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Applicability of quantitative oculomotor and SARA assessment in children

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ABSTRACT

Background: In clinical practice, eye movements can provide an early diagnostic marker for early onset ataxia (EOA). However, quantitative oculomotor assessment is not included in the most frequently used and age-validated ataxia rating scale in children, the Scale for the Assessment and Rating of Ataxia (SARA). We aimed to investigate the applicability of semi-quantitative eye movement assessment by the International Cooperative Ataxia Rating Scale ($ICARS_{OCM}$) and Ocular Motion Score (OMS_{7-10}) complementary to SARA measurements in children.

Methods: In 52 typically developing children (aged 4–16 years; n = 4 per year of age), three independent assessors scored saccadic eye movements and ocular pursuit according to the $ICARS_{OCM}$ and matching parameters from the OMS_{7-10}. For $ICARS_{OCM}$, we determined 1) construct validity for coordinated eye movements by correlation with OMS_{7-10}, $ICARS_{EYE-HAND-COORDINATION}$ and SARA subscale scores, 2) agreement percentage and inter-rater agreement (Fleiss Kappa) and 3) age-dependency.

Results: Spearman's rank correlations of $ICARS_{OCM}$ with OMS_{7-10} and ICARS- and SARA subscales were moderate to fair (all $p < .001$). Inter-rater agreement of ICARS-$_{OCM}$ was 80.8%; (Fleiss Kappa: 0.411). $ICARS_{OCM}$ scores revealed a similar exponentially decreasing association with age as the other SARA (sub) scores, reaching a plateau at 10 years of age.

Interpretation: $ICARS_{OCM}$ has a valid construct for the measurement of coordinated eye movement performance and is reliably assessable in children. $ICARS_{OCM}$ reveals a similar age-dependent relationship as the other ataxia subscales, reflecting the physiological maturation of the cerebellum. In children, these data may implicate that $ICARS_{OCM}$ can reliably contribute to coordination assessment, complementary to the SARA subscales.

1. Introduction

Early Onset Ataxia (EOA) concerns a group of rare, heterogeneous genetic and metabolic disorders that reveal ataxia of cerebellar origin before the 25th year of life (prevalence 14.61 per 100 000 [1]). Ataxia involves motor incoordination of the voluntary muscles by underlying dysfunction within a complex cerebellar motor network including the basal ganglia, cerebral cortex and peripheral motor- and sensory pathways. In these patients, cerebellar output fails to properly anticipate direction, force and speed of intentional movements, resulting in ataxic features and motor patterns including dysdiadochokinesis, intention tremor, dysarthria, and oculomotor abnormalities such as dysmetria of saccades, gaze-evoked nystagmus and saccadic intrusions during ocular pursuit and fixation. In patients with EOA, the ataxic disease presentation is often mixed with other features of movement disorders, such as dystonia and myoclonus [2–4]. On some occasions, these comorbid features may be indicative of the underlying diagnosis. However, often these comorbid features can also contribute to the phenotypic heterogeneity and complicate the diagnostic process. Additionally, due to the development and maturation of the cerebellum throughout childhood [5,6],

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Abbreviations

$ICARS_{OCM}$ International Cooperative Ataxia Rating Scale, oculomotor subscale (regarding gaze-evoked nystagmus, saccades and ocular pursuit)
$ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$ the sum of the scores on the finger-to-finger test (left and right) and drawing Archimedes' spiral
EOA Early Onset Ataxia
$OMS_{7\text{-}10}$ Ocular Motion Score, items 7-10 (i.e. gaze-evoked nystagmus; saccadic intrusions during fixation, saccades and ocular pursuit)
SARA Scale for the Assessment and Rating of Ataxia

physiologically immature ataxia-like movement features can resemble symptoms of EOA [6,7]. As a consequence, the clinical phenotypic differentiation between EOA and other initiating developmental phenotypes is considered to be difficult and incomplete [8,9].

In clinical practice, eye movements have been shown to provide an early quantifiable and diagnostic marker for EOA disorders [10–12]. For instance, it is well known that patients with EOA may have slower and less accurate saccades than typically developing children [13]. Furthermore, specific eye movement features can point to the underlying diagnosis, such as Friedreich's ataxia and Niemann Pick disease type C [14,15]. Yet, semi-quantitative oculomotor parameters are not included in the most frequently used and age-validated ataxia rating scale in children, the Scale for the Assessment and Rating of Ataxia (SARA).

