Remote Optometry, a forced change for clinicians, academics and researchers: What comes next?

We are reaching the end of 2020, a very unique year that will remain in our memory for a long time and for many reasons. Few things about the pandemic are worth talking positively about in any way, except that as with cold weather and no clothes "need teaches naked woman to spin yarn" to survive the winter. The need to keep optometry going during the pandemic lead to a new appreciation of the use of digital tools which, until recently, were mostly used for personal communication and entertainment. Now these tools are used to deliver eye care remotely, to improve the quality of education, and remotely operate research. As an example, Dan Coates at University of Houston and Susana Chung at the University of California Berkeley have developed psychophysical tools (remote2020) that allow optometry students to participate in experiments, both as patient and as practitioner, to understand both their own visual function and the importance of different clinical vision tests, using their personal smartphone either from their own home or from a laboratory at the university.

Great challenges tend to create great opportunities and the remote delivery of optometric education is a good example of this. Now that the first steps have been taken it is up to the optometric community to decide if we want to keep moving optometry towards a stronger line of tele-eye care. The future needs tele-optometry and great benefits are expected in areas such as management of myopia, dry eye and low vision. The momentum has been generated by the difficult times we are experiencing. We should take advantage of this and start thinking about which laws, technology and mindset need to be adopted to make tele-optometry a reality. Human contact is unlikely to be fully replaced by virtual contact; however, digital encounters in optometry are promising, they will potentially increase access to optometric services for a wider patient population, thereby saving both vision and money. Much research is required to improve these processes, but perhaps we have already reached the point of no return? Let's embrace the challenge!

The editorial team wish you all a better and happier year for 2021!

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Vision status and reading test results in adolescents in Norway

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Abstract

Uncorrected vision anomalies may cause headaches and may affect reading and academic performance. The purpose of this study was to quantify the frequency of vision anomalies, frequency of eye examinations, and use of corrective eye wear in adolescents in Norway, and to explore whether such vision anomalies affect reading test results or frequency of headaches.

A cross-sectional study was performed in 436 adolescents (42.0% males) aged 16–19 years living in South-East Norway. Cycloplegic autorefraction, habitual stereoacuity, and habitual monocular amplitudes of accommodation were measured, and all participants reported the frequency of eye examinations, the use of spectacles and/or contact lens wear, and the frequency of headaches. Reading comprehension and decoding skills were evaluated for a subgroup of the participants (189 participants, 34.4% males) by their performance in national reading tests. Vision anomalies were defined as having refractive errors, poor habitual stereoacuity, or poor habitual amplitude of accommodation in at least one eye.

Overall, 44.0% were classified as having a refractive error, and a total of 61.9% were measured to have vision anomalies. More frequent headaches were associated with poor habitual amplitude of accommodation when adjusted for sex (p=0.04). The frequency of poor reading comprehension was higher in the group of adolescents with vision anomalies (n=109, 31.2%) compared with those with no vision anomalies (n=80, 18.8%; p=0.05). Of those with vision anomalies, 33.5% had never had an eye examination, and 63.9% reported not wearing a correction.

In Norway, there is no mandatory vision screening after 4 years of age. The results here show that a nation-wide programme of regular eye examinations and proper treatment of vision anomalies for all children and adolescents in Norway should be considered. Identifying and treating children with common eye problems in primary and secondary school will improve educational attainment and increase each child's chances of succeeding in further education.

Keywords: Refractive error, accommodation, hyperopia, headache, reading comprehension

Sammendrag

Ukorrigerte synsfeil kan gi hodepine og påvirke lesing og skoleprestasjoner. Hensikten med denne studien var å undersøke forekomsten av synsfeil, hyppigheten av synsundersøkelser og bruken av synskorreksjon blant ungdommer i Norge, samt undersøke om vanlige synsfeil påvirker resultatene på lesetester eller hyppigheten av hodepine.

En tverrsnittstudie ble utført på 436 ungdommer (42,0% menn) i alderen 16–19 år som alle bodde i Sørøst-Norge. Brytningsfeil ble målt under cycloplegi ved hjelp av autorefraktor, det ble målt habituell visus og habituell akkommodasjonsamplitude, og alle deltakerne rapporterte om hyppigheten av synsundersøkelser, bruken av briller og/eller kontaktlinser, samt hyppigheten av hodepine. For et utvalg av ungdommene (189 deltakere, 34,4% menn) ble leseforståelse og ordavkodingsferdigheter undersøkt ved hjelp av resultater fra nasjonale kartleggingsprøver i lesing. Synsfeil ble definert som å ha en brytningsfeil og/eller redusert habituelt stereosyn eller redusert habituell akkommodasjonsamplitude på minst ett øye.

Totalt ble 44,0% klassifisert som å ha en brytningsfeil og 61,9% ble klassifisert som å ha en synsfeil. Resultatene viste at det var en sammenheng mellom hyppig hodepine og redusert akkommodasjonsamplitude, når forskjellen mellom kjønn ble justert for (p = 0,04). Forekomsten av redusert leseforståelse var høyere blant ungdommene som hadde synsfeil (n=109, 31,2%) sammenlignet med de uten synsfeil (n=80, 18,8%; p = 0,05). Blant ungdommene med synsfeil, hadde 33,5% aldri hatt en synsundersøkelse, og 63,9% rapporterte at de ikke brukte synskorreksjon.

I Norge er det ingen obligatorisk oppfølging av syn etter at et barn er 4 år. Resultatene fra denne studien viser derimot at innføring av et nasjonalt system for gjennomføring av regelmessige synsundersøkelser og behandling av synsfeil for alle barn og ungdommer i Norge bør vurderes. Å identifisere og behandle barn med vanlige synsproblemer – i grunnskolen og i videregående skole – vil både forbedre skoleprestasjonene og øke sjansene for å lykkes i videreutdanning.

Nøkkelord: Brytningsfeil, akkommodasjon, hypermetropi, hodepine, leseforståelse

Introduction

Perseverance and efficient performance at school requires good visual acuity, as well as sustained accommodation and convergence (Narayanasamy et al., 2016). Common vision anomalies that remain untreated have been reported to affect reading and academic performance, in particular uncorrected hyperopia (Kulp et al., 2016; Narayanasamy et al., 2015a; Rosner & Rosner, 1997; Shankar et al., 2007; van Rijn et al., 2014), uncorrected astigmatism (Harvey et al., 2016; Narayanasamy et al., 2015b), and reduced stereoacuity (Kulp et al., 2016). Furthermore, vision anomalies have been reported to be more prevalent in children and adolescents with dyslexia compared with controls (Vikesdal et al., 2020), and hyperopia, astigmatism, and strabismus are reported to be associated with attention deficit hyperactivity disorder (Reimelt et al., 2018).

Hyperopia is often associated with anisometropia, binocular dysfunctions, and an increased risk of amblyopia (Cotter et al., 2011; Ip et al., 2008; Klimek et al., 2004; Kulp et al., 2014; Pascual et al., 2014). Since low-to-moderate degrees of hyperopia do not necessarily reduce visual acuity in children and adolescents (Mutti, 2007), hyperopia is prone to remain undetected. A comprehensive eye examination with the use of cycloplegia is usually needed to detect the correct refractive error (Morgan et al., 2015; Sun et al., 2018; Zhu et al., 2016).

Hyperopia has been reported to be the most prevalent refractive error in adolescents in Norway, whereas the prevalence of myopia was found to be low (L. A. Hagen et al., 2018). Even though Norway is a highly developed country with a well-established welfare system, there is no mandatory vision screening after a child is 4 years old (Norwegian Directorate of Health, 2006). Beyond this age, the child's guardians are solely responsible for initiating and ensuring appropriate follow-up of eye health and visual function in their children. As a consequence, in Norway, some children and adolescents with common vision anomalies may never have had their eyes examined and may therefore not have been offered treatment that could have improved their visual acuity, their perseverance for doing near work, or their ability to read for longer periods. Proper treatment of common vision anomalies has been reported to reduce symptoms such as asthenopia, tiredness, and headache (Abdi & Rydberg, 2005; Sterner et al., 2006). To our knowledge, there are no previous reports of the prevalence of common vision anomalies, frequency of eye examinations, and use of corrective eye wear in adolescents in Norway.

The purpose of this study was to quantify the frequency of common vision anomalies, the frequency of eye examinations, and the use of spectacles and/or contact lenses, as well as to explore the association between (i) vision anomalies and headaches (often a symptom of vision anomalies), and (ii) vision anomalies and reading test results, in 16–19 years old adolescents in Norway.

Methods

A cross-sectional study was performed in 2015–2016 on 439 adolescents aged 16–19 years (mean ± *SD* age: 16.7 ± 0.9 years; 41.9% males) living in South-East Norway. The majority of the participants (89.5%) were of Northern European Caucasian ethnicity. Cycloplegic autorefraction was measured in all participants with a Huvitz HRK-8000A Auto-REF Keratometer (Huvitz Co. Ltd., Gyeonggi-do, Korea) 15–20 minutes after administering 1% cyclopentolate hydrochloride (Minims single dose; Bausch & Lomb UK Ltd., Kingston, England); 1 drop was used in eyes with blue to green irides and 2 drops in eyes with green to brown irides. This was to ensure that sufficient depth of cycloplegia was reached with minimal amount of side effects for the participants. The depth of cycloplegia was monitored by a trained optometrist, who evaluated the dilation of the pupil, before performing the autorefraction. If sufficient depth of cycloplegia was not reached after 15–20 minutes, an additional drop of cyclopentolate was administered. The participants were recruited at two upper secondary schools, and all measurements were performed at the schools by a group of five qualified optometrists. Details on recruitment, as well as the prevalence of refractive errors and ocular biometry data have been presented previously (L. A. Hagen et al., 2018).

Habitual stereoacuity was measured as retinal disparities ranging from 15 to 480 seconds of arc (″) with the TNO Stereotest (Laméris Ootech, WC Ede, Netherlands) at 40 cm distance. Habitual monocular amplitude of accommodation was measured in dioptres (D) three times for each eye by the pushup method using the Royal Air Force (RAF) ruler (Burns et al., 2020). The mean of the three measurements was used in the analyses.

A face-to-face interview was performed to gather information on age, sex, ethnicity, and frequency of eye examinations. The participants responded to a questionnaire related to the use of corrective eye wear (spectacles and/or contact lenses) and the frequency of headaches when reading or doing near work. The questionnaire used in the study can be found online – in the Norwegian language (L. A. Hagen et al., 2020). Three participants did not respond to the questionnaire and were excluded from further analyses. This gave a total study sample of 436 adolescents (16.7 ± 0.9 years; 42.0% males; 89.7% of Northern European Caucasian ethnicity).

A reading test was administered by the school teachers with the aim to identify students with poor reading skills (defined as test score below an acceptable level), while the test was not designed to distinguish students with medium and good reading skills. The reading test used was a standardised national assessment ["Obligatorisk kartleggingsprøve, Lesing, Vg1"; The Norwegian Directorate for Education and Training, Norway (Utdanningsdirektoratet, 2014)] taken by the students at the time they entered upper secondary school (age 15–16 years). Reading comprehension was tested by a complex subject text and a fictional text – both with related questions (max 19 + 15 points) to be answered within 20 and 15 minutes, respectively, while decoding skills were tested with a word chain test of 5 minutes duration (max 74 points). In the analyses here, test scores below acceptance (11, 9, and 41 points, respectively) were defined as fails. Reading test results were available for a subgroup of the participants (189 participants; 43.3% of all, 34.4% males, 93.1% Northern European Caucasians), who all reported having grown up in Norway.

