OCULOMOTOR DEFICITS IN CHILDREN ADOPTED FROM EASTERN EUROPE

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TITLE: Oculomotor deficits in children adopted from Eastern Europe

RUNNING TITLE: Oculomotor deficits in Eastern Europe adoptees

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ABSTRACT

Aim: We aim to assess oculomotor behaviour in children adopted from Eastern Europe, who are at high risk of maternal alcohol consumption.
Methods: This cross-sectional study included 29 adoptees and 29 age-matched controls. All of them underwent a complete ophthalmological examination. Oculomotor control, including fixation and saccadic performance, was assessed using a DIVE device, with eye tracking technology. Anthropometric and facial measurements were obtained from all the adopted children, to identify features of fetal alcohol spectrum disorders (FASD). Fixational and saccadic outcomes were compared between groups and the effect of adoption and FASD features quantified.
Results: Oculomotor performance was poorer in adopted children. They presented shorter (0.53 versus 1.43 milliseconds in the long task and 0.43 versus 0.82 in the short task) and more unstable fixations (with a bivariate contour ellipse area of 27.9 versus 11.6 degree^2 during the long task and 6.9 versus 1.3 degree^2 during the short task) and slower saccadic reactions (278 versus 197 milliseconds). Children with sentinel finding for FASD showed the worst oculomotor outcomes.
Conclusion: Children adopted from Eastern Europe present oculomotor deficits, affecting both fixation and saccadic skills. We highlight prenatal exposure to alcohol as the main cause for these deficits.

KEY NOTES

- Children adopted from Eastern Europe present poorer oculomotor control than age-matched peers, with larger saccadic reaction times.
- Adoptees show shorter and less stable fixations both in short and long fixational tasks.
- The presence of FASD features is related to less stable fixations in adopted children.

INTRODUCTION

Children adopted from Eastern Europe are at increased risk of neurodevelopmental, behavioural, social and emotional disorders. The reason underlying these deficits may be exposure to toxic substances such as alcohol, tobacco, or other drugs during pregnancy and high levels of deprivation before adoption (1). Although the prevalence of prenatal exposition to alcohol in these children is unknown, fetal alcohol spectrum disorders (FASD) may be as high as 52% (2,3).

Prenatal exposure to alcohol is the leading cause of intellectual and developmental disabilities in the Western World (4), and is completely preventable. While its consequences are wide-ranging, from minor to serious, deficits are lifelong. FASD is a heterogeneous term to describe the wide range of adverse effects associated with prenatal alcohol exposure (5). Under this umbrella several alcohol-related diagnoses are included: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome, alcohol-related birth defects, alcohol-related neurodevelopmental disorder and neurobehavioral disorder associated with prenatal alcohol exposure. FAS is the most severe clinical diagnosis, encompassing physical defects, cognitive, behavioural, emotional and adaptive functioning deficits.

As a result of alcohol effects on the developing brain, children with FASDs exhibit deficits in visual-spatial skills, executive functioning, motor function, attention, learning and memory, with impaired impulse control and problem-solving, as well as difficulties with abstract reasoning, auditory comprehension and pragmatic language use (6–8).

The study of oculomotor skills in children may provide insights into the underlying cognitive impairments in this disorder. Visual fixation is the ability to maintain gaze on a certain location, directing the image to the fovea, while saccades are high-velocity eye movements that quickly redirect the eye so that the image of an object is brought directly to the fovea. Steady visual fixation is a prerequisite for proper visual function. However, small fixational eye movements are necessary to overcome visual fading resulting from a stable image on the retina (9).

Visual fixation may be unstable not only in congenital or acquired ocular disorders (10), but also in certain neurological impairments interfering with oculomotor development (11,12). Oculomotor studies have been used to examine the associations between cognitive control and brain circuitry in several neurologic disorders, such as attention deficit/hyperactivity disorders, autism or schizophrenia (13). Oculomotor tasks are useful to investigate neural bases of impulse control without the bias of verbal, motor or learning skills. For this reason, performance on certain oculomotor tasks has been proposed as a unique model for investigating relationships between brain and behaviour (13). Recent evidence suggests that visual fixation in newborn infants may even predict long-term neurocognitive development, especially visual motor performance and visual function (14).