The SARA is used to quantify ataxia severity [16,17]. The SARA is an eight-item, 40-point scale, originally developed in adults with neurodegenerative adult onset ataxia (AOA) by deriving it from a more detailed (19-item, 100-point) ataxia rating scale, the International Cooperative Ataxia Rating Scale (ICARS) [17,18]. Especially in children with a short attention span, the adapted and shorter version (SARA) is considered to be more suitable for clinical use than the ICARS. However, a potential downside is that, in contrast with ICARS, quantitative oculomotor parameters are not included in the SARA. During SARA development, oculomotor parameters were deliberately omitted from the scale. The underlying reason was that the scale was initially designed in adult ataxic patients with neurodegenerative disease progression (AOA), in whom inter-rater agreement on the oculomotor scores was low. In AOA patients, this was attributed to potential extra-cerebellar neuro-degenerative influences on eye movements [16]. However, in young children with non-degenerative EOA, this influence could be expected to be smaller. Furthermore, any influence on coordinative eye movements could theoretically influence the other SARA scores as well, such as for instance the SARA nose-finger test (involving eye-hand coordination). In previous studies, we have shown that all SARA parameters are, to some extent, influenced by several other extra-cerebellar factors (including for instance age related maturation of the central nervous system and muscle weakness) [4,19,20]. Nevertheless, we have shown that the SARA still provides a reliable instrument for quantitative ataxia assessment in EOA patients, as long as (inevitable) potentially confounding factors are taken into account [8]. In this perspective, we reasoned that the measurements of semi-quantitative eye movements could make a worthwhile contribution in children. Especially during advanced EOA disease stages, we have previously shown that severe comorbid muscle weakness can seriously hamper the quantification of ataxia progression [19,20]. Under these circumstances, coordinated oculomotor parameters could still be quantifiable, enabling continued ataxia measurements from the initial to the advanced disease stages. Especially for the evaluation of innovative therapeutic strategies in rare EOA disorders, such information could make an important contribution [19,20]. In perspective of the above, we hypothesized that insight in the applicability of quantitative cerebellar oculomotor parameters could contribute to the quantification of ataxia, allowing longitudinal ataxia measurement during all stages of EOA disease progression.

In order to achieve our goal to interpret oculomotor scores in developing and ataxic children, data in typically developing children would be needed, first. In the present study on the applicability of cerebellar oculomotor assessment in children, we aimed to determine the validity, reliability, and age-dependency of coordinated eye movements in typically developing children. For this purpose, we addressed the quantification of saccades and ocular pursuit, separately. Saccades concern fast eye movements between fixation points, whereas continuous ocular pursuit allows us to keep a (moving) target on the fovea without moving our head. The saccadic initiation of horizontal saccades and pursuit movements is generated by the contralateral frontal eye field, whereas continuous pursuit is generated by the ipsilateral parietal-occipital region [21,22]. Depending on the motor task, all parts of the cerebellum are involved in eye movements [23]. In accordance with a simplified cerebellar model, the vestibulo-cerebellum is especially involved in maintaining good posture (scored by $SARA_{GAIT/POSTURE}$), and coordinating eye movements (saccades and smooth pursuit). The spino-cerebellum is especially involved in coordinating kinetic movements, including hand-eye coordination (scored by $SARA_{KINETIC}$). Finally, the cerebro-cerebellum is especially involved in motor learning, and also in the coordination of eye movements supporting motor learning tasks [24]. From a phylogenetic point of view, the vestibulo-cerebellum develops earlier than the spino-cerebellum and cerebro-cerebellum [25]. In this perspective, one would hypothesize that paediatric eye movements involved in postural control might develop before those involved in eye-hand coordination.

In developing children, we thus aimed to investigate the applicability and additional contribution of oculomotor parameters ($ICARS_{OCM}$) to quantitative coordination assessment by the SARA. In order to contribute, we would expect that $ICARS_{OCM}$ scores should specifically reveal construct validity for eye movement coordination (represented by Ocular Motion Scores (OMS)) and also for motor coordination including SARA- and ICARS (gait/posture, hand-eye coordination). Furthermore, we would expect that $ICARS_{OCM}$ inter-rater agreement would be comparable to that of other SARA (sub)score parameters. Finally, in typically developing children, we would expect that oculomotor scores would follow a similar developmental pattern as the other ataxia rating scale parameters measuring coordination.