Spherical equivalent refractive errors (SER = sphere + ½ cylinder) in both eyes were used to categorize the refractive error. Myopes were defined as having SER ≤ −0.75D in at least one eye, moderate-to-high hyperopes as having SER ≥ +2.00D in at least one eye, and low hyperopes as having +1.00D ≤ SER < +2.00D in at least one eye – the latter was given that there were no myopia or moderate-to-high hyperopia in the other eye. Emmetropes were defined as having −0.75D < SER < +1.00D in both eyes, except from the emmetropes who had more than 1.00DC astigmatism in at least one eye who were categorized as having astigmatism only. Anisometropia was defined as a difference in SER ≥ 1.00D between the two eyes. Poor stereoacuity was defined as habitual stereoacuity poorer than 120″, and poor accommodation was defined as habitual monocular amplitude of accommodation lower than 8D in at least one eye; this is 2–3D less than Hofstetter's minimum age formula: 15 − (0.25 × age) for 16–19-year-olds (Cacho-Martínez et al., 2014). In two participants, habitual monocular amplitude of accommodation was measured in one eye only due to amblyopia in the other eye; both participants were categorized as having poor habitual amplitude of accommodation. Accommodation data is missing for one male participant. Binocular visual dysfunction (BVD) was defined as having poor habitual stereoacuity (poorer than 120″) and/or poor habitual amplitude of accommodation (lower than 8D in at least one eye).

Differences in prevalence and mean values between groups were assessed by the chi-square test and Welch's two independent sample *t*-tests. Ordinal logistic regression analyses were performed with the frequency of headache as the dependent outcome variable, and odds ratios (OR) and 95% confidence intervals (CI) are presented. The significance level was set at 0.05. All statistical analyses were performed using R statistical software, version 3.6.1 (R Core Team, 2019).

The study followed the tenets of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics in Southeast Norway. All participants gave informed consent prior to inclusion in the study.

Results

Refractive errors, stereoacuity, and accommodation

Table 1 summarizes the frequency of refractive errors in all participants and grouped by sex. Overall, 44.0% were classified as having a refractive error in at least one eye. There was a tendency that refractive errors were more common in females than males [47.0% vs 39.9%; $\chi^2(1)=2.2, p=0.14$], and myopia was significantly more prevalent in females than males [14.2% vs 7.1%; $\chi^2(1)=5.4, p=0.02$]. Astigmatism (more than 1.00DC in at least one eye) and anisometropia were present in 11.9% and 3.2% of all participants, respectively, with higher frequency in the moderate-to-high hyperopes (34.5% and 34.5%, respectively) and myopes (34.7% and 8.2%, respectively) compared with the low hyperopes (6.3% and 0.0%, respectively). Anisometropia was not present in the group of emmetropes.

Habitual stereoacuity poorer than 120″ was found in 14.9% [females: 12.7%, males: 18.0%; $\chi^2(1)=2.4, p=0.12$], whereas habitual amplitude of accommodation lower than 8D was found in 25.3% (of n=235; accommodation data is missing for one male participant) [females: 27.7%, males: 22.0%; $\chi^2(1)=1.8$, p=0.18]. Table 2 shows that poor habitual stereoacuity and/or poor habitual amplitude of accommodation was most frequent in moderate-to-high hyperopes (poor stereoacuity only: 17.2%, poor amplitude of accommodation only: 41.4%, combination of both: 24.1%). The mean habitual monocular amplitude of accommodation in the best eye was significantly poorer in those who were moderate-to-high hyperopes (n=29; 8.6±2.0 D) compared with those who were not [n=407; 10.5±2.2 D, Welch's $t(32.7)=4.77$, $p<0.001$]. In the group of emmetropes, 9.0% had poor habitual stereoacuity only, 20.1% had poor habitual amplitude of accommodation only, whereas 2.9% had a combination of both. This gives a total of 270 participants (61.9% of all; females: 64.8%; males: 57.4%) who had refractive error and/or binocular visual dysfunction (BVD; defined as poor habitual stereoacuity and/or poor habitual amplitude of accommodation).

Table 1: *Prevalence of refractive errors in all participants and grouped by sex.*

	All (n=436)		Females (n=253)		Males (n=183)	
	%	n	%	n	%	n
Emmetropia	56.0	244	53.0	134	60.1	110
Refractive errors overall	44.0	192	47.0	119	39.9	73
Low hyperopia	21.8	95	23.7	60	19.1	35
Moderate-high hyperopia	6.7	29	5.1	13	8.7	16
Myopia	11.2	49	14.2	36	7.1	13
Astigmatism only	4.4	19	4.0	10	4.9	9

Overall, regular headaches were reported by 8.5%, while 66.1% reported rarely experiencing headaches. Significantly more females than males reported regular headache [regular headache: females 12.6%, males 2.7%; rare headache: females 57.3%, males 78.1%; $\chi^2(2)=24.2$, $p<0.001$]. As shown in Table 3, more frequent headaches were associated with poor habitual amplitude of accommodation (model A; p = 0.04) and having moderate to high hyperopia (model B; p = 0.04), when adjusted for sex.

Table 2: *Frequency (%) of binocular vision dysfunction (BVD) grouped by refractive error.*

	n	Poor stereo-acuity only	Poor accommo-dation only	Both	No BVD
All	435*	9.0	19.5	5.7	65.7
Emmetropes	244	9.0	20.1	2.9	68.0
Low hyperopes	94*	8.5	18.1	8.5	64.9
Moderate-high hyperopes	29	17.2	41.4	24.1	17.2
Myopes	49	6.1	8.2	4.1	81.6
Astigmatism only	19	5.3	15.8	5.3	73.7

Note: BVD = binocular visual dysfunction [defined as poor habitual stereoacuity (TNO > 120") and/or poor habitual amplitude of accommodation (less than 8D in at least one eye)]
* Accommodation data is missing for one participant

Frequency of eye examinations and use of corrective eye wear

Table 4 summarizes the self-reported frequency of eye examinations and the use of corrective eye wear overall and grouped by refractive error. Overall, 39.0% reported never having had an eye examination, whereas 47.7% reported having had an eye examination within the last three years. A total of 33.5% of those with refractive errors and/or BVD reported never having had an eye examination; significantly more males than females [41.9% vs 28.0%; $\chi^2(1)=5.5$, p=0.02].

Overall, 72.0% reported never wearing any correction, whereas 14.0% reported wearing a correction frequently. Corrective eye wear was most frequently worn by the myopes (frequent wear: 71.4%). In those with refractive errors and/or BVD, 63.9% reported never wearing any correction. More males (71.4%) than females (59.1%) of those with refractive errors and/or BVD reported never wearing any correction, but the association between the frequency of wearing corrective eye wear and sex did not reach significance [$\chi^2(2)=4.4$, p=0.11].

Reading test results

Reading test results were available in a subsample (n=189). Of these, 25.9% failed at least one of the reading comprehension texts, with no difference in the frequency of fails between females and males (25.8% vs 26.2%). There was a near significant association between failing at least one of the reading comprehension texts and having a refractive error and/or BVD [31.2% fail in those with refractive error and/or BVD (n=109) vs 18.8% fail in those without refractive error and/or BVD (n=80); $\chi^2(1)=3.7$, p=0.05]. When restricting the analyses to the group of participants who reported never wearing a correction (n=123), the association between failing at least one of the reading comprehension texts and having a refractive error and/or BVD reached significance [29.5% fail in those with refractive error and/or BVD (n=61) vs 14.5% fail in those without refractive error and/or BVD (n=62); $\chi^2(1)=4.0$, p=0.04]. In those who reported not wearing a correction, mean score on the reading comprehension texts was significantly lower in those with refractive error and/or BVD (n=61; 25.1 ± 4.9 points) compared to those without refractive errors and/or BVD [n=62; 28.3±7.3 points, Welch's $t(104.3)=2.82$, p=0.006].

Decoding skills were tested with a word chain test, and overall, 18.5% failed this test. There were more males than females who failed the decoding skills test [27.7% vs 13.7%; $\chi^2(1)=5.5$, p=0.02], but no associations were found between failing the decoding skills test and having a refractive error and/or BVD.

Discussion

This is the first report that explores the frequency of refractive errors, and accommodative and binocular visual dysfunctions – and the associations between these common vision anomalies, headaches and reading test results – in a representative sample of 16–19 years old adolescents in South-East Norway. Regular headaches were more frequent in females than males and were found to be associated with poor habitual accommodation. Refractive errors and/or accommodative or binocular visual dysfunctions were revealed in more than 60% of the adolescents – with a higher frequency of poor reading comprehension in those with vision anomalies compared to those with normal visual function. This is in line with several other reports that show that common eye problems interfere with learning (Harvey et al., 2016; Kulp et al., 2016; Narayanasamy et al., 2015a; Rosner & Rosner, 1997; Shankar et al., 2007; van Rijn et al., 2014). Learning difficulties that arise in primary or secondary school will affect the chances of success in further education. It is therefore a societal concern when, of the adolescents in Norway who had vision anomalies, about 30% reported never having had an eye examination, and about 60% reported not wearing a refractive correction.

Hyperopia is known to be associated with accommodative and binocular vision anomalies, as well as increased risk of amblyopia (Cotter et al., 2011; Klimek et al., 2004; Kulp et al., 2014; Pascual et al., 2014). In the adolescents in Norway, hyperopia

Table 3: *Ordinal logistic regression models with the frequency of headache ("regular", "sometimes" or "rare") as the outcome variable and "sex" as a potential confounder.*

Outcome variable: Frequency of headache	Model A β	Model A OR (2.5 - 97.5 CI)	Model A *p*		Model B β	Model B OR (2.5 - 97.5 CI)	Model B *p*
Potential confounder: Sex, female	0.71	2.03(1.51 – 2.76)	< 0.001	Sex, female	0.76	2.14(1.58 – 2.92)	< 0.001
Predictor: Accommodation, poor	0.34	1.40(1.02 – 1.91)	0.04	Moderate-high hyperopia	0.80	2.23(1.02 – 4.75)	0.04

Note: Model A: the state of habitual amplitude of accommodation (poor vs normal) as predictor. Model B: moderate-to-high hyperopia in at least one eye as predictor. Odds ratios (OR) and confidence intervals (CI) are presented.

Table 4: *Frequency (%) of eye examinations and use of corrective eye wear, overall and grouped by refractive error.*

	Eye examination (%)			Corrective eye wear (%)		
	Recent	> 3 years old	Never	Frequent	Sporadic	Never
All (*n*=436)	47.7	13.3	39.0	14.0	14.0	72.0
Emmetropes						
With no BVD (*n*=166)	35.5	16.3	48.2	3.6	11.5	84.9
With BVD (*n*=78)	47.4	12.8	39.7	5.1	18.0	76.9
Low hyeropes*						
With no BVD (*n*=61)	31.2	13.1	55.7	1.6	9.8	88.5
With BVD (*n*=33)	54.6	15.2	30.3	9.1	12.1	78.8
Moderate-high hyperopes (*n*=29)	75.9	3.5	20.7	41.4	24.1	34.5
Myopes (*n*=49)	87.8	10.2	2.0	71.4	18.4	10.2
Astigmatism only (*n*=19)	47.4	10.5	42.1	0.0	10.5	89.5
All with refractive error and/or BVD						
All (*n*=29)	55.0	11.5	33.5	20.5	15.6	63.9
Females (*n*=164)	59.8	12.2	28.0	22.6	18.3	59.1
Males (*n*=105)	47.6	10.5	41.9	17.1	11.4	71.4

Note: BVD = binocular visual dysfunction (defined as poor habitual stereoacuity and/or poor habitual amplitude of accommodation).