The aim of this study was to assess oculomotor control in children adopted from Eastern Europe and to investigate its correlation with clinical features of alcohol exposure during pregnancy.

METHODS

Participants

The study involved two cohorts of children, aged between 4 and 19 years. The first cohort included children from Eastern Europe legally adopted by Spanish families. We contacted them through the adoption agency in our city via a letter explaining our project and offering them the chance to participate. The second cohort was composed of healthy non-adopted children age-paired with the first group, with less than a year's age difference between pairs. They were recruited from healthy children visited in the Paediatric Ophthalmology Unit for visual screening or minor refractive disorders, healthy siblings of patients and family members of the employees of the Department of Ophthalmology. All the children with a diagnosis of genetic, metabolic or neurologic disorders were excluded from the study.

The study protocol was approved by the local ethics committee (Aragon Ethics Medical Research Committee) and written informed consent was obtained from the parents or guardians of each child. Children older than 12 years of age were required to give a written assent accepting their participation in the study. All procedures adhered to the tenets of the Declaration of Helsinki.

Examination

Ophthalmological assessment

All children underwent an ophthalmological assessment including best-corrected visual acuity, stereoacuity, ocular motility, refraction under cycloplegia and funduscopy assessment. Visual acuity was assessed monocularly with logMAR optotypes.

Anthropometric measurements

Anthropometric and facial measurements related to FASD diagnosis were obtained from all the adopted children. Height, weight, occipital frontal circumference (OFC) and facial features were recorded following the four-Digit Diagnostic Code (15). The four digits in the code reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: growth deficiency, FAS facial features, central nervous system structural and functional abnormalities and prenatal alcohol exposure. Each feature is ranked independently on a four-point Likert scale with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong presence of the FASD feature. The facial features measured were: palpebral fissure length (PFL), upper lip thickness and philtrum smoothness. Upper lip and philtrum were independently measured using the five-point pictorial Likert scale presented on the Lip Philtrum Guide 1 for Caucasians used in the four-digit Diagnostic Code. Since prenatal exposure to alcohol may rarely be confirmed, FAS diagnosis is made when meeting all the other three criteria.

Oculomotor control examination

Fixation and saccadic assessments were performed in a quiet room under mesopic illumination. Children were positioned on a chair with no head immobilization at approximately 50 cm distance from the screen to ensure efficient tracking. They were asked to fixate the different targets on the screen, trying not to move their heads.

All the examinations were carried out using a prototype of Device for an Integral Visual Examination (DIVE), which includes a 12-inch screen of 2160 x 1440 pixels and an eye tracker positioned below the screen to record all eye movements during the test. The maximum temporal resolution of the eye tracking system is 60 Hz, with an accuracy of 0.5 degree and a spatial resolution under optimal conditions of 0.1 degree according to manufacturer’s data. Two operators, who had been given the same training in eye tracking with infants by the first author prior to the start of the study, performed the data recordings.

Prior to the fixation study, a calibration procedure of the eye tracker was performed according to the manufacturer´s guidelines using the software provided. The study included two different parts. The first part presented a long fixational task. It consisted of a high-contrast cartoon of a child of 3 degree x 1.56 degree appearing on the centre of the screen, who talked to the participant for 10 seconds. During the second part of the exam, short fixational tasks were presented. The fixation target consisted of a picture of a bee. Sixteen different visual stimuli were randomly displayed all over the screen with a fixed distance of 9.26 degree between every two consecutive stimuli. Each stimulus was presented for three seconds, with no stimuli overlap.