2. Methods

2.1. Participants

We included 52 typically developing children between 4 and 16 years of age (two males and two females per year of age). Exclusion criteria were: neurological or skeletal disorders that could interfere with coordination, a positive Gower's manoeuvre, the use of medication that could theoretically interfere with coordination performance, and the inability to follow regular education at primary schools. Children with attention deficit hyperactivity disorder or attention deficit disorder were not excluded. In included children, we assessed $ICARS_{OCM}$ and OMS scores from videotaped ICARS and SARA performances (data collected by Brandsma et al.)

[6]. This study was approved by the medical ethical committee of the University Medical Center Groningen (UMCG, the Netherlands) and was executed in accordance with the Declaration of Helsinki (2008). All parents/caretakers and children older than 12 years of age gave informed consent, children younger than 12 years of age provided informed assent.

2.2. Assessment

Videotaped oculomotor performances were performed in a horizontal plane and scored off-line. During the test performances, the videorecorder was in front of the child, zoomed in and focused on the eyes. An overview of all tested oculomotor performances, ($ICARS_{OCM}$ $OMS_{7\text{-}10}$) [18,26], including the official test and scoring instructions is provided in Supplementary Table I. Three investigators, including two paediatric neurologists and one researcher, independently assessed the video fragments strictly according to ICARS and OMS guidelines. When videotaped performances did not fulfil the defined requirements for a score, the score was rounded off to the next (less favourable, higher) score that was still fulfilled. For compatibility reasons with the study data by Brandsma et al. [6], we determined the mean scores of each performance per child.

The ICARS is a 19-item, 100-point rating scale for the assessment of cerebellar ataxia, measuring gait/posture, eye movements, kinetic function and speech [18]. The $ICARS_{OCM}$ subscale is a 6-point rating subscale focussing on horizontal eye movements for the assessment of gaze-evoked nystagmus ($ICARS_{OCM\text{-}GAZE\text{-}EVOKED\text{-}NYSTAGMUS}$), abnormalities of ocular pursuit ($ICARS_{OCM\text{-}PURSUIT}$), and dysmetria of saccades ($ICARS_{OCM\text{-}SACCADE}$). For further information, see Supplementary Table I.

The OMS is a rating scale exclusively designed for the measurement of oculomotor function [26,27]. For the current study, we assessed all coordinative oculomotor parameters from the OMS, including items 7, 8, 9 and 10 (involving fixation (in)stability and gaze-evoked nystagmus, saccades and ocular pursuit). The summed score from these items is denominated as $OMS_{7\text{-}10}$. For further information, see Supplementary Table I.

In the same 52 children, we assessed the oculomotor data ($ICARS_{OCM}$ and OMS scores) and compared outcomes with previously obtained ICARS and SARA sub-scores for the measurement of posture and kinetic function [6]. This included ICARS hand-eye coordination (the finger-to-finger and Archimedes scores; referred to as $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$), SARA gait/posture and SARA kinetic parameters (referred to as $SARA_{GAIT/POSTURE}$ and $SARA_{KINETIC}$ subscores, respectively).

2.3. Statistical analysis

To assess the construct validity of the $ICARS_{OCM}$, we determined (Spearman's) correlations between $ICARS_{OCM}$ and $OMS_{7\text{-}10}$ (measuring the construct of OCM coordination) and we determined correlations between $ICARS_{OCM}$ and the other ICARS and SARA subscales (measuring the construct of motor coordination; including $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$, $SARA_{GAIT/POSTURE}$ and $SARA_{KINETIC}$). Correlations <0.10 were interpreted as poor; 0.10-0.60 as fair; 0.61-0.80 as moderate; 0.81-0.90 as very strong and 0.91–1.00 as perfect [28]. We assessed the inter-rater agreement of the $ICARS_{OCM}$ by Fleiss Kappa and agreement percentage. Fleiss Kappa <.20 was interpreted as slight; 0.21-0.40 as fair; 0.41-0.60 as moderate; 0.61-0.80 as good and >0.81 as very good [29]. In accordance with Brandsma et al. [6], we assessed age-dependency by fitting an exponential decay trend line to the $ICARS_{OCM}$ ($ICARS_{OCM\text{-}SACCADE}$ and $ICARS_{OCM\text{-}PURSUIT}$), and $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$ subscale scores. All statistical tests were two-sided and the significance level was set at alpha = .05.