* Accommodation data is missing for one participant.

was the most common refractive error (L. A. Hagen et al., 2018), and the results here confirmed high frequency of poor habitual amplitude of accommodation (65.5%), poor habitual stereoacuity (41.3%), astigmatism (34.5%), and anisometropia (34.5%) in the moderate-to-high hyperopes (see Results and Table 2). Since most children are hyperopic at birth and in early childhood (Mutti et al., 2018), it is likely that the moderate-to-high hyperopic adolescents have had a hyperopic refractive error throughout their whole life. When left untreated, hyperopia and accommodative or binocular vision anomalies may cause headaches and tiredness (Abdi & Rydberg, 2005; Borsting et al., 2003; Sterner et al., 2006) reducing near work perseverance and therefore academic performance (Kulp et al., 2016; Narayanasamy et al., 2015a; Palomo-Álvarez & Puell, 2008; Shankar et al., 2007; van Rijn et al., 2014).

Regular headaches were, in the adolescents in Norway, reported by more females (12.6%) than males (2.7%). These results were comparable with a previous report on regular headache (defined as more than 6 days per month) in young adults in Norway [11.6% and 4.4% in 20–29 years old females (*n*=4002) and males (*n*=3106), respectively] (K. Hagen et al., 2000). Another study in adolescents in Norway (age 12–18 years) reported headaches to be a major health issue that caused loss of up to nine days of activity each year (Krogh et al., 2015). In the mentioned study regular headaches (more than 1 day per week) were present in 21.0% of females (*n*=276) and 9.5% of males (*n*=212) (Krogh et al., 2015). For migraine, several studies have reported a higher frequency in females than males, whereas for other headache categories, the difference between females and males seems to be smaller (Buse et al., 2013; Stovner et al., 2006). Note that the data in our study did not differentiate between migraine and other headache categories.

More frequent headaches were found to be associated with poor habitual amplitude of accommodation, and with moderate-to-high hyperopia, when corrected for sex (see Table 3). The association between regular headaches and moderate-to-high hyperopia may be a consequence of the high frequency of poor habitual amplitude of accommodation in the moderate-to-high hyperopes (65.5%; see Table 2), partly caused by uncorrected hyperopic refractive errors that exceed the individuals' accommodation ability. Common consequences of poor accommodation are reduced visual acuity at near (blurred text when reading) and asthenopia (Abdi & Rydberg, 2005; Borsting et al., 2003; Sterner et al., 2006). Other factors could, however, also have affected the reported frequency of headaches. A previous study in 13–18 years old adolescents in Norway (*n*=5847) found negative lifestyle factors such as being overweight, smoking, and low levels of physical activity to be associated with regular headaches (Robberstad et al., 2010), but did not include any measurements of refractive errors or visual function. While 9% of the adolescents in our study experienced regular headaches, 66% reported rarely experiencing headaches. Since headaches may impair daily functioning in activities such as reading and learning, it is important to identify the adolescents who suffer from headaches at an early stage and to offer appropriate treatment. The associations found in this study, between regular headaches and poor amplitude of accommodation as well as moderate-to-high hyperopia, show the importance of a comprehensive eye examination to identify possible vision anomalies in these cases.

A higher frequency of poor reading comprehension and a lower mean reading comprehension test score were found in the adolescents in Norway with uncorrected vision anomalies compared to those with normal visual function. This is in line with previous reports of a higher frequency of vision anomalies in children and adults who have difficulties reading (Palomo-

Álvarez & Puell, 2008; Quaid & Simpson, 2013; Vikesdal et al., 2020). No associations were found between decoding skills and having refractive errors, accommodative or binocular vision dysfunctions in the adolescents in Norway. In line with this, correction of hyperopia in 9–10 years old children has been reported to improve reading fluency, however, not decoding of words (van Rijn et al., 2014). van Rijn et al. (2014) suggested poor accommodation to have a greater impact on the speed and fluency of reading – skills that are important for reading comprehension – than on the ability to identify single words such as in decoding tasks.

Since undetected vision anomalies may cause reduced visual function and consequently affect performance at school, it is of great concern that, of the adolescents in Norway with refractive errors, accommodative anomalies, or binocular vision dysfunctions, as many as 30% reported never having had an eye examination and furthermore, that around 60% of the adolescents with vision anomalies did not wear a correction (see Table 4). Reports show that 25% of upper secondary school students in Norway have not completed their upper secondary education (3 years full-time) within five years, and more males (30%) than females (19%) drop out of upper secondary education (Statistics Norway, 2019). Note that both dropouts of upper secondary education (Statistics Norway, 2019) and the lack of eye examinations and corrective eye wear (Table 4) were more prevalent in males compared with females. There are no reports of the association between vision anomalies and dropouts of upper secondary school in Norway, but it is plausible that early detection and proper treatment of common eye and vision problems could have made reading and learning easier for some of these students, and possibly helped them to reach their educational goals (Dudovitz et al., 2016). The high frequency of undetected vision anomalies in adolescents in Norway underscores the importance of having a well-established system for detection, correction, and follow-up of vision problems in schoolchildren at an early age – and as soon as the need develops. A well-established system must ensure that each individual child has the best visual conditions, with the aim to facilitate optimal ocular development and the best possible academic performance.

A limitation in this study was that the reading test results were restricted to a single test in a subgroup of the participants, which may make the test results vulnerable to confounding factors such as distractions, motivation, and interest. However, the results in this study were in line with previous studies on the association between reading and common vision anomalies (Palomo-Álvarez & Puell, 2008; Quaid & Simpson, 2013; Vikesdal et al., 2020).

Conclusion

This study revealed refractive errors, accommodative anomalies, or binocular vision dysfunctions in about 60% of 16–19-year-olds in Norway. Poor reading comprehension was more frequent in those with vision anomalies compared to those with normal visual function, headaches were found to be associated with poor accommodation, and about 30% of the adolescents with vision anomalies had never had an eye examination. These results suggest that a better public health system to detect and treat vision anomalies in children and adolescents in Norway is needed. A well-established system that ensures the performance of a comprehensive eye examination with cycloplegia and a proper choice of treatment for children and adolescents who need it, will make education easier for school children and students who suffer from vision anomalies.

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Headache, eyestrain, and musculoskeletal symptoms in relation to smartphone and tablet use in healthy adolescents

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Abstract

Neck pain and headache are leading causes of years lived with disability globally, and the prevalence is gradually increasing from school age to early adulthood. These symptoms have been linked to the use of digital devices. However, there is little knowledge related to this topic in adolescents, who spend increasingly more time using digital media. The aim of the study was to investigate eyestrain, headache, and musculoskeletal symptoms in relation to the use of tablets and smartphones in healthy adolescents with normal vision. Fifty healthy adolescents aged 11 – 13 years (mean = 12.1 ($SD = 0.53$)) with normal vision and development participated. A vision examination was performed by an authorised optometrist and an interview questionnaire measuring eyestrain, headache, and musculoskeletal symptoms in relation to screen use was filled out. In addition, screen time, ergonomics, participation in sports, and outdoor time were obtained. Forty-nine (98%) of the 50 children used a smartphone and 17 (34%) used a tablet. Overall, 12% to 41% experienced symptoms of headache, neck pain, tiredness and/or tired eyes while using smartphones and tablets. Nine (18%) experienced at least one symptom often or always while using their device. Musculoskeletal pain and headache were significantly associated with vision and eyestrain. Tablet use was associated with increased symptom scores compared to smartphone use. Increased screen time and shorter viewing distance were associated with eyestrain, headache, and neck pain. Children with neck, shoulder, and back pain were significantly (2.1 hours) less physically active than children without these symptoms. Most adolescents with good health and vision had no symptoms while using smartphones and tablets. However, a significant proportion still experienced symptoms of headache, neck pain, tiredness and tired eyes, and these symptoms were associated. Symptoms increased with screen time, shorter viewing distance and reduced participation in sports. This suggests that even healthy children with good vision may develop vision symptoms and musculoskeletal pain. Awareness should be raised among parents, teachers, eye– and health–care personnel, of the importance of good visual ergonomics and physical activity to promote health in adolescents.

Keywords: screen time, screen distance, neck pain, visual ergonomics, children, vision, refractive error.

Sammendrag

Nakkesmerter og hodepine er hovedårsaker til sykefravær globalt, og forekomsten øker gradvis fra skolealder til tidlig voksen alder. Disse symptomene har blant annet vært knyttet til bruk av digitale enheter. Imidlertid er det lite kunnskap relatert til dette temaet hos barn og unge, som i økende grad bruker mer tid på digitale medier. Målet med studien var å undersøke symptomer på syn- og øyeplager, hodepine og muskel- og skjelettplager relatert til bruk av nettbrett og smarttelefon hos friske skolebarn med normalt syn. Femti friske skolebarn i alderen 11 – 13 år (gjennomsnitt = 12,1 ($SD = 0,53$) med normalt syn og normal utvikling deltok. En autorisert optiker utførte en synsundersøkelse og fylte inn et intervjuskjema som undersøkte syn- og øyeplager, hodepine og muskel- og skjelettplager i forbindelse med skjermbruk. I tillegg ble skjermtid, ergonomi, fysisk aktivitet og tid utendørs registrert. Førtini (98%) av de 50 barna brukte smarttelefon og 17 (34%) brukte nettbrett. Tilsammen opplevde 12% til 41% symptomer på hodepine, nakkesmerter, tretthet og/eller øyeanstrengelse mens de brukte smarttelefoner og nettbrett. Ni (18%) opplevde minst ett symptom ofte eller alltid mens de brukte enheten. Muskel- og skjelettsmerter og hodepine var signifikant assosiert med syn- og øyeanstrengelse. Nettbrettbruk var assosiert med mer symptomer sammenlignet med smarttelefonbruk. Økt skjermtid og kortere skjermavstand var assosiert med øyeanstrengelse, hodepine og nakkesmerter. Barn med nakke-, skulder- og ryggsmerter var signifikant (2,1 timer) mindre fysisk aktive enn barn uten disse symptomene. De fleste skolebarn med god helse og godt syn hadde ingen symptomer når de bruker smarttelefoner og nettbrett. Imidlertid opplevde en betydelig andel fortsatt hodepine, nakkesmerter, tretthet og trette øyne, og disse symptomene var assosiert med hverandre. Symptomene økte med skjermtid, kortere skjermavstand og redusert fysisk aktivitet. Dette tyder på at friske barn med godt syn også kan utvikle syn- og øyeplager samt smerter i muskler og skjelett. Foreldre, lærere, øye- og helsepersonell bør bli mer bevisst og oppmerksom på viktigheten av god visuell ergonomi og fysisk aktivitet for å fremme helsen hos ungdommer.

Nøkkelord: skjermtid, skjermavstand, nakkesmerte, visuell ergonomi, barn og unge, syn, refraktiv status.

Introduction

Children and adolescents in Norway, and globally, spend increasingly more time performing visually demanding near tasks using digital screens, both at school and during their spare time (Løvgren & Svagård, 2019; Norwegian Media Authority, 2020; Saunders & Vallance, 2017; Twenge & Campbell, 2018; Winther et al., 2015). Near tasks require precise and accurate coordination between the visual system and the head-stabilizing muscles, which necessitates a robust visual system to maintain clear and comfortable vision over time. Uncorrected vision problems, such as refractive errors, accommodation anomalies or convergence deficits, can induce unhealthy postures leading to non-ergonomic viewing positions, such as protruding head or asymmetrical neck postures, and headaches (Blehm et al., 2005; de Vries et al., 2016; Dotan et al., 2014; Johnston et al., 2017; Rosenfield, 2011; Sanchez-Gonzalez et al., 2019). Further, digital screen-use has been found to cause headache, eyestrain, and upper body musculoskeletal pain in children and adolescents. The severity of symptoms increases with static non-ergonomic postures, vision problems and prolonged viewing time (Blehm et al., 2005; Costigan et al., 2013; de Vries et al., 2016; Eitivipart et al., 2018; Hakala et al., 2012; Johnston et al., 2017; Kim et al., 2016; Rosenfield, 2011; Sanchez-Gonzalez et al., 2019; Wirth et al., 2018; Xie et al., 2017).

