CHAPTER 9

Summary and General discussion
SUMMARY

Ataxia is characterized by the loss of smooth goal directed movements.\textsuperscript{1-4} The cerebellum and its networks are crucial for the fine tuning of smooth goal directed movements, and disruption in any of these pathways is likely to result in ataxia.\textsuperscript{1-4} Ataxia starting before the age of 25 years is referred to as Early Onset Ataxia (EOA)\textsuperscript{5-7} and comprises many different underlying etiologies.

EOA concerns a group of rare mostly metabolic or genetic disorders with an estimated prevalence of 14.6 per 100,000 individuals.\textsuperscript{8} The clinical presentation of EOA is heterogeneous with either a “core ataxic” phenotype (in which ataxia is the dominant movement disorder) or a “combined or comorbid ataxic” phenotype (in which other movement disorder features are dominant or even prevail over the ataxia). This may hamper uniform recognition and phenotypic assessment of ataxia.\textsuperscript{9,10} The assessment of EOA is also hampered by concurrence of normal, immature motor coordination which can resemble ataxic features.\textsuperscript{11} Both the phenotypic heterogeneity and the occurrence of immature motor behavior makes the assessment of children with EOA challenging.

For adequate surveillance of the severity of ataxia, different rating scales are applicable for children. The most frequently used are the “International Cooperative Ataxia Rating Scale” (ICARS),\textsuperscript{12} the “Scale for Assessment and Rating of Ataxia” (SARA)\textsuperscript{13} and the “Brief Ataxia Rating Scale” (BARS).\textsuperscript{14} These scales were found to be reliable biomarkers in adults, in whom it was indicated that the scales are only influenced by the severity of ataxia.\textsuperscript{12-16} In children however, the reliability of ataxia rating scales have never been tested before. We hypothesize that determining the pediatric reliability could elucidate whether comorbid features and immature motor behavior in children could influence ataxia rating scale scores.

The main aim of the thesis is to determine the reliability of diagnostic tools for EOA patients. The first part (chapters 2-6) focuses on the reliability of quantitative ataxia rating scales. The second part describes the neurologic evaluation of the phenotypic characterization of EOA patients (chapter 7) and provides a diagnostic algorithm to elucidate the underlying etiology in EOA patients (chapter 8).

In chapter 2, a comparative pilot study of ataxia rating scales is presented, performed in 52 typically developing children. Outcomes reveal high reliability of all tested ataxia rating scales with an Intraclass Correlation Coefficient (ICC) of 0.90 (95% CI 0.80 – 0.95) for inter-observer agreement. An important finding of this study is the age-dependency of the rating scale scores. Younger healthy children reveal physiologically higher rating scale scores than older children. At about the age of 12 years, the developmental influence of age disappears and rating scale scores start to approximate adult values.

In chapter 3, we described a cross-sectional study on the speech sub-scale of the ICARS and SARA in 52 healthy children and 40 EOA patients. This study demonstrates age-dependency
of the speech sub-scale in healthy children but this effect appears small and negligible in EOA patients. To determine whether the speech sub-scale is feasible in an international study (with a potential language bias), we tested a syllable repetition task. Outcomes reveal comparable results for the official speech sub-scale and the syllable repetition task, implicating that language does not affect international rating scale studies.

In chapter 4, we undertook a large European multicenter study, including 156 children from nine different countries, to determine the reliability of the SARA in further extent. This study strongly confirms the pilot data obtained in a single center and provided normative reference values for the application of the SARA in typically developing children (four to sixteen years).

After determining the reliability of ataxia rating scales in healthy children, the reliability of the scales were also tested in EOA patients. In chapter 5 and chapter 6 we described the reliability, the convergent and discriminant validity of ataxia rating scales. In a cross-sectional study of 40 EOA patients, we showed high reliability of ataxia rating scales with inter- and intra-observer agreement ranging from 0.91 to 0.99 (Intraclass Correlation Coefficient). As age-dependent influence and the variability of the ataxia rating scale scores was higher in the youngest children (under 8 years), interpretation of these scores seems less reliable. Therefore, we investigated whether a surrogate marker with a smaller variability, such as the SARA sub-scale gait, could be used instead. The convergent validity, addressing the question whether the SARA sub-scale gait measures the same as other coordination scales, is high. Also, the SARA sub-scale gait is strongly correlated with total SARA scores (r = 0.935; p<0.001). Based on these findings, it is implicated that the SARA sub-scale gait may provide a tool for the quantitative estimation of ataxia severity in young EOA children (under 8 years of age). Although the reliability and convergent validity of ataxia rating scales was high, the discriminant validity of the ataxia rating scales (i.e. do they only measure the severity of ataxia) appeared low. This is attributed to the fact that ataxia rating scale scores were also influenced by comorbid movement disorder features such as dystonia, myoclonus, chorea, and muscle weakness.