We identified fixations and saccades using a well-established dispersion-based algorithm (16). We calculated fixation stability by the bivariate contour ellipse area (BCEA), which quantifies the area in degrees squared ($degree^2$) of the ellipse containing a certain percentage of the fixation positions registered during the measurement procedure (17). Therefore, a smaller value for BCEA is indicative of greater fixation stability (Figure 1). The BCEA encompassing P=68.2% of fixation samples was calculated using the following equation:

$$BCEA = 2 * k * \pi * \sigma_x * \sigma_y * (1-p^2)^{1/2},$$

where σ_x is the standard deviation of horizontal eye position, σ_y is the standard deviation of vertical eye position, p is the Pearson product moment correlation coefficient of horizontal and vertical eye positions, and k is obtained from P, such that $P=1-e^{-k}$.

Saccadic performance was assessed by the saccadic reaction time (SRT), defined as the lapse of time between the presentation of the new stimulus and the initiation of the saccadic movement towards the stimulus.

Statistical analysis
All data were analysed using SPSS 21.0 statistical software (SPSS Inc. Chicago, Ilinois, USA). Descriptive characteristics and oculomotor outcomes were reported by the mean, standard deviation and ranges. Normal distribution of all the parameters analysed was assessed both by visual inspection of the distribution and using Shapiro-Wilk test, which is more appropriate for the sample size of the study. Visual function outcomes (i.e. visual acuity and refractive defect) significantly deviated from a normal distribution and Kruskal-Wallis test was used to compare them between groups. However, since all the oculomotor control parameters followed a normal distribution, performance in adopted and non-adopted children was compared using the Student's t-test. When adopted children were divided into two groups for further analysis, study groups were compared by means of analysis of the variance (ANOVA) with Bonferroni's multiple comparisons correction. Finally, multivariate analyses were performed including gender, age and sentinel findings for FASD as independent variables and oculomotor outcomes as dependent variables.

RESULTS
A total of 58 children were included in the study, 29 adoptees and 29 controls. Only one adopted child had to be excluded due to lack of cooperation for performing the oculomotor control test. Mean age was 12.07 ± 3.39 years in non-adopted children and 11.93 ± 3.31 years in adopted children. Differences were not statistically significant (p=0.873).

Facial features of all adopted children were measured, as well as anthropometric measurements were obtained. They had a mean weight centile of 26.72 (range 1-89) and a mean height centile of 30.83 (range 1-87). Mean occipital frontal circumference centile was 19.10 (range 1-85), with mean palpebral fissure length of -1.29, philtrum smoothness of 3.17 and upper lip thickness of 3.10, as measured following the four-Digit diagnostic code five-point pictorial Likert scale from Lip-Philtrum Guide 1 for Caucasians. We found sentinel findings for FASD in 14 adopted children (48.26%).

Although visual function was slightly worse in the adopted group, as shown in Table 1, differences were not statistically significant, except for visual acuity both in the right and the left eye. However, binocular visual acuity was normal (at least 0.1) in all the children, except for one adopted child, who had a visual acuity of 0.3 in logMAR scale.

Funduscopic exam was normal in all the children from the control group, while seven adopted children showed optic disc pallor and three optic hypoplasia.

As presented in Table 2, oculomotor control was poorer in adopted children, both in long fixation and short fixation tasks, with shorter and less stable visual fixations. When fixation was required for longer periods of time (10 seconds versus 3 seconds) adoptees presented more intrusive saccades, as shown by the number of fixations performed for every stimulus presented. Saccadic reaction times were also longer in adopted children.

Among the group of children adopted, those with sentinel findings for FASD presented the worst oculomotor performance. When the sample was divided into three groups, control group, non-FASD adoptees and FASD adoptees, a statistically significant tendency was found in all the fixational and saccadic outcomes, except for the duration of the longest fixation during the long fixational task and the number of fixations during the short fixational task. Most important outcomes are plotted in Figure 1.

Linear regression models adjusting for age, gender, visual acuity and refractive error showed that FASD diagnosis was related to BCEA both in short and long fixational tasks ($p=0.039$ and 0.014 respectively), while being adopted was only related to the duration of the longest fixation during the short fixational task ($p=0.046$) and none of the other oculomotor outcomes.

