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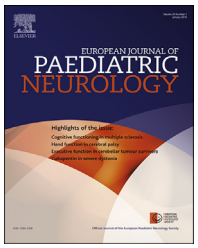

Original Article

Development of global rating instruments for pediatric patients with ataxia telangiectasia

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ABSTRACT

Introduction: Ataxia telangiectasia (AT) is a neurodegenerative disorder with cerebellar and extrapyramidal features. Interventional and epidemiological studies in AT should rely on specific scales which encompass the specific neurological features, as well the early progressive course and the subsequent plateau. The aim of this study was to build a scale of the CGI type (Clinical Global Impression) which is disease specific, as well as to check the feasibility of the ICARS scale for ataxia in this population.

Methods: We recruited 63 patients with ataxia, aged 10.76 ± 3.2 years, followed at 6 international AT centers, 49 of them (77.8%) with classical AT. All patients were evaluated for ataxia with ICARS scale. In patients with AT, two CGI scales were scored, unstructured as structured for which separate anchors were provided.

Results: Mean ICARS score was 44.7 ± 20.52, and it's severity positively correlated with age (Spearman correlation, $r = 0.46$, $p < 0.01$). Mean CGI score was 2 (moderately involved). There was a high correlation between the structured and unstructured CGIs (Spearman correlation, $r = 0.87$, $p < 0.01$). Both CGI scales showed positive correlation between severity and increasing age (Spearman correlation $r = 0.59$, $p < 0.01$ for structured CGI and $r = 0.61$, $p < 0.01$ for unstructured).

Discussion: We succeeded to build two CGI scales: structured and unstructured, which are disease specific for AT. The unstructured scale showed better connection to disease course;

Abbreviations: AT, ataxia telangiectasia; ICARS, international cooperative ataxia rating scale; SARA, scale for the assessment and rating of ataxia; BARS, brief ataxia rating scale; CGI, clinical global impression.

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the sensitivity of the unstructured scale could be improved by adding anchors related to extrapyramidal features. In addition we showed that ataxia can be reliably measured in children with AT by using ICARS.

1. Introduction

Ataxia-Telangiectasia (AT) is a genetic disorder with ominous neurodegenerative course, caused by mutations in the ATM gene.[1,2] Cerebellar neurodegeneration with progressive ataxia, starts early in life around walking age and steeply deteriorates leading to wheel chair use towards the second decade of life.[2–5] Dysarthria, dysmetria and impairment of eye movements with characteristic oculomotor apraxia are additional major cerebellar symptoms, but extrapyramidal symptoms as chorea, dystonia or bradykinesia may be even more disabling.[2–6]

Conducting clinical studies on AT patients requires a quantitative measurement of ataxia, as well as extrapyramidal movement disorder, eye movements, dysarthria and impaired communication[4,6] Crawford et al., 2000 made the first attempt to build such a scale, but this is not clinically used due to its shortcomings.[7] Meanwhile, interventional studies are hampered by the lack of universal rating scale for measuring the complex neurological impairment in AT or they assess only ataxia.[8–12] Nissenkorn et al., 2013, tried to combine three scales in order to evaluate ataxia as well as extrapyramidal movement disorder in another interventional study.[6]

However, the clinically used scales for measurement of ataxia, as the International Cooperative Ataxia Rating Scale (ICARS),[13] Scale for the Assessment and Rating of Ataxia (SARA)[14] or Brief Ataxia Rating Scale (BARS),[15] were neither developed nor validated in patients with AT. Moreover, the data on their usage in children under the age of 10 years is limited.

The aim of our study was to collect pilot data on the feasibility of ICARS in AT pediatric patients, including children younger than 10 years of age, as well as to develop a disease specific scale of the Clinical Global Impression (CGI)[16,17] type that could help in the assessment of AT patients longitudinally as well as in interventional studies.

2. Materials and methods

Children with AT, aged 5–18 years from six centers specialized in treating pediatric ataxia, especially AT were recruited: Sheba Medical Center, Israel, Department of Neurology, Nizam's Institute of Medical Sciences, Hyderabad, India, Civili Hospital, Brescia, Italy, La Sapienza University, Rome, Italy, Jaslok Hospital, Mumbai, India and Vijaya Health Center, Chennai, India.

The diagnosis of AT was established based on the criteria below: typical clinical picture plus one of the following: 1. a proven mutation in the ATM gene 2. Deficient *ATM* protein proven by Western blotting 3. Elevated α-fetoprotein, cerebellar atrophy on MRI and immune deficiency/chromosomal breakage/T-cell lymphoreticular malignancy.[4,6] Children with suspected AT, fulfilling partially the above criteria were also eligible for enrollment. In addition, up to 20% of the cohort per site could be children with ataxia of other etiologies.

Patients were enrolled after their caregivers provided an informed consent. The study was performed in one single session, during the regular neurologic clinic follow up. Data on patients' demographics and illness duration were collected.

A qualified neurologist/pediatrician/pediatric neurologist completed the scoring of ataxia by using three different validated scales for ataxia: ICARS,[13] SARA[14] and BARS.[15]

A second rater (preferably a clinician with experience in treating children with AT) completed independently the unstructured CGI (CGI-unstructured), according to his/her clinical judgment and the recommended guidelines included in Table 1. After completing the unstructured CGI, the same rater completed the structured CGI (CGI-structured) using the anchors provided in Table 2. The anchors included 5 subdomains – ataxia of gait, dysmetria, dysarthria, extrapyramidal movements and eye movements. Each domain was scored on a 5 point scale from 0 (uninvolved) to 4 (very severe). The final CGI-structured score was calculated according to the different domains as illustrated: 0 (asymptomatic) – no symptoms, 1 (mild) – at least two mild symptoms, 2 (moderate) – at least two moderate symptoms, 3(severe) – at least two severe symptoms, 4 (very severe) – at least two very severe symptoms.

The study was approved by the institutional review board IRB 0432-13-SMC at Sheba Medical Center, and subsequently by the local ethics committee at each site (NIH registration: NCT01942850).

2.1. *Data analysis*

All measured variables and derived parameters were tabulated by descriptive statistics. Categorical variables were summarized in tables providing sample size, absolute and relative frequency overall and by age group. Quantitative (continuous) variables were summarized in tables providing sample size, arithmetic mean, standard deviation, minimum, median, and maximum values and 95% CI (Confidence Interval) for means of variables overall and by age group. Spearman correlation coefficients were calculated for testing the relation between ordinal and continuous variables or between two continuous parameters. The two-sample T-test for