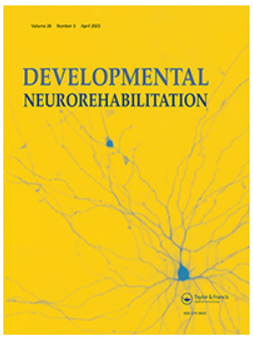

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Developmental Profiles in Children and Young Adults with Alexander Disease

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ABSTRACT

Purpose: The study aims to describe the developmental profile of children and young adults with Alexander disease [AxD] infantile form, analyzing their clinical features, adaptive behavior and neuropsychological skills.

Methods: Participants were eight children or young adults (Mean age = 11 years; SD = 6.86; range = 5–23) and their parents. A multi-method approach was adopted to assess participant competencies: (1) an online parent survey, (2) a semi-structured interview with parents, and (3) a direct assessment of the participant's neuropsychological skills.

Results: Only four parents and their children completed all measures, and a common developmental profile could not be identified. The participants experienced substantial impairment in gross-motor skills, memory and narrative macrostructure. Most parents reported a regressive trend in at least one area.

Conclusions: The high individual variability and the regressive trend highlight the need for an accurate and periodic assessment of each individual's developmental profile.

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Adaptive behavior; Alexander disease; development; leukodystrophy; neuropsychological assessment

Introduction

Alexander disease (AxD) is a rare leukodystrophy caused by dominant variants in the Glial Fibrillary Acidic Protein (GFAP) gene.[1] The estimated prevalence is one case per 2.7 million individuals.[2] Four clinical subtypes of AxD have been identified based on the age at symptoms onset: neonatal form (with onset within 30 days from birth), infantile form (with onset before two years of age), juvenile form (with onset between 2 and 12 years of age), and adult form (with onset after 12 years of age).[3–6]

The neonatal form is the most severe. Children with this form usually show severe developmental delay, hypotonia, and spastic quadriplegia. They frequently show gastrointestinal problems and generalized seizures. Death usually occurs within a few years of symptom onset.[6] The infantile form is the most common, accounting for 63% of the reported cases.[7] This form is characterized by seizures, macrocephaly, ataxia and developmental delay.[8,9] In addition, children with the infantile form of AxD typically present progressive psychomotor delay, loss of developmental milestones and pyramidal signs.[10,11] Intellectual