DISCUSSION

In this study, we explored oculomotor performance in children adopted from Eastern Europe. Adoptees demonstrated poorer oculomotor skills with more unstable fixations and slower saccadic reactions. We propose alcohol exposition during pregnancy as the main biological and environmental determinant, since sentinel findings for FASD are related to poor oculomotor performance.

Measurement of functional vision is complex. Although visual acuity can be accurately measured as the finest detectable visual stimulus, it does not always reflect visual functioning in daily life, especially in children with motor or cognitive difficulties (18,19). As an example of this challenge, all the children included in our study, except for one, had visual acuity within normal ranges, even those with unstable fixation.

Oculomotor skills are related to general neurodevelopment in children (20,21). Oculomotor tasks are easy to understand and perform by children of any age, without the bias of associated verbal, motor or learning disorders. Additionally, fixational behaviour and saccadic responses can be very precisely measured. The oculomotor system is therefore ideal for investigating the underlying relationships between brain and behaviour. It provides a unique model for the study of the neural bases of voluntary behaviour and inhibitory skills. Different cognitive processes may be investigated assessing oculomotor performance. While fixational tasks examine cognitive control and inhibitory skills, assessing the ability to maintain gaze on a visual stimulus, visually guided saccade tasks provide information regarding attention and global oculomotor control.

The oculomotor system involves several brain regions and networks including the superior colliculus, the frontal eye field, the posterior parietal cortex, supplementary eye fields, dorsolateral prefrontal cortex, basal ganglia, thalamus and cerebellum (22).

Oculomotor skills are among the most affected functions in many neurological disorders, both congenital and acquired (11,23). Children with perinatal brain damage present significantly more difficulties in visual fixation, saccades and smooth pursuit, than in basic visual functions, as visual acuity (24). Oculomotor behaviour provides useful information regarding brain functioning and general neurodevelopment. Furthermore, fixational and saccadic skills may even predict long-term neurodevelopment in neonates and young infants (14,25). Risk factors for brain damage, such as prematurity or low birth weight, seem to also be risk factors for impaired visual fixation, with an increasing risk the more severe the brain damage is (26).

Oculomotor studies have proven to be a useful tool in a wide range of cognitive and psychopathologic entities, such as autism, schizophrenia, attention deficit/hyperactivity disorders and several neurodegenerative diseases (27–29). School-aged children with autism spectrum disorder make shorter fixations with an increased number of saccades when viewing certain visual stimuli (27). Patients with attention deficit/hyperactivity disorders present a deficit in oculomotor control, related with a deficit in inhibitory control and in the recruitment of attention resources (30).

Children with FASD experience difficulties in daily life, both in school and out-of-school time. They frequently display deficits in overall intellectual performance, executive functioning, attention, visual-spatial abilities, planning, motor skills, learning and memory (6,31). However, FASD consequences are not always prominent enough to be detected by health care professionals and remain undiagnosed (7).

As far as oculomotor control, previous studies have already reported increased SRT and increased errors in saccades (32), similar to the delay we found in saccadic reactions. Recent studies demonstrated that eye movement control tasks directly relate to other psychometric outcomes and assess multiple cognitive domains in children diagnosed of FASD (21). Eye movement tasks have even been proposed as a screening or adjunct tool in the assessment of FASD (21). However, much less has been reported about fixational performance related to prenatal alcohol exposure.

Our findings confirm a deficit of inhibitor skills of the saccadic system in children adopted from Eastern Europe, with the prenatal exposition to alcohol as the most plausible cause. To the best of our knowledge, this is the first study reporting fixational deficits in adopted children, at high risk of maternal alcohol consumption, using an objective and quantitative assessment. Nevertheless, conclusions provided should be further confirmed with larger studies. The main limitation of our study was the lack of accurate perinatal information from adoptees, including potential consumption of other toxics during pregnancy, as well as the lack of neurologic and cognitive assessments in some of the included children. We encourage further studies including wider neurological exams to be performed.