Neck and back pain, and headache are leading causes of years lived with disability globally, and the prevalence is gradually increasing from school age to early adulthood (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018;

Gustafsson et al., 2018; Joergensen et al., 2019). The knowledge regarding risk factors and interventions in children and adolescents is limited. Studies indicate associations between spinal pain and headache, and screen time, bad ergonomics, obesity, and socioeconomic and psychosocial factors, with a higher pain prevalence in females (Batley et al., 2019; Ben Ayed et al., 2019; Bonthius & Hershey, 2020; Connelly & Sekhon, 2019; Gustafsson et al., 2018; Joergensen et al., 2019; Sa & Silva, 2017; Szita et al., 2018). Headache and neck and shoulder pain are among symptoms reducing everyday life activities in adolescents (Hakala et al., 2012), for example, headaches have been found to cause an average yearly loss of 9 days of activity (Krogh et al., 2015). Treatments are both pharmacological and non-pharmacological; physical therapy, lifestyle modifications, psychological and cognitive-behavioural therapy (Bonthius & Hershey, 2020; Hauer & Jones, 2020; Lee et al., 2019). Nonpharmacological treatment typically involves extensive treatment regimes, requiring high motivation from both child and carers (Buchbinder et al., 2015). In contrast, correcting vision problems receives little attention. Approximately 20% of school children require an optical correction to obtain good vision, however, this is rarely mentioned as a potential treatment to prevent and relieve musculoskeletal pain and headache in children (Dotan et al., 2014; Gil-Gouveia & Martins, 2002), even if this is an easily applicable and cost-effective solution. One reason is that vision problems are often not detected due to the lack of compulsory eye examinations during primary and secondary school in most countries (Falkenberg et al., 2019; Hagen et al., 2018; Hopkins et al., 2019; Vikesdal et al., 2019).

It is essential to promote visual and musculoskeletal health so that children are able to perform prolonged periods of digital screen viewing without increasing the risk of future health problems. The purpose of this study was to investigate headache, eyestrain and musculoskeletal symptoms in relation to smartphone and tablet screen use in healthy adolescents with good vision.

Methods

Study sample

This was a cross-sectional study of 11 – 13-year-old children (7th grade) at three schools in Gran and Lunner municipality, Norway, during the school year 2016-2017. All 118 children attending 7th grade were invited to participate and written informed consent was obtained from 83 children (mean = 12.1 years (SD=0.53) and their parents. All children were given a vision examination at school by an authorized optometrist (TRJ). The inclusion criteria were healthy children with normal development and good vision. The study protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2015/1887) and followed the Declaration of Helsinki. Data collection was undertaken as part of a MSc thesis (TRJ) at University of South-Eastern Norway (unpublished).

Vision examination

The vision examination consisted of habitual monocular and binocular distance (6 m) and near (40 cm) visual acuity (VA), retinoscopy and cover test (6 m and 40 cm). Near point of convergence (NPC) and monocular and binocular accommodation amplitude (AA) were assessed using an RAF ruler (Neely, 1956). For analysis, spherical equivalent refraction (SER) was calculated in dioptres (D). Refractive errors were defined as emmetropia (−0.50 < SER < +0.50 D), hyperopia (SER ≥ +0.50 D), myopia (SER ≤ −0.50 D), astigmatism (≤ −0.75 DC) and anisometropia (≥ 1.00 D) (Falkenberg et al., 2019; O'Donoghue et al., 2010). Children were included if they had habitual near visual acuity of 0.0 logMAR and no binocular anomalies (horizontal phorias >10 pd, binocular AA ≤ 10 D, NPC > 10 cm). Thirty-four of the children had previously had an optometric examination, and 27 wore glasses for distance and/or near (reading glasses were used for all near vision tests). Children were excluded if they failed the vision examination or if they had, by parental report, a diagnosis of learning disabilities (e.g., dyslexia), attention deficit hyperactivity disorder (ADHD/ADD), developmental delay or migraine. Further, children were excluded if they had an injury, systemic disease or daily medication associated with vision or the musculoskeletal system. Fifty children fulfilled the inclusion criteria and were interviewed with a questionnaire. Of the 33 children who were excluded, two were advised to see their local optometrist. Results of the vision examination for all children can be found in Table 1.

Table 1: *Monocular and binocular results from the vision examination.*

		Included (n=50) Mean [95% CI]	Excluded (n=33) Mean [95% CI]
Age		12.1 [11.8, 12.3]	12.1 [11.9, 12.3]
Habitual distance visual acuity (logMAR)	RE	-0.05 [-0.08, -0.02]	-0.02 [-0.06, -0.02]
	LE	-0.08 [-0.10, -0.05]	-0.04 [-0.08, 0.00]
	Bin	-0.13 [-0.15, -0.10]	-0.08 [-0.11, -0.05]
Refractive error (SER)	RE	+0.08 [-0.01, 0.17]	+0.19 [0.00, 0.38]
	LE	+0.01 [0.01, 0.19]	+0.18 [-0.02, 0.38]
Accommodation amplitude (D)	RE	13.3 [12.9, 13.7]	12.9 [12.4, 13.5]
	LE	13.6 [13.2, 14.0]	13.1 [12.5, 13.7]
	Bin	14.4 [14.0, 14.7]	13.9 [13.5, 14.4]
Horizontal heterophoria[1] (pd)	6 m	-0.5 [-0.93, -0.11]	1.5 [-0.15, 3.19]
	40 cm	-1.6 [-0.26, -0.15]	2.9 [-0.74, 5.14]
NPC (cm)	40 cm	5.86 [5.60, 6.10]	6.42 [5.46, 7.36]

[1] Negative value denotes exophoria.
Note: Vision data from the excluded children have been added for comparison.

Interview questionnaire

A questionnaire was used to investigate how the participants used their smartphones and tablets and their experience of symptoms during use (see Appendix). The questionnaire comprised two parts: 1) Screen time, visual ergonomics (postures, lighting conditions), sports, time outdoors, and 2) Headaches, tiredness, eyestrain, and musculoskeletal symptoms during screen use. Part 1 contained both pre-set categorical answers and space to add free comments. The preferred smartphone viewing distance was measured during the reading of a standardised text message with 1.8 mm font size (iPhone 7, Apple Inc., USA). At 40 cm, the minimum angle of resolution (MAR) is calculated to be 3.1 seconds of arc, giving an acuity demand of 0.5 logMAR (decimal VA 0.3). This was well above visual acuity threshold for all participants. Part 2 had 15 symptom items that were repeated for smartphones and tablets separately; ten items regarding vision from the Convergence Insufficiency Symptoms Survey (Borsting et al., 2003) adapted to the aim of this study, and five items related to musculoskeletal symptoms. All symptom questions were scored on a 5-point scale: Never (0), Rarely (1), Sometimes (2), Often (3), Always (4). The child could see the questions and response options in writing, but questions were read aloud and scored by TRJ. For analysis, scores 0–1 were aggregated into "No symptoms" and scores 2–4 into "Symptoms" (Gustafsson et al., 2018). A total eyestrain symptom score was calculated combining all eye symptoms (8; max score 32), and a total musculoskeletal symptoms score was calculated combining all musculoskeletal symptoms (5; max score 20). The headache and tiredness symptoms were scored separately as they may be associated with both eyestrain and musculoskeletal symptoms (Rosenfield, 2011). Total symptom score included all 15 symptom items.

Statistical analysis

Raw data were assessed for normality using Q-Q plots and the Shapiro-Wilk test. Dependent variables were analysed using paired sample *t*-tests. Independent variables were compared using one-way analysis of variance (ANOVA) and independent-samples *t*-tests. Chi-square independence tests were used to evaluate associations between categorical variables. Pearson's correlation coefficient (r) was used to investigate associations between continuous variables. Point-biserial correlations were run to determine the relationship between categorical and continuous variables. Correlation coefficients (r) above 0.3 were included. Analysis using refractive error included right eye only, as there were no significant differences between right and left eyes (paired sample *t*-test, $p > 0.05$). A statistical difference was set at $p < 0.05$ (two-tailed), and analyses were performed in IBM SPSS Statistics (Version 24, US).

Results

The smartphone and tablet symptoms questionnaire was completed by 50 healthy children (32 females, 18 males) with normal vision. As shown in Table 1, the average monocular and binocular visual acuities were good, the mean refractive error (SERs) was +0.08 and +0.01 for the right and left eye, respectively. Forty-nine children (98%) used a smartphone and 17 (47%) used a tablet on a daily basis (outside school hours). The children spent on average 1.8 hours using their smartphone and 1 hour on their tablet on a weekday. During the weekend they spent significantly more time using their smartphone (2.6 hours, $t(47) = -4.9, p < 0.001$) and tablet (1.7 hours, $t(16) = -3.98, p = 0.001$). The mean time spent outdoors was 17.7 hours per week, and the children participated in sports on average 4.7 hours per week.

The mean viewing distance to the smartphone was 33.3 cm, range 16–52 cm, with a calculated visual acuity demand of 0.58 logMAR. The most common posture when using a smartphone was sitting, $n = 33$ (69%) or lying down, $n = 16$ (33%). Only two children reported that standing was their preferred posture/position. These were also the most common postures when using a tablet (sitting, $n = 9$ (53%), lying down, $n = 8$ (47%)). Forty-three children (90%) preferred to support the smartphone using their hands. For tablet use, six (35%) preferred their hands, and seven (41%) preferred the table/lap as support. The most preferred lighting was ambient indoor room lighting for 27 (55%) of the children when using their smartphone or tablet. However, 17 (35%) stated that they most often used their device in a dark room, with no other lighting than the device screen itself.

Symptoms

Table 2 shows the reported presence of vision or musculoskeletal symptoms while using smartphones and tablets. Thirty-three children (67%) had no symptoms while using their smartphone. The most commonly reported symptoms were tired eyes $n = 15$ (31%), neck pain $n = 14$ (29%) and tiredness $n = 11$ (22%). Headache was reported by six (12%) children. The mean total symptom score was 6.6 for smartphone use, and females had significantly higher total symptom score ($t(47) = -2.24, p = 0.03$) and more eyestrain ($t(48) = -2.57, p = 0.013$) during smartphone use compared to males. Although the overall symptom scores were low, eight (16%) children reported experiencing one or more symptoms often or always, and 13 (27%) children reported three symptoms or more when using their smartphone (see Table 2). About half (53%) of the children reported no symptoms when using their tablet. Table 2 shows that the most common symptoms related to tablet use were tired eyes $n = 7$ (41%), tiredness $n = 7$ (41%) and neck pain $n = 5$ (29%). Two (12%) children reported headache when using a tablet. Three (18%) children reported often or always experiencing one or more symptoms, and five (29%) children reported three symptoms or more when using their tablet. The mean total symptom score was 7.7 for tablet use, and this was significantly higher than for smartphone use (paired *t*-test; $t(15) = 3.24, p = 0.005$). Also, higher scores were found for eyestrain ($t(15) = 3.72, p = 0.002$), neck pain ($t(15) = 2.61, p = 0.020$), and tiredness ($t(15) = 2.45, p = 0.027$) during tablet use compared to use of smartphones.