3. Results

3.1. Construct validity

Correlation between $ICARS_{OCM}$ and $OMS_{7\text{-}10}$ was significant ($r_s = 0.654$; $p < .001$), interpreted as moderate. Correlation between $ICARS_{OCM}$ and $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$ was significant ($r_s = 0.539$; $p < .001$), interpreted as fair. The correlations between $ICARS_{OCM}$ and $SARA_{KINETIC}$ and between $ICARS_{OCM}$ and $SARA_{GAIT/POSTURE}$ were also significant and interpreted as fair ($r_s = 0.451$, $p = .001$ and rs = 0.353, $p = .010$, respectively).

3.2. Inter-rater agreement

The inter-rater agreement percentage between the three observers was 80.8%; Fleiss Kappa was moderate (0.411; 95% CI: .407 - 0.414, $p < .001$).

3.3. Age-dependency

An exponential decay trend line could be fitted to model $ICARS_{OCM}$ mean score per child as a function of age. $ICARS_{OCM}$ reached an observable plateau value at ≈10 years of age, $ICARS_{OCM\text{-}PURSUIT}$ at ≈13 years of age, $ICARS_{OCM\text{-}SACCADE}$ at ≈7 years of age and $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$ at ≈13 years of age (see Fig. 1a–d). In the absence of gaze-evoked nystagmus in typically developing children, $ICARS_{OCM\text{-}GAZE\text{-}EVOKED\text{-}NYSTAGMUS}$ scores were negligible.

4. Discussion

In typically developing children from 4 to 16 years of age, we investigated the construct validity, reliability and age dependency of oculomotor assessment by $ICARS_{OCM}$. In children, our results show that $ICARS_{OCM}$ reveals construct validity, acceptable inter-rater agreement and age-dependency, similar to other SARA-subscore tasks. These results may implicate that $ICARS_{OCM}$ can provide a suitable tool for measuring oculomotor coordination in addition to the SARA.

Our hypothesis was that $ICARS_{OCM}$ would reveal sufficient construct validity for the measurement of both coordinated eye movements (determined by $OMS_{7\text{-}10}$) and motor coordination, determined by $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$, $SARA_{GAIT/POSTURE}$ and $SARA_{KINETIC}$ subscores. In accordance with our hypothesis, correlation with $ICARS_{OCM}$ was significant for eye movements as well as for motor coordination, implicating that $ICARS_{OCM}$ is applicable for the intended test construct. As could be expected, the correlation between $ICARS_{OCM}$ and $OMS_{7\text{-}10}$ (measuring coordinated eye movements) was stronger than the correlation between $ICARS_{OCM}$ and $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$, $SARA_{GAIT/POSTURE}$, or $SARA_{KINETIC}$ (measuring motor coordination in general). This could be attributed to the fact that (in contrast with $ICARS_{OCM}$ and $OMS_{7\text{-}10}$), $ICARS_{EYE\text{-}HAND\text{-}COORDINATION}$, $SARA_{GAIT/POSTURE}$ and/or $SARA_{KINETIC}$ tasks involve visually guided coordinated motor performances of the limbs, as well. Interestingly, the correlation between $ICARS_{OCM}$ and $SARA_{GAIT/POSTURE}$ (attributed to the vestibulo-cerebellar domain) versus $ICARS_{OCM}$ and $SARA_{KINETIC}$ (attributed to the spino-cerebellar domain) was similar. This could be explained by the fact that $ICARS_{OCM}$ measuring saccades, nystagmus and over- or undershoot still requires accurate motor performance by both