CONCLUSION

In conclusion, our study provides insights regarding the difficulties faced by children adopted from Eastern Europe. They present poor oculomotor control, with unstable fixation and slower saccadic movements. Oculomotor deficits may negatively affect their ability to maintain gaze and attention on the selected target and to accurately move from one stimulus to another, interfering in most tasks of daily life, from reading to interacting with others. Furthermore, oculomotor skills can be trained and rehabilitated in some cases. Proper assessment of oculomotor skills in high-risk children, as adoptees from Eastern Europe, may help to understand underlying difficulties and to enhance rehabilitative strategies.

ABBREVIATIONS

BCEA, bivariate contour ellipse area
FAS, Fetal alcohol syndrome
FASD, fetal alcohol spectrum disorders
SRT, Saccadic reaction time

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CONFLICT OF INTEREST

VP, BM, DG and MO are co-founders of DIVE Medical Start-up.

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TABLES

Table 1. Comparison of visual function outcomes in adopted children and control group.

	NON-ADOPTED CHILDREN	ADOPTED CHILDREN	p
Visual acuity, right eye	-0.01 (0.06)	0.02 (0.06)	**0.019**
Visual acuity, left eye	-0.01 (0.15)	0.02 (0.07)	**0.002**
Refractive error, right eye (dioptres)	1.59 (2.32)	2.48 (3.48)	0.195
Refractive error, left eye (dioptres)	1.84 (2.71)	1.86 (3.87)	0.066
Stereoacuity (degree^2)	130 (145)	224 (227)	0.093
Strabismus (%)	3.45	20.69	0.051

Results are presented as mean (SD)

Table 2. Oculomotor performance from children examined.

	NON-ADOPTED CHILDREN	ADOPTED CHILDREN	p
Long fixation task			
Number of fixations	11.05 (4.22)	16 (8.08)	**0.009**
Mean duration of fixations	1.43 (1.44)	0.53 (0.40)	**0.015**
Longest fixation	3.88 (3.02)	2.11 (2.51)	**0.034**
Fixation stability (BCEA)	11.58 (9.69)	27.92 (38.41)	0.077
Short fixation task			
Number of fixations	3.21 (0.90)	3.52 (1.62)	0.379
Mean duration of fixations	0.82 (0.31)	0.43 (0.27)	**<0.001**
Longest fixation	1.72 (0.62)	0.83 (0.60)	**<0.001**
Fixation stability (BCEA)	1.31 (1.43)	6.91 (9.53)	**0.005**
Saccadic reaction time (SRT)	196.66 (65.08)	278.12 (71.42)	**<0.001**

Results are presented as mean (SD).

	NON-ADOPTED CHILDREN	ADOPTED CHILDREN	p
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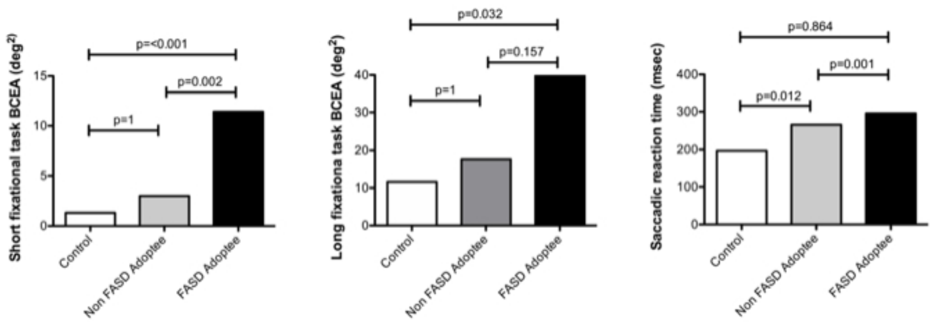

Figure 1. Barplots comparing oculomotor skills in control group and adoptees, divided by the presence of sentinel findings for FASD.

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