[30]. However, low scores may also reflect the effects of worsening nystagmus, and as a result visual function, during times of increased psychological stress[1,4,31].

Adults with IINS may be unable to drive due to their best documented visual acuity being subnormal or as a result of the increased level of psychological stress imposed by the driving test. The UK Driver and Vehicle Licensing Agency (DVLA) stipulates that group 1 drivers must attain a visual acuity of 6/12 (approximately equivalent to 0.3 LogMAR) with both eyes open for distance and a sufficient visual field[26]. Near half the group (17/35) met the UK driving standard of a visual acuity of 0.3 logMAR, but only 1 in 5 (7/35) were driving at the time of study participation, and 2/35 had given up driving. Our data suggests that adults with IINS report reduced visual functioning in driving, which is likely a combination of both nystagmus and non-nystagmus related factors, in keeping

with previous similar studies. Additional factors unrelated to nystagmus may also influence one's ability to drive with confidence, including contrast sensitivity and depth perception. Consequently, limitations on driving may have an adverse effect on employability and independence.

There remains much debate amongst nystagmus researchers as to the "best" objective outcome measure in nystagmus. The standard remains the eXpanded Nystagmus Acuity Function (NAFX), which is an acuity factor based on nystagmus waveform parameters[32]. The NAFX requires eye movement recordings and analysis software, which are not easily accessible to most practitioners, and do not give an indication of the effects on everyday life. Subjective measures of visual function, such as 'time to see', reading speed[8] , contrast sensitivity[33], gaze dependent VA[34] and QoL assessments[24] may be equally or even more relevant.

Despite reasonable social functioning scores, the most substantial effect of IINS in this study was on mental health, role difficulties and well-being, to a greater extent than would be expected from the documented level of visual acuity, particularly the mental health subscale. McLean et al[17] recently identified 6 broad areas of everyday living as important to people with nystagmus based on 21 individual semi-structured patient interviews: relationships; standing out/being different; feelings about inner self; daily functioning; restriction of movement (i.e. around education/personal/work opportunities) and the future. As a result, a nystagmus-specific quality-of-life questionnaire (NYS-29) was developed[18], with a different personal and social subscale. This could make it a better tool for assessing the additional domains of wellbeing than other vision-related QoL tools. The NYS-29 was not published at the time of our data collection.

Part of the significant effect on mental health may be due to the awareness of the appearance of 'wobbling' eyes and negative attention received from others as a result of this. Adults with IINS also perceived that they were less able than their peers. Adults with strabismus are known to adopt adaptive techniques to disguise their squint, such as placing their hair over the squinting eye or avoiding

eye contact[10]. Similarly, due to the bilateral conjugate nature of IINS, direct eye contact may be avoided. Feelings of hopelessness, negativity and poor confidence are themes recurrent amongst these adults[6,17].

Although there is much anecdotal evidence of the substantial effect of IINS on QoL, little empirical data is available. Moreover, adults with nystagmus often have associated strabismus (15/35 or 43% of our group), so one may expect that when the two entities co-exist, the effects on the individual's quality of life would be greater, although this was not specifically accounted for as a confounding factor in this study Strabismus alone is well known to have debilitating effects on a person's quality of life, mood, independence and livelihood[10-16]. Many patients with strabismus suffer from severe anxiety and depression due to their ocular deviation. Negative social effects include difficulties in socialising and impaired employment prospects, with adults often belonging to lower socioeconomic groups, which may be due to limited job prospects and perceived employer prejudice[14]. The psychosocial effects of nystagmus have been likened to strabismus with both 'cosmetic' and functional implications.

Limitations of this study include the small size, the 'snap-shot' nature of a cross-sectional study, self-administration of the questionnaire and the use of a non-nystagmus-specific vision-related QoL questionnaire. However, despite these limitations, the effects on psychosocial functioning are clearly documented, particularly on mental health, and provide clear evidence to clinicians regarding the effects on quality of life despite the 'best documented' visual acuity.

The World Health Organisation recognises that disability is 'a complex phenomenon, reflecting the interaction between features of a person's body and features of the society in which he or she lives' [33]. Given the psychosocial impact of nystagmus, as described in this small study, it is not surprising that some adults with IINS patients report that they are living with a disability. Based on current clinical assessments of children and adults, the real life effects of nystagmus may be grossly underestimated.

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