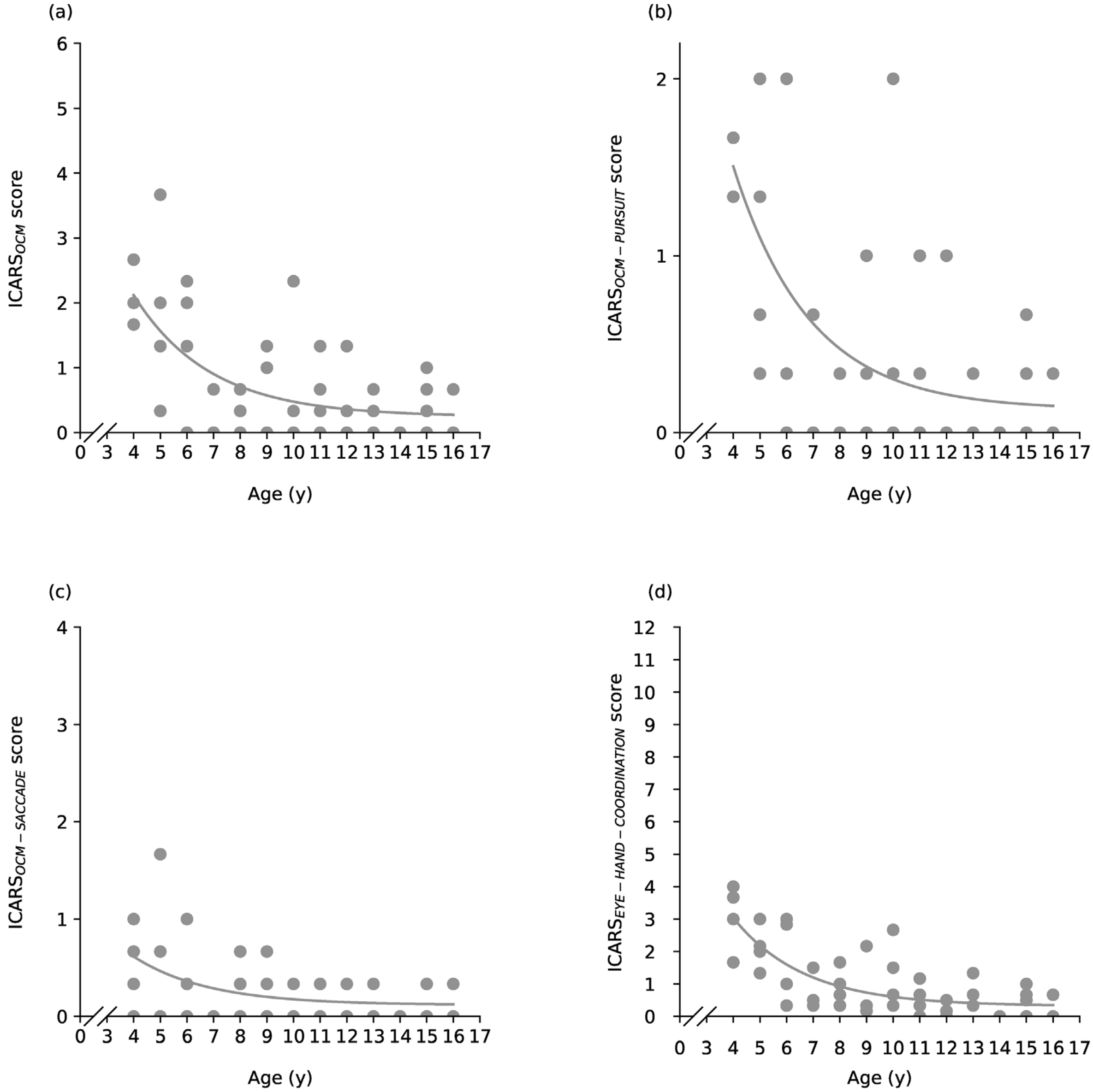

Fig. 1. Age-relationship of oculomotor scores in typically developing children from 4 to 16 years of age. Exponential decay trend lines were used to fit the data as a function of age. Values range from the minimum to the maximum score achievable on that coordination test. (a) ICARS$_{OCM}$, (b) ICARS$_{OCM-PURSUIT}$, (c) ICARS$_{OCM-SACCADE}$, and (d) ICARS$_{EYE-HAND-COORDINATION}$. All evaluated oculomotor scores revealed age-dependency. ICARS$_{OCM-SACCADE}$ parameters reached a plateau score at an earlier age than ICARS$_{OCM-PURSUIT}$ scores.
ICARS$_{OCM}$: score of the International Cooperative Ataxia Rating Scale's oculomotor subscale (regarding gaze-evoked nystagmus, ocular pursuit, and dysmetria of the saccade; referring to items 17, 18 and 19 of the official ICARS score-sheet). The ICARS$_{OCM}$ is depicted as mean score by three assessors.
ICARS$_{OCM-PURSUIT}$: ICARS$_{OCM}$ parameter for ocular pursuit; referring to item 18 of the official ICARS score-sheet. The ICARS$_{OCM-PURSUIT}$ is depicted as mean score by three assessors.
ICARS$_{OCM-SACCADE}$: ICARS$_{OCM}$ parameter of saccadic eye movement; referring to items 17 and 19 of the of the official ICARS score-sheet. The ICARS$_{OCM-SACCADE}$ is depicted as mean score by three assessors.
ICARS$_{EYE-HAND-COORDINATION}$: summed ICARS scores from the Archimedes' spiral and the finger-to-finger test performances. The ICARS$_{EYE-HAND-COORDINATION}$ is depicted as mean score by three assessors.