Table 2: *Frequency of symptoms.*

		Smartphone (n=49) n (%)	Tablet (n=17) n (%)
Vision symptoms	Tired eyes	15 (31)	7 (41)
	Uncomfortable eyes	7 (14)	2 (12)
	Double vision	4 (8)	0 (0)
	Blurred vision	4 (8)	1 (6)
	Jumping letters	1 (2)	0 (0)
	Eye pain	6 (12)	3 (18)
	Sore eyes	4 (8)	1 (6)
	Pulling feeling around eyes	2 (4)	2 (12)
	≥ 3 symptoms	8 (16)	2 (12)
Musculo-skeletal symptoms	Neck pain	14 (29)	5 (29)
	Shoulder pain	4 (8)	1 (6)
	Back pain	1 (2)	3 (18)
	Arm/hand pain	1 (2)	1 (6)
	Hand/finger pain	4 (8)	1 (6)
	≥ 3 symptoms	2 (4)	0 (0)
	Headache	6 (12)	2(12)
	Tiredness	11 (22)	7(41)
Overall symptoms	No symptoms	33 (67)	9 (53)
	≥ 3 symptoms	13 (27)	5 (29)
	Often or always ≥ 1 symptom	8 (16)	3 (18)

Associations between symptoms and viewing distance, screen time and participation in sports

Shorter viewing distance to the smartphone was related to increased neck pain ($r = -0.35, n = 49, p = 0.014$. Further, eyestrain during smartphone use was related to neck and shoulder and back pain ($r = 0.71, n = 49, p = 0.000$), and arm/hand pain ($r = 0.48, n = 49, p < 0.001$). Eyestrain was also associated with increased neck and shoulder pain during tablet use ($r = 0.53, n = 17, p = 0.027$). The children with best VA had less eyestrain ($r = 0.47, n = 49, p = 0.001$) during smartphone use and less shoulder pain ($r = 0.55, n = 17, p = 0.023$) during tablet use than those with poorest VA. Eyestrain ($r = 0.369, n = 49, p = 0.001$) and total symptom score ($r = 0.50, n = 49, p = 0.000$) were significantly correlated to the experience of tiredness during smart phone use.

Increased time using a tablet was significantly associated with sore eyes and blurred vision ($r = 0.63, n = 17, p = 0.007$), and more time using a smartphone was associated with headache ($r = 0.34, n = 49, p = 0.016$). Reduced participation in sports was related to increased neck, shoulder and back pain during both tablet ($r = -0.59, n = 17, p = 0.015$) and smartphone use ($r = -0.36, n = 49, p = 0.01$), and increased presence of headache during smartphone use ($r = -0.42, n = 49, p = 0.003$). Analysis of variance showed that seven (41%) of the tablet users, and 17 (35%) of the smartphone users who reported neck, shoulder and back pain, were significantly less physically active (on average 2.1 hours per week) compared to children without these symptoms when using tablets $F(1,15) = 4.974, p = 0.041$, or smartphones ($F(1,47) = 7.122, p = 0.010$). There were no significant associations between screen time and participation in sports.

Further, headache showed significant positive correlations with eyestrain ($r = 0.62, n = 49, p < 0.001$), and associations with neck, shoulder and back pain ($\chi^2(1, n = 49) = 15.50, p < 0.001$) and arm/hand pain ($\chi^2(1, n = 49) = 11.82, p = 0.001$) during smartphone use. Headache was also associated with eyestrain ($r = 0.86, n = 17, p < 0.001$) and neck and shoulder pain, ($\chi^2(1, n = 17) = 5.44, p = 0.02$) during tablet use.

In summary, short distance to the screen, increased screen time, and reduced participation in sports may increase the risk of symptoms of eyestrain, headache, and upper body musculoskeletal pain in otherwise healthy children with good vision. Also, eyestrain, headache, and upper body musculoskeletal pain are correlated symptoms.

Discussion

This study found that most healthy adolescents with good vision reported low scores on symptoms of headache, eyestrain and musculoskeletal pain while using their digital device. Still, about one-third experienced symptoms of tired eyes and/or neck pain and 12% reported headache. Three symptoms or more were present in about one-third, and almost 20% experienced symptoms often or always while using their devices. Also, girls experienced more symptoms than boys. This is in line with earlier studies showing that eyestrain, headache, and neck pain are generally common in the adolescent population, and that girls have more complaints than boys (Batley et al., 2019; Ben Ayed et al., 2019; Gheysvandi et al., 2019; Gustafsson et al., 2018; Gustafsson et al., 2019; Joergensen et al., 2019; Kim et al., 2016). Studies of symptoms specific to digital screen use in adolescents are scarce. We have identified only three studies, and our results support and elucidate these studies (Hakala et al., 2012; Ichhpujani et al., 2019; Lui et al., 2011). A Hong Kong study showed that approximately one third of 8-13-year-olds experienced musculoskeletal symptoms during electronic game use, and neck complaints (28%) were most commonly reported (Lui et al., 2011). In the Hong Kong study, headaches and eyestrain were not reported. Among Finnish 12–16-year-olds, neck and shoulder pain (21%), headache (20%) and eye symptoms (14%) were the most often reported computer-associated symptoms (Hakala et al., 2012). A more recent Indian study found that 18% of 11–17-year-olds experienced eyestrain after working on digital devices, however, they did not investigate musculoskeletal pain or headaches (Ichhpujani et al., 2019). The slight differences in symptom frequencies compared to the current study, are most likely due to differences in population, study design, and sample size. One important difference is that the current study had very strict inclusion criteria related to vision and general health, contributing with new knowledge of screen related symptoms in healthy adolescents with good vision.

The present study is, to our knowledge, the first study showing correlations between neck, shoulder and back pain, and vision/eyestrain in healthy adolescents with good vision. These associations have only previously been shown in adults (Mork, 2019; Mork et al., 2019; Sanchez-Gonzalez et al., 2019). Eyestrain and headache were also associated with arm/hand pain during smartphone use. The most likely explanation is that almost all children (90%) supported their smart phone only with their hands, whereas lap/table were used as tablet-support. Further, our study showed strong correlations between eyestrain and headache. This supports other studies examining vision problems in relation to headaches (Akinci et al., 2008; Dotan et al., 2014; Falkenberg et al., 2019; Gil-Gouveia & Martins, 2002; Gunes et al., 2016; Hendricks et al., 2007). These associations are not surprising, as near tasks, such as screen use, require high visual-motor function and precise coordination between the visual system and the head-stabilizing muscles. Even small imbalances have been shown to provoke eyestrain, headaches, and musculoskeletal symptoms (Blehm et al., 2005; de Vries et al., 2016; Johnston et al., 2017; Rosenfield, 2011; Sanchez-Gonzalez et al., 2019).

Shorter viewing distance to the smartphone was related to increased neck pain. In our study, the average distance was 33 cm, and seven children held their smartphone at less than 25 cm. Our findings are in line with other studies in school children of a similar age (Ichhpujani et al., 2019; Salmerón-Campillo et al., 2019), but are 10 cm longer than the average viewing distances measured in a study of young adults reading from smartphones and tablets (Miranda et al., 2018). The differences in viewing distance are most likely due to different methods, tasks, and setups. Often, as in the current study, viewing distance is a point measure between the cornea and the handheld display while reading a short text. Miranda and colleagues however, measured convergence distance to reading a continuous text for a much longer period, while using an eye tracker. Shorter viewing distances have been shown to increase the load on the visual system and binocular vision, increasing the risk of eyestrain and neck pain (Ichhpujani et al., 2019; Jaiswal et al., 2019; Long et al., 2017; Sanchez-Gonzalez et al., 2019). Therefore, longitudinal studies are necessary to understand the mechanisms behind preferred short viewing distances when using handheld devices in both children and adults. Increased screen time was associated with increased presence of eyestrain and headache in the current study, in line with several studies (Alonso-Blanco et al., 2011; Costigan et al., 2013; Fernandez-de-las-Penas et al., 2011; Hakala et al., 2012; Kim et al., 2016; Moon et al., 2016; Taehtinen et al., 2014; Torsheim et al., 2010). It is exhausting for both vision and head-stabilising musculature to perform continuous near work with short viewing distances (Blehm et al., 2005; Sanchez-Gonzalez et al., 2019). The current study supports the theory that longer viewing distances and taking breaks while using digital screens may be important in preventing symptom development.

Neck pain, eyestrain, and tiredness scores were higher during tablet use compared to smart phone use in the present study. To our knowledge, this has not been shown in earlier studies. One explanation could be differences in viewing time and continuous use without breaks. This is unlikely as screen viewing time did not differ significantly between tablet and smartphone in this study. The frequency of breaks was not registered when using the different devices. Another explanation could be differences in position or support while using the digital device. In this study, there was no difference in position, while there was a difference in how the device was supported. The preferred tablet support was in the lap or on a table, while hands were preferred when using the smartphone. This difference in support indicates increased head flexion angle during tablet compared to smartphone use, increasing the load on the neck and inducing neck pain (Eitivipart et al., 2018; Oliveira & Silva, 2016; Straker et al., 2008). This is supported by studies showing that mechanical load on the neck muscles increases 3-5 times during seated tablet computer use compared to seated neutral posture in adults (Vasavada et al., 2015). Further, neck imbalance may increase the load on the visual system explaining the increased eyestrain and tiredness symptoms when using the tablet (de Vries et al., 2016; Johnston et al., 2017; Sanchez-Gonzalez et al., 2019).

Decreased participation in sports was related to increased neck, shoulder and back pain, and headache during tablet and smartphone use. This is in line with indications of a relation between neck pain and reduced muscle endurance and strength of neck and back musculature in adolescents (Andias & Silva, 2019). This suggests that reduced physical activity and lack of muscle strength and endurance can increase the risk of musculoskeletal pain symptoms. Moderate physical activity has been shown to be protective regarding neck, shoulder and back pain in adolescents (Hakala et al., 2012; Myrtveit et al., 2014). As such, this supports public health advice of being physically active, and both parents and schools should encourage and facilitate participation in sports for adolescents.

In this study, 35% stated that they most often used their device with no other lighting than the device screen light itself. We did not find any associations between lighting conditions and symptoms, in contrast to other studies. This is probably due to differences in study design, where our participants self-reported on lighting conditions in natural settings, while other studies are controlled lab experiments. Too large a difference in luminance between the screen and immediate surroundings may lead to contrast glare, thereby increasing the load on the visual system and the risk of eye and musculoskeletal symptoms (Antona et al., 2018; Mork, 2019; Mork et al., 2019).

A strength of this study was the strict inclusion criteria related to health and visual status, providing new knowledge of symptoms and associated risk factors in adolescents while using digital devices. Although the data are from a relatively small sample, the study population of fifty 11– to 13–year-old Norwegian adolescents is representative for 7th grade school children in Norway (Statistics Norway, 2020), strengthening the potential generalisability of the study results to healthy Norwegian adolescents of the same age. Further, similar findings have been shown in adults. Since the data collection, the use of digital devices in Norwegian schools has escalated, and many children use a tablet computer as their main tool for school– and homework. Combined with even easier access to private digital devices, this study probably underestimates the viewing times spent on digital viewing (Norwegian Media Authority, 2020) and the frequency of symptoms. Frequency of breaks during screen viewing and viewing distance to tablet were not registered in this study, something that may have allowed us to elaborate some of the results. However, it has been shown that tablets are held at a similar distance to our measured smartphone distance (Salmerón-Campillo et al., 2019), and that the viewing distance is the same for smartphones and tablets (Miranda et al., 2018). The school setting did not allow the use of cycloplegic refraction, which is the standard clinical practice for refraction of children. This limits the conclusion to be drawn on the average hyperopic refractive error found in these children. However, the results are similar to other larger studies on Norwegian adolescents (Falkenberg et al., 2019; Hagen et al., 2018). A cycloplegic refraction would have shifted the refractive errors slightly towards more hyperopia (on average +0.5 D) in the whole sample (Yazdani et al., 2018), and we doubt this shift would have affected the results significantly. Another limitation is the use of self-reported symptoms and visual ergonomics, which could bias the results. However, an experienced optometrist asked the questions, and could explain and ask follow-up questions, minimising recall errors. Despite this, our study contributes important knowledge of headache, eyestrain, and musculoskeletal pain in adolescents, which may guide further research and clinical practice. Larger, controlled studies are necessary to elucidate the prevalence of these symptoms related to screen use, and must in addition include psychosocial variables such as stress and quality of life, as they are known to be associated with the experience of pain in adolescents.