In chapter 7, we presented a cross-sectional study in 40 EOA patients to determine phenotypic reliability. All video-taped patients were assessed by seven observers. The inter-observer agreement on phenotypic characterization appeared moderate with a Fleiss’ Kappa of 0.45 (95% CI: 0.38 – 0.51), reflecting the phenotypic difficulties in assessing combined movement disorder phenotypes in EOA children.

In chapter 8, we provided a clinical diagnostic algorithm focused on genetic testing after excluding acquired forms of EOA. The algorithm integrates clinical, neuroradiologic and genetic features to guide the clinician in the diagnostic work-up in EOA patients.
GENERAL DISCUSSION

Reliability of quantitative diagnostic measures of Early Onset Ataxia

The three most frequently used ataxia rating scales (ICARA, SARA, and BARS) are reliable biomarkers for the assessment of ataxia severity in adults. In adults, ataxia rating scales are indicated to be influenced only by the severity of ataxia. In the first part of the thesis, we showed that ataxia rating scales are also reliable biomarkers for the assessment of ataxia in children as well, with similar inter-observer agreement outcomes as in adults (0.91-0.99 versus 0.91-0.98, respectively). However, in children, age, comorbid movement disorder features and muscle weakness can also influence (and confound) ataxia rating scale scores. As a clear physiologic age-dependency on ataxia rating scale scores was present, one may derive that cerebellar development and maturation is expressed by immature motor coordination that resemble ataxic features. As these features fulfill the official rating scale criteria, they may theoretically induce “falsely positive” ataxia rating scale scores. To compensate for these influences, pediatric ataxia rating scale scores should include an age-correction, the highest in the youngest children as they reveal the strongest effect by immaturity. To date the SARA is the only ataxia rating scale in children which reliability is determined to full extent. However, the variability of total SARA scores was higher in the younger children, reflecting their larger range of normal neurodevelopment. In children aged 4 to 8 years, this may affect the interpretation of total SARA scores. Therefore, we evaluated whether the SARA sub-scale gait with less variation but a high correlation with total SARA scores could be used instead to estimate the ataxia severity in the youngest children. In the future, we hope to elucidate the application of the SARA sub-scale gait into further extent.

Interestingly, the timing of the optimum value of the SARA sub-scale gait and kinetic corresponded with the development of the vermis (for gait and axial stability at the age of 8 years) and cerebellar hemispheres (for kinetic motor functions at the age of 13 to 14 years).

In pediatric EOA, we also investigated the influence of other potentially confounding factors such as comorbid movement disorders and other (non)-neurological features. Ataxia rating scale scores, solely depended on the severity of the most prominent movement disorder. This is due to the fact that other hyperkinetic movement features can resemble ataxic features. For example, myoclonic jerks of an action myoclonus may fulfill the official rating scale criteria to induce a positive score. This implicates that comorbid features may also induce “falsely positive” ataxia rating scale scores.

Other neurological comorbidities, such as muscle weakness influences ataxia rating scale scores as well. The data in chapter 5, confirms previously obtained data in Friedreich ataxia patients, revealing a positive correlation between muscle weakness and ataxia rating scale scores. This is explained by the fact that sufficient muscle strength is needed to perform smooth goal directed movements. In paretic patients, the lack of muscle strength can enhance sloppiness which, again, may be interpreted as ataxia. Furthermore, it is important to realize
that severe muscle weakness can induce a maximal plateau score. For example, when severely paretic patients are unable to lift their legs against gravidity, the heel-shin slide test will be automatically quantified with the maximal score.

In addition to the described confounding factors one might anticipate that there are still other confounding factors such as a neuro(no)pathy. To date, there is no clinical study that separately evaluated the effect of a neuro(no)pathy on ataxia rating scales, although we would expect such a confounding effect as well.

To summarize, quantitative ataxia rating scales in pediatric EOA are reliable biomarkers for the assessment of ataxia. However, in contrast to application of rating scales in adults, application in children should also involve interpretation for age, concurrent movement disorders and muscle strength.

Reliability of phenotypic diagnostic measures of Early Onset Ataxia

EOA comprises a group of rare heterogeneous disorders not only regarding etiology but also with respect to the clinical phenotype. In children, comorbid hyperkinetic movement disorders, such as myoclonus, chorea or dystonia can even prevail over ataxia. This may be attributed to the propagation of a disturbed signal within the cerebellar networks, involving afferent connections from the subthalamic nucleus, whereas cerebellar output signals, through the thalamus and the cerebral cortex may affect the basal ganglia. Together with the frequent comorbidity of other (non)-neurological features and the early evolution of the disease, this may complicate the phenotypic characterization of EOA patients. This complexity was illustrated by the study results of chapter 7, revealing only moderate agreement by movement disorder specialists on the neurologic phenotypic assessment. This emphasizes the necessity to provide the clinician with supportive markers for uniform assessment. The SARA sub-scale gait could serve as such a supportive marker. If the relative contribution of the SARA sub-scale gait exceeds 30% of the total SARA score, the presence of ataxia as primary movement disorder becomes more likely. This implicates that early in the EOA disease course, the evaluation of gait is potentially helpful to discern between cerebellar ataxia and other (comorbid) movement disorders.