cerebellar domains [23]. Altogether, in perspective of the reliable test construct for coordinated eye movements, one may deduce that ICARS$_{OCM}$ could provide a useful tool for measuring oculomotor coordination in children.

The ICARS$_{OCM}$ agreement percentage of ≈80% and the moderate, but significant Fleiss Kappa (interpreted as acceptable), was in line with previously reported moderate inter-rater agreement data on other SARA subscale scores (including subscores for SARA speech.) [6,30] Given its construct validity and sufficiently significant inter-rater agreement, we deduce that paediatric oculomotor assessment by ICARS$_{OCM}$ can be reliably used as complementary information to the SARA. Analogous to previously reported age-dependency of ICARS and SARA parameters [6], we hypothesized that ICARS$_{OCM}$ scores would be age-dependent, in line with the maturation of the underlying cerebellar compartment. Accordingly, we observed that ICARS$_{OCM}$ scores reflected similar age-dependency to the other ataxia rating scale parameters [6]. In accordance with ICARS$_{POSTURE/GAIT}$[6], ICARS$_{OCM-SACCADE}$ reached a plateau at a relatively young age (at ≈7 years of age), whereas the ICARS$_{EYE-HAND-COORDINATION}$ and other kinetic ataxia rating scales have been shown to remain age dependent until ≈13 years of age [6]. It is tempting to speculate that this can be attributed to the maturation order of different cerebellar domains, i.e. the vestibulo-cerebellum before the spino-cerebellum [24]. Furthermore, we observed that $ICARS_{OCM-PURSUIT}$ scores reached a plateau at a later age than $ICARS_{OCM-SACCADE}$. These observations appear in line with the phylogenetic perspective that cerebellar control over saccadic eye movements is obtained at an earlier stage than ocular pursuit [25]. Although we cannot exclude an additional mathematical influence by the number of subdivisions per subscale on the scores, it is thus tempting to speculate that the complexity of the task influences the time at which flawless performance is obtained, reflecting maturation. Finally, we observed that the total $ICARS_{OCM}$ approximated its plateau in between those for $ICARS_{OCM-SACCADE}$ and $ICARS_{OCM-PURSUIT}$, which is attributed to the influence from both contributing subscores.

There are some limitations to this study. Firstly, vertical eye movements are not an official part of the $ICARS_{OCM}$ and were therefore not taken into account. As a result, the correlation with the OMS-item 'fixation in multiple gaze directions' (item 8) was assessed in the horizontal plane. However, in a typically developing cerebellum, one would expect the same results in the vertical plane. Secondly, in a group of typically developing children, subtle deviations in saccadic movement and ocular pursuit [26] may be more difficult to quantify than more pronounced deviations under pathological conditions. Furthermore, under pathological conditions, a broad range of scores will mathematically induce higher inter-rater agreement values [6]. If $ICARS_{OCM}$ would be used for what it was initially intended for, i.e. the quantification of coordinated oculomotor movements in EOA-patients, one could thus expect to obtain higher inter-rater agreement values than presented in this study.

In conclusion, according to the observed construct validity, reliability and age-dependency of $ICARS_{OCM}$, our data indicate that paediatric oculomotor assessment is applicable in addition to the SARA. Since oculomotor parameters may provide an a useful quantitative diagnostic marker to distinguish between ataxia and other coordination disorders and since oculomotor parameters can measure eye coordination from the early up to the advanced EOA stages, we conclude that the $ICARS_{OCM}$ subscale could be considered to be a useful and suitable tool for complementary measurement together with the SARA.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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