Conclusions

Most adolescents with good health and vision had no symptoms while using smartphones (67%) and tablets (53%). However, a significant proportion still experienced headache, neck pain, tiredness and tired eyes, and these symptoms were associated. Symptoms increased with screen time, shorter viewing distance and reduced participation in sports. This suggests that even healthy children with good vision may develop vision symptoms and musculoskeletal pain. Awareness should be raised among adolescents, parents, teachers, eye– and healthcare personnel, of the importance of good visual ergonomics while using digital devices to promote health. Further, this study supports public health advice of being physically active, and both parents and schools should encourage and facilitate participation in sports for adolescents.

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Retinal function in incontinentia pigmenti: a long-term electrophysiological follow-up

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Abstract

Incontinentia pigmenti (IP) is a rare, X-linked, dominantly inherited disease affecting mostly females, which is best characterized as an autoimmune disease. It is a multi-system disorder affecting ectodermal tissues. Ocular abnormalities usually occur early in childhood, with subsequent retinal detachment and vision loss. Vision rarely remains intact until adulthood. We present the 17-year visual electrophysiological follow-up of such a rare patient and her mother. The mother was only a carrier, but the daughter developed various manifestations of IP. The aim of our investigations was to obtain information on the progression of functional deterioration in IP.

Electroretinography (ERG), multifocal electroretinography (mfERG), visual evoked potentials (VEP), ultrasound (US) and optical coherence tomography (OCT) were performed at regular intervals between the patient's ages of 9 and 26 years (2003 to 2020).

From 9 to 22 years of age, a characteristic picture of spared vision with minimal ophthalmoscopic alterations and fluctuating ERG anomalies were observed in the left eye. It was only between the ages of 22 and 23 that subjective symptoms developed, and then complete loss of vision in the affected eye ensued rapidly. The right eye remained clinically asymptomatic throughout the observation period. The mother remained completely asymptomatic, but she showed similar ERG alterations.

Electroretinography is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it readily detects their functional effect even in the absence of clinical symptoms. Thus, it is recommendable not only for the long-term functional follow-up of these patients, but probably also for early disease-specific screening. ERG recordings from the presented case suggest that the characteristic, asymmetric pattern of retinal functional involvement may be traced back to the different degrees to which the two eyes were exposed to the intermittent reactivations of the disease.

Keywords: incontinentia pigmenti, retina, visual electrophysiology, optical coherence tomography, ultrasound examination.

Sammendrag

Incontinentia pigmenti (IP), også kalt Bloch-Sulzbergers syndrom, er en sjelden arvelig tilstand med X-bundet dominant arvegang. Den påvirker stort sett kvinner og kan best beskrives som en autoimmun sykdom. Den er en multisystem tilstand som påvirker ektodermalt vev. Øyeforandringer begynner ofte i tidlig barndom og etterfølges av netthinneavløsning og tap av syn. Normalt syn bevares sjeldent til voksen alder. Her presenteres en elektrofysiologisk oppfølging over 17 år av en jente og hennes mor. Moren var kun bærer av genet, mens datteren utviklet diverse symptomer forbundet med IP. Målet med undersøkelsen var å skaffe informasjon om utviklingen av reduksjon av synsfunksjon ved IP. Elektroretinografi (ERG), multifokal elektroretiografi (mfERG), visuelt fremkalte potensial (VEP), ultralyd og OCT ble utført jevnlig fra pasienten var 9 år gammel til hun hadde fylt 26 år (2003 til 2020). Fra 9 års alder og frem til hun var 22 år var det kun små oftalmoskopiske endringer og varierende grad av unormale ERG funn i det venstre øyet. Det var først i 22–23 års alder at pasienten utviklet subjektive symptomer, og deretter fulgte i løpet av kort tid fullstendig synstap i det venstre øyet. Det høyre øyet forble klinisk asymptomatisk gjennom hele observasjonsperioden. Moren forble også asymptomatisk, men tilsvarende varierende grad av unormale ERG funn ble observert. ERG er en nøyaktig indikator når det gjelder okulær immunrespons eller betennelsesreaksjon ved IP, og registrerer effekten av endringer av synsfunksjonen uten at pasienten rapporterer symptomer. ERG anbefales derfor, ikke bare for langtids oppfølging av disse pasientene, men også for tidlig IP-spesifikk screening. ERG resultatene fra denne casen indikerer at den karakteriske asymmetriske effekten på retinal funksjon kan spores tilbake til hvilken grad hvert øye ble påvirket ved gjentatte reaktiveringer av sykdommen.

Nøkkelord: incontinentia pigmenti, retina, visuell elektrofysiologi, OCT, ultralyd.

Introduction

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is an X-linked, dominantly inherited multi-system disease affecting mostly females. Its estimated prevalence is 0.0025% (Swinney et al., 2015). It is a disorder causing dermatological, dental, ocular and neurological alterations. The diagnosis can be made by either histopathologic examination of skin biopsies or by genetic analysis of X-chromosome mutations. Deletions comprising exons 4-10 of *IKBKG*/NEMO gene in Xq28 locus can be found in 80-90% of IP probands (Berlin et al., 2002; Chen et al., 2015; Smahi et al., 2000). The skin lesions are usually the first to appear, days or weeks after birth (Goldberg & Custis, 1993). IP is best characterized as an autoimmune disease (Bruckner, 2004; Piccoli et al., 2012).

Ocular abnormalities, such as strabismus, corneal opacification, cataract and/or vascular retinopathy with epiretinal membrane formation may occur (Holmstrom & Thoren, 2000; O'Doherty et al., 2011). Subsequent retinal detachment develops generally in early childhood. The excessive neovascularization of the retina and the vitreous can cause fibrosis manifesting as pseudoglioma (Brown, 1988). The process has a very poor prognosis, it often leads to total blindness (Wald et al., 1993). Severe visual deterioration has been reported in 35–77% percent of the cases (Holmstrom & Thoren, 2000; Swinney et al., 2015). Only a few publications have reported late retinal involvement (Cates et al., 2003; Chen et al., 2015).

No therapy is known to prevent blindness as a sequela of IP. There is some evidence to indicate that cryotherapy or laser therapy may be helpful (Jandeck et al., 2004; Rahi & Hungerford, 1990). Contrary to this, peripheral nonperfusion and neovascularization often remain stable showing spontaneous regression over time without treatment (Cates et al., 2003; Chen et al., 2015). Fluorescein angiography (FLAG) was suggested for early detection of the vascular abnormalities of the peripheral part of the retina associated with IP (Goldberg, 1994). Later, for the detection of structural abnormalities and progression of retinal damage, spectral-domain optical coherence tomography

(OCT), in combination with FLAG were applied (Basilius et al., 2015; Chen et al., 2015; Liu et al., 2018; Mangalesh et al., 2017). Repetitive FLAG examinations in infants or very young children necessitate repetitive general anaesthesia and require a specialized examination team, which is usually not readily available. FLAG is also an invasive method; therefore, its use should be limited. It must be added here that in infants the progression of the retinal damage can be rather fast, with not enough time remaining to prevent blindness.

Changes in retinal and optic nerve function can be detected with electrophysiological tests after 2–3 years of age, without general anaesthesia. These tests are not invasive and are readily available; therefore, they are optimal for follow up of the retinal function in IP, even when the visual disturbance does not develop in infancy. Still, we found only one case report where ERG was utilized, in a 13-month-old girl, only on one occasion and under general anaesthesia (Ferreira et al., 1997). Here, we demonstrate the effectiveness of visual electrophysiological methods in the detection of changes in the functioning of the different retinal cells through the seventeen-year follow-up of an IP patient and her mother, an asymptomatic carrier of the same dysfunctional gene.

Methods

The protocol adhered to the tenets of the Declaration of Helsinki, with informed consent obtained from each participant or their legal guardians. Besides the routine ophthalmological examinations (refractometry, Snellen visual acuity, tonometry), Goldmann kinetic and static perimetry (Octopus 1-2-3 V10.17, greyscale), ultrasound and optical coherence tomography (OCT: Heidelberg Spectral, Heidelberg Engineering, Germany) were also performed. Ocular refraction was measured with a NIDEK 510A refractometer (Nidek, Japan). For the Snellen acuity measurements, the patient sat 5 metres from the chart. Retinal fundus photos, anterior segment images (TRC-50DX, Topcon, Tokyo, Japan), and ultrawide-field images (Optos California, Optos Inc., Marlborough, USA) were also taken.

For the electrophysiological tests, the Roland Instrument (Electrophysiological Diagnostic System, Wiesbaden, Germany) was used, according to the relevant ISCEV standards (Hood et al., 2012; Marmor et al., 2009; Marmor et al., 2003; McCulloch et al., 2015). Visual evoked potentials (VEP), pattern electroretinograms (PERG), standard electroretinograms (ERG), and electrooculograms (EOG) were recorded with the Reti-port system. Multifocal electroretinograms (mfERGs) were recorded with the Reti-scan system. VEPs were evoked with 60′ and 15′ reversing black and white checkerboard pattern stimulation, while for PERG, 40′ check-size was used. The refraction was corrected to the distance from the monitor. For the mfERG recordings, pupil dilation was used, both in the monocular and binocular conditions. Before testing standard ERG, the patient's pupils were also fully dilated (≈7.9 mm). For pupil dilation, 0.5% Tropicamide eye drops (ATC: SO1FA06) were applied three times over 90 minutes (one drop at a time, the last drop at the beginning of dark adaptation). For dark adaptation, the patient was kept in a totally darkened room for 30 minutes. ERGs were recorded with DTL (Dawson-Trick-Litzkow) electrodes (Dawson et al., 1979). During the stimulation, the patient fixated on a red point in the centre of the Ganzfeld stimulator. Electrophysiological testing usually lasted 2 to 3 hours (with breaks between the tests).

Case presentation

Initial presentation

A 9-year-old girl was referred to our laboratory for electrophysiological examinations in 2003 with the preliminary diagnosis of inveterate chorioretinitis. As she had no previous complaints of visual disturbance, ophthalmological examination was performed only because of mild strabismus of her left eye. In this eye, a central retinal vascular abnormality was found. In the temporal periphery of the retina, pigment clumps were detected without abnormal vessels (see Figure 1).

Figure 1: *Fundus photograph of the left eye at the age of 9. Note the dragged optic disc and some mild pigment clumps in the upper temporal, peripheral part of the retina.*

The patient's history revealed erythematous, vesicular skin lesions some days after birth, which were resistant to antibiotic treatment. This was the first occasion when the possibility of IP emerged. Later she exhibited several characteristic systemic symptoms, including delayed tooth eruption, patchy hair loss, and hearing loss. Subsequent genetic testing confirmed the diagnosis: *IKBKG*/NEMO: Xq28, NM_001099856, nonsense mutation of the pathogenic c.388C>T, p.Arg130Ter (rs137853323) in heterozygous formation was identified in the patient and in her mother, too.