In therapeutic studies, ataxia rating scale outcomes are frequently used as primary endpoints. For adequate interpretation of the scores, it is advisory to identify potentially confounding factors and to determine the exact movement disorder phenotype, especially when small fluctuations in ataxia rating scale scores are regarded as therapeutic effects. This is illustrated by a recent study performed in a phenotypically heterogeneous group of ataxic patients treated with riluzole. The investigators eventually concluded that riluzole was effective for the treatment of ataxia, as the improvement of only 1 point on the SARA scores was regarded as effective. This study did not correct for the potentially confounding effects of the heterogeneous phenotype. Therefore we advise homogeneous patient inclusion (regarding age and phenotype) for therapeutic trials to elucidate the true effect on the tested intervention.
Diagnostic work-up

In perspective of the heterogeneity of EOA etiologies and the difficult phenotypic assessment, the diagnostic work-up may be difficult and time-consuming. New diagnostic algorithms for movement disorder assessment involve Next Generation Sequencing (NGS) techniques.\textsuperscript{30,31} NGS techniques enable the sequencing of multiple disease associated genes, instead of one at the time by traditional Sanger sequencing. In other heterogeneous disorders such as epilepsy, early onset dystonia and myoclonus, NGS techniques have resulted in higher diagnostic yield, lower costs and shorter diagnostic work-up.\textsuperscript{30-32} In collaboration with the Childhood Ataxia and Cerebellar Group of the European Pediatric Neurology Society (CACG-EPNS) we developed such a clinical diagnostic algorithm with emphasis on neuroradiology and genetic work-up. We hope that uniform approach will lead to a higher diagnostic yield, homogeneous data entry in international databases and to the identification of new ataxia associated genes in the future.

FUTURE PERSPECTIVES

Scales

In children younger than 4 years of age, determining the reliability of ataxia rating scales may be helpful. In perspective of the large variation of SARA total scores in children 4 to 8 years of age, the use of the SARA sub-scale gait may be preferable in younger children (<4 years of age). Furthermore, subsequent studies focusing on other confounding factors related to ataxia rating scales such as neuro(no)pathy may provide important insight in the pediatric construct of these instruments.

Diagnostic possibilities

As the new diagnostic algorithm has not been tested in children, a study regarding the diagnostic yield is important. A possible approach to determine the diagnostic yield of a NGS EOA panel is to use it in the evaluation of children. At the same time an independent group of ataxia experts should review the clinical history and neurological examination to form a diagnostic plan, consisting of neuroradiology, laboratory investigations and genetic testing.\textsuperscript{32} In such a way the diagnostic yield of the NGS EOA panel could be determined. Also the time taken to reach a diagnosis and the influences on healthcare related costs can be compared between both strategies.

Therapeutic options

To date there are no treatment options for degenerative ataxias. The use of invasive and non-invasive stimulation treatments are upcoming treatment modalities. In ataxic patients, non-invasive treatment techniques like Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are proven to be save and feasible and result in improvement of ataxic features. However, the use of TMS and tDCS were mostly performed in patients with
ataxia primarily caused by cerebrovascular disease.\textsuperscript{33-35} To clarify the effect of these techniques in degenerative ataxias a randomized placebo-controlled trial is needed. To date, Deep Brain Stimulation (DBS) is not an effective treatment for ataxic patients, but the technique may be applied as treatment for comorbid symptoms such as tremor or dystonia. Interestingly, in the DBS treated patients the ataxic symptoms improved as well,\textsuperscript{36-38} potentially due to the effect on basal ganglia-cerebellar networks. Further research is warranted to elucidate whether DBS provides an effective treatment option in pediatric ataxias, focusing on finding the best target for ataxia improvement.

In degenerative cerebellar ataxias the current treatment focuses on preservation of functional performance by physiotherapy. Recently, specific rehabilitation techniques with exercise videogaming (exergames) showed that ataxic symptoms may be ameliorated and that functional performance improved.\textsuperscript{39} In future research, the best type of exergame for each EOA phenotype must be identified. For instance, is the use of static or dynamic balance training sufficient or is kinetic training also necessary. Secondly, it is important to determine whether the training effect persists over time or that continuous training is required to sustain the effect. For exploration of the new therapeutic options, the implementation of the current knowledge on the ataxia rating scale data may hopefully provide a reliable basis for interpretation of the scales.

CONCLUSIONS

This thesis shows that quantitative diagnostic tools such as ataxia rating scales are applicable and reliable tools in children. However, for optimal interpretation of ataxia rating scale outcomes, the recognition of confounding factors such as age, comorbid movement disorders and other (non-)neurological features is crucial. Hopefully, these data may contribute to the surveillance of EOA disease progression and to reliable interpretation of future innovative treatment strategies for EOA patients.
REFERENCES