The ophthalmological status at this time was as follows: the left eye had mild exo-deviation (8Δ). The axial length of both eyes the eyes was 24 mm. There was only mild astigmatism (RE +0.5DC at 180°, LE +0.75DC at 10°). The Snellen acuity was 1.0 on the right eye and 0.8 on the left eye (without correction).

Ophthalmoscopy of the left eye revealed a dragged optic disc, from which abnormal vessels ran towards the macular area. The picture resembled retinopathy of prematurity, but the patient was not born prematurely. Some smaller pigment clumps were found in the upper temporal peripheral part of the retina without visible abnormal vessels. The retina of the right eye was free of abnormalities. The visual acuity of the left eye improved to 0.9–1.0 after one year of orthoptic treatment. Kinetic perimetry showed normal isoptres on the right eye, while the isoptres were mildly narrowed on the left side, corresponding to the mild peripheral pigment defect.

As the patient cooperated well, it was possible to test the retinal and optic nerve function with standard electrophysiological methods. The results were compared to our laboratory controls (see Figure 2) and the responses from the two eyes were also compared. The patient's dark-adapted 0.01 ERG (rod response) and the dark-adapted 3.0 ERG (combined rod-cone response) showed extreme side differences. The amplitudes of the responses from the right eye were subnormal, while the waveform was normal. On the left eye, where the central retinal vascular abnormality was found, the responses were supernormal, and the 'b' wave of the left eye's response continued in an abnormal elevation, instead of slowly returning to the baseline, as seen in healthy recordings. We examined the possibility of an artefact, but we ruled it out, as the resistance of the electrode was below 5 kOhm, the patient cooperated well (no muscle artefact), and the phenomenon was detected in the left eye only (see Figure 3A).

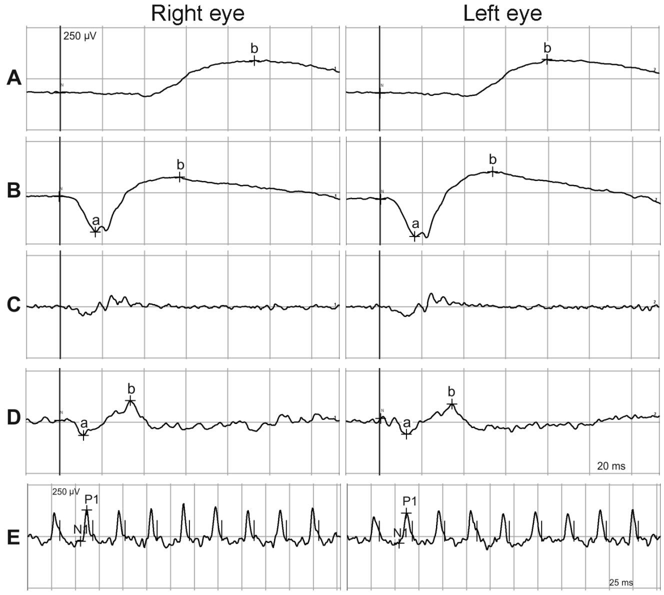

Figure 2: *Standard ERGs from an 18-year-old control patient from the reference pool of our laboratory, recorded according to ISCEV standards. Note the similarity between the two eyes. 'a' and 'b' indicate the two main wave components. A: dark-adapted 0.01 ERG; B: dark-adapted 3.0 ERG; C: dark-adapted oscillatory potentials; D: light-adapted 3.0 ERG; E: light-adapted 30 Hz flicker ERG. For relevant laboratory normal values see Table 1.*

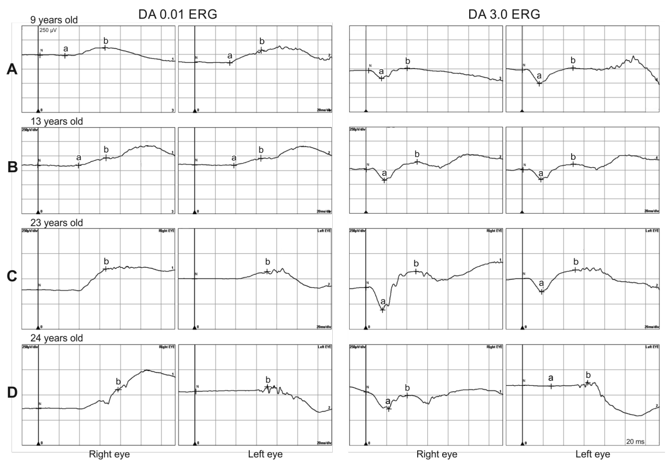

Figure 3: *Electroretinography at different time points during the follow-up: dark-adapted 0.01 and dark-adapted 3.0 ERGs recorded at (A) 9 years of age (2003), (B) 13 years of age (2007), (C) 23 years of age (2017) and (D) 24 years age (2018). 'a' and 'b' indicate the two main wave components. Note the marked difference between the eyes, the changing amplitudes and the late, high-amplitude positive deflection that gradually turns into a deep negative deflection.*

The oscillatory potentials (OP), the photopic ERG and the flicker responses were normal in both eyes without waveform alterations or differences between the eyes. PERG was normal in both eyes. As for VEP, the P100 peak times of the VEPs were normal in the right eye. The waveform of the left eye's response was bifid and only mildly subnormal.

The 4-year follow-up

The next electrophysiological follow-up took place four years later (2007), at the patient's age of 13. The reason for this long interval was that the patient had no visual complaints. Visual acuity was 1.0 for the right eye and 0.8 for the left eye, without correction. The extreme side difference of the dark-adapted 0.01 and 3.0 ERGs described 4 years previous had disappeared by this time. However, the elevation anomaly of the 'b' wave remained (see Figure 3B), what is more, it was now observable in both eyes, which was a further piece of evidence against this anomaly being an artefact. The oscillatory potentials (OP), the light-adapted 3.0 ERG (cone response) and the flicker responses were mildly, but not significantly, subnormal on both sides. Because of the central retinal alterations and mild strabismus of the left eye, we recorded mfERG with both monocular and binocular stimulation. The mfERG was normal in both eyes, without side differences (see Figure 4A). This result proved that there was no hypoplasia or other structural damage in the macula, despite the characteristic ophthalmoscopic picture of the left retina.

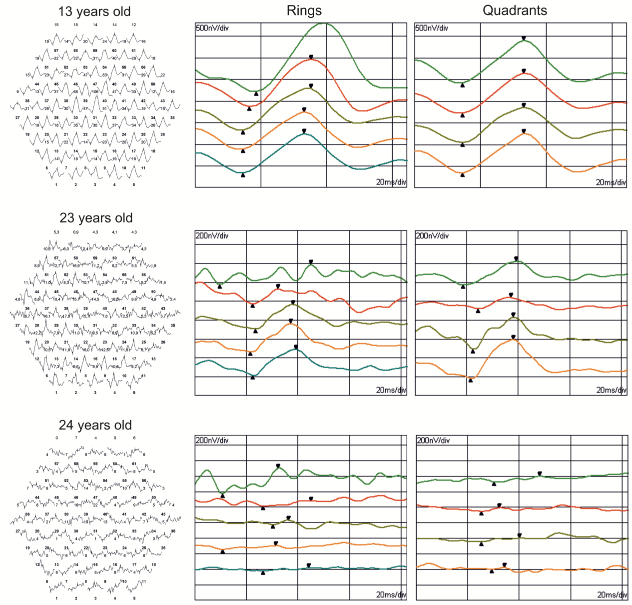

Figure 4: *Changes of mfERGs recorded from the left eye. Left side: the trace arrays, middle: ring analysis, right side: quadrant analysis. Top: 13 years of age, normal status; Middle: 23 years of age, severe functional loss in the 1st and 2nd rings and in the 2nd quadrant. Bottom: 24 years of age, nine months after the successful cataract and epiretinal membrane surgery. The central 30 degrees of the retina are almost completely unresponsive.*

The 6-year follow-up

Two years later, in 2009, another follow-up examination took place. At that time the ophthalmological examination revealed some proliferative membrane spreading towards the periphery from the disc. Surgical therapy was not indicated because the abnormalities were confined to the central part of the retina (thus photocoagulation or cryotherapy were no options either), and the visual acuity was also satisfactory (0.6). The electrophysiological parameters did not show any remarkable change as compared to the status 2 years previous, so they are not discussed in detail.

The 14-year follow-up

The patient's vision in her left eye started to deteriorate rapidly due to cataract formation when she was 22, and by the age of 23, it had dropped to 0.2. We saw her again because of this complaint in October 2017. Both ERG and mfERG indicated the progression of the functional disturbances (see Figures 3C and 4B). Behind the cataract, the ultrasound examination showed sheet-like echo sources that spread from the optic disc towards the nasal and temporal peripheral parts of the retina (see Figure 5A). The anatomical alterations were also observable in the OCT scans (see Figures 6A and 6B). See also Figure 8A for an anterior segment image.

Due to further progression of the cataract, the visual acuity dropped to 0.04 by February 2018 (see Figure 6A). Electrophysiological examinations were performed before surgery to objectively evaluate the possibility of visual improvement after surgery.

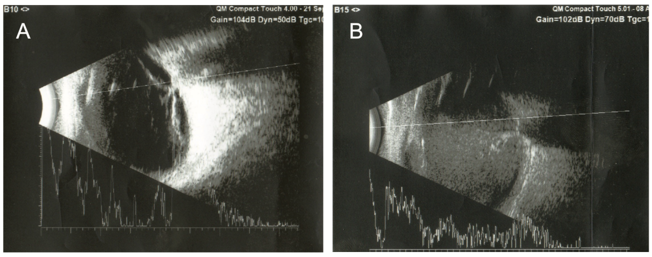

Figure 5: *Ultrasound images of the left eye of the patient. A: Before the cataract surgery (2017). Note the proliferative membranes under the cataract. B: Nine months after the surgery (2018): emulsified silicon oil and the recently formed proliferated membrane was detected.*

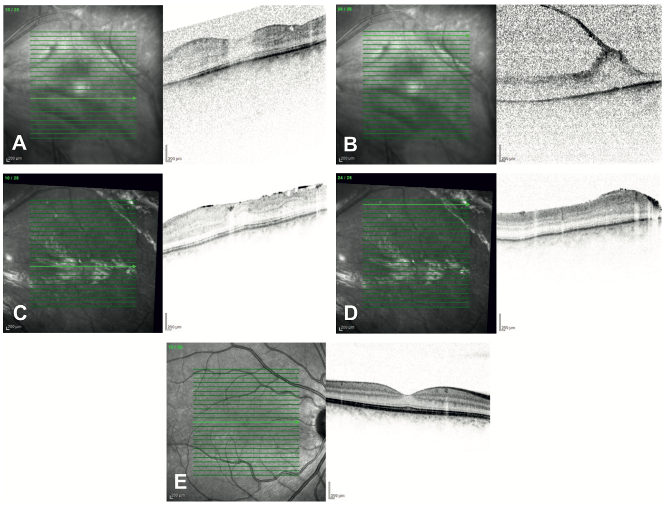

Figure 6: *SD-OCT images of the left eye before and after the cataract surgery. A: foveal section before the surgery. B: section in the zone of traction before the surgery. C: foveal section after the surgery. D: section at the same level as B after the surgery. E: image of the unaffected right eye.*

The amplitudes of both the 'a' and 'b' waves of the dark-adapted 3.0 ERG from the left eye were significantly attenuated (compared to the responses of the opposite eye), and this time the 'b' wave was not followed by a positive deflection but by a negative one (see Figure 3C), while the anomaly still showed as a positive deflection in the right eye. The peak time of the VEPs from the left eye was delayed (130–133 ms) and the amplitude of these responses was subnormal (6.68 μV).

Combined cataract extraction, vitrectomy (membrane peeling and silicon oil implantation), and peripheral laser coagulation were performed without complications. The removed membranes were sent for immunohistochemical analysis, which revealed a complex immunophenotype positivity for GFAP, vimentin, S-100, AE/*AE3*, and SMA to various extents (Janaky et al., 2020).

The visual acuity improved to 0.7 by the third day after the surgery. The macula was free from tractioning membranes previously seen on OCT scans (see Figures 6C and 6D). No visual loss or any retinal sign of IP developed in the right eye (see Figure 6E).

Six months after the surgery, the visual acuity of the left eye started to deteriorate again, and nine months after the surgery emulsification of the silicone oil was detected along with elevation of the retina (see Figure 7A). The patient was then 24 years old. The silicone was removed.

Six months after the repeated vitrectomy, the ultrasound showed a recently formed proliferative membrane and remnants of silicon oil or blood in the vitreous (see Figure 5B). Neovascularization of the iris developed, too. The capsule was thickened and the vitreous was hazy (see Figure 8B).

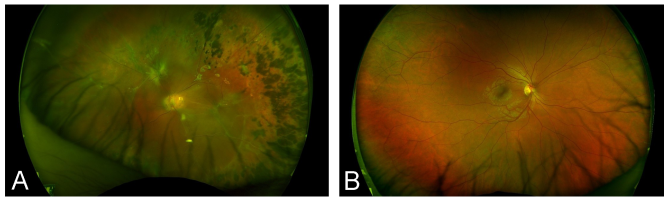

Figure 7: *A: ultrawide-field image of the left eye six months after the removal of the silicon oil. B: ultrawide-field image of the unaffected right eye.*

The electrophysiological examinations revealed severe functional loss of the left retina and optic nerve (see Figure 3D). Light perception was completely lost in this eye. The VEPs were extinguished. The EOG was extinguished, too (LP: DT ratio: 0.8), reflecting the severe functional loss of the retinal pigment epithelium. In the right eye, the dark-adapted 3.0 ERG was subnormal with a bizarre waveform (see Figure 3D). Despite the subnormal ERG, however, the patient had no complaint about vision in this eye and the visual acuity was 1.0. The mfERG and the EOG (LP: DT ratio: 2.5) recorded from the right eye were also normal.

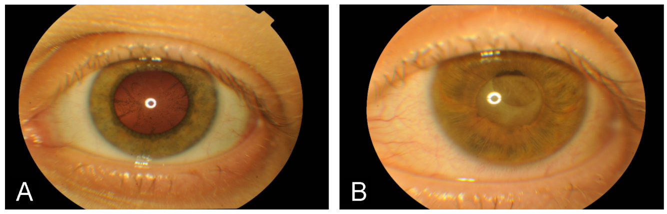

Figure 8: *A: anterior segment image of the left eye before the cataract surgery - the posterior subcapsular cataract prevents clear imaging of the retina. B: anterior segment image of the left eye six months after the removal of the silicon oil; iris neovascularization, capsular thickening and hazy vitreous.*

The 17-year follow-up

The last visit took place in February 2020. The right eye's electrophysiological parameters (VEP, PERG, ERG) were normal for the first time during the follow-up, while the left eye's responses were totally extinguished. Accordingly, the sight of the right eye was spared (acuity: 1.0), but the left eye was completely insensitive to light. Visual acuity and ERG values recorded during the follow-up are given in Table 1.

Table 1: *Visual acuity (VA) and ERG parameters during the follow-up.*

			DA 0.01 ERG				DA 3.0 ERG						
	eye	VA	b (ms)	b (μV)	diff (μV)	lc (μV)	a (ms)	a (μV)	diff (μV)	b (ms)	b (μV)	diff (μV)	lc (μV)
2003	R	1	67	142	-	-	16	164	-	40	205	-	-
	L	0.8	83	297	+155	+123	17	250	+86	50	250	+45	240
2007	R	1	68	125	+1	+205	18	205	-	50	369	+82	164
	L	0.9	70	124	-	+220	18	205	-	50	287	-	123
2017	R	1	68	205	+82	-	18	264	+100	50	400	+136	123
	L	0.2	69	123	-	–164	16	164	-	50	264	-	–164
2019	R	1	65	164	-	+164	24	205	-	38	123	-	-
	L	-	-	-	-	–287	-	-	-	-	-	-	–327
LN		1	80.5 (±8.69)	237.3 (±93.65)	N/A	N/A	19.95 (±4.28)	201.02 (±75.97)	N/A	47.95 (±7.14)	341.55 (±88.34)	N/A	N/A

Note: R: right, L: left; 'a' and 'b' denote the corresponding wave components of the ERG. Peak times and amplitudes are shown for each component in milliseconds and microvolts, respectively. Difference between the amplitudes of the two eyes (diff) is given in microvolts (where applicable). The difference between the eyes is shown after the eye with the highest amplitude. Late component ('lc') values are given if a late wave component after the 'b' wave was detected at the given follow-up visit. The magnitude of the late deflection is given in microvolts and is marked as + (upward) or –(downward). LN: laboratory normal values. Laboratory normal values are given as mean ± SD.

A summary of the follow-up of the patient's mother

As the genetic analysis confirmed the presence of the mutant NEMO gene in the mother, we tested her retinal function, too. Two examinations were performed. The first one took place in 2003 (at the age of 32), and the second one in 2017 (at the age of 46). Typical skin problems at birth were not possible to confirm. She had no systemic manifestation of the disease. Her visual acuity was good (1.0 in both eyes without correction), and there were no ophthalmoscopic abnormalities of the retina. No visual field defect was detected either. The ERG recorded from her right eye was normal, but the responses of the left eye — tested both at 32 and 46 years of age — were subnormal. The amplitudes recorded from the left eye were approximately half of those recorded from the right eye on both occasions, indicating subclinical loss of retinal function. The mfERG, PERG, VEP, and EOG were normal in both eyes on both occasions.

Discussion

In the described case, the patient and her mother both had the mutant *IKBKG*/NEMO: Xq28, NM_001099856 gene, but systemic manifestations of IP developed only in the patient. It was one of those cases when clinical ocular involvement occurred only late in the course of the disease. From 9 to 22 years of age, a characteristic picture of spared vision with minimal unilateral ophthalmoscopic alterations and fluctuating ERG anomalies were observed. The right eye remained unaffected throughout the observation period, apart from minor electrophysiological alterations. It was only between the ages 22 and 23 that actual clinical manifestations appeared, but then complete loss of vision in the affected eye developed rapidly.

The initially detected extreme difference between the eyes, the constantly detectable but asymptomatic changes of electrical activity also in the unaffected right eye, the appearance of a late supernormal positive deflection, and progressively deteriorating ERG of the affected eye were probably the most characteristic findings. Besides, we observed a late, high-amplitude wave component that appeared as the continuation of the 'b' wave. It is difficult to explain with certainty what brought these changes about, but an intermittent reactivation of the autoimmune process is a probable explanation (Chen et al., 2015; Conte et al., 2014; Smahi et al., 2000). The phenomenon that IP may affect the two eyes to differing extents is known, but its background is uncertain. IP is a rare disease, and no study has ever focused on this aspect. In this specific case, the only meaningful difference in this context was the vascular anomaly in the left eye, which could have meant a higher autoimmune challenge to this eye, hence the different pattern of involvement. Extreme differences between the eyes and temporarily supernormal ERG due to retinal toxicity would not be an entirely new finding. It has been observed, for instance, in cases of mercury and lead poisoning (Tanabe et al., 1992; Tessier-Lavigne et al., 1985). In this sense, if we compare the electrophysiological responses of the left and right eyes at the different time-points during the follow-up, we can formulate a hypothesis regarding the temporal dynamics of retinal damage in this case.

As for the unaffected right, eye, the 'a' and 'b' waves were initially subnormal (with a pronounced attenuation of the 'b' wave) and without the characteristic late, high-amplitude anomalous component recorded from the left eye. This means that the corresponding cell types (predominantly rods and bipolar Müller cells) were affected at an early stage of the process (lower immunological challenge). At the patient's first presentation, this difference between the eyes was the most remarkable electrophysiological finding. The supernormal responses of the left eye probably reflect hyperexcitability due to the higher immunological challenge to this eye because of the vascular anomaly. Later during the follow-up, the 'a' and 'b' waves normalized, but the late anomaly also appeared in this eye. Regarding this late, high-amplitude anomaly of the ERG, we were in doubt for some time if it was an artefact or a unique finding. Finally, based on the characteristic pattern of appearance in time and after we have ruled out all possible sources of artefact, we concluded that this phenomenon was uniquely associated with the disease process. The bulk of this late segment of the ERG in humans, historically also known as the 'c' wave (Granit, 1933) is generated in the retinal pigment epithelium, and is usually of small amplitude or missing. Nilsson and Wrigstad (1997) pointed out that this segment can be a sensitive indicator of damage to the retinal pigment epithelium in hereditary diseases. Thus, we assume that this finding reflects the immunological challenge to the retinal pigment epithelium (RPE). Notably, the phenomenon appeared in the clinically unaffected eye later, so it seems that it took longer until signs of RPE involvement appeared. This might indicate a cumulative effect with gradual involvement of different cell types, which was masked in the left eye by the higher exposure to the immunological process (where the cumulative effect showed as destruction and function loss).

An even more intriguing finding is that by the time the patient completely lost her vision in the left eye (after ongoing deterioration evidenced by the recordings), the electrophysiological findings of her right eye became normal for the first time in her history. Long-term follow-up of IP patients suggests that the progress of the disease may halt spontaneously at any stage (Holmstrom & Thoren, 2000). It is impossible to tell at this point if this is what we are seeing, but the sudden normalization of the parameters (never seen previously during the follow-up) is suggestive of such a scenario. Naturally, this also presupposes that the eye-specific trigger had been localized in the left eye and was consumed up in the destructive process that culminated in the blindness of this eye. This complete recovery after 17 years suggests that in the right eye the process caused functional disturbance only, that is, the ERG findings did not indicate significant cell destruction.

As for the rapid worsening of the patient's vision after surgery, it was an unexpected complication, most probably related to the use of silicone oil. It is known that the emulsification of silicone oil might lead to complications. However, those typically include glaucoma and keratopathy (Miller et al., 2014). The immunogenic properties of silicone have also had much attention in the literature, especially in connection with breast implants (Cohen Tervaert et al., 2017). While the literature does not confirm that silicone causes immunologically mediated disease, it is obvious that the presence of silicone in the body means constant stimulation to the immune system, which has also been demonstrated in retinal detachment surgeries with silicone oil (Pastor et al., 2001). The number of observations is low, though. The most we can say about this finding at this point is that it was probably a case of unexplained visual loss following the removal of silicone oil (Moya et al., 2015; Oliveira-Ferreira et al., 2020) which may have been caused by the reactivation of the immune process. The markedly subnormal responses recorded from the right eye seem to support this point.

Finally, the results show that ERG is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it readily detects their functional effect even in the lack of clinical symptoms. Thus, we propose that children in whom IP is suspected, regardless of whether clinical symptoms are already present, should undergo electrophysiological testing for the early detection of ocular involvement.

Conclusions

Electroretinography is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it readily detects their functional effect even in the absence of clinical symptoms. Thus, it is recommendable not only for the long-term functional follow-up of these patients but probably also for early disease-specific screening. The ERG recordings from the presented case suggest that the asymmetric pattern of retinal functional involvement may be traced back to the different degrees to which the two eyes were exposed to the intermittent reactivations of the disease. Given the lack of long-term comprehensive follow-ups in IP, and especially ones that involve electrophysiological methods, it is impossible to tell at this point if these findings are entirely patient specific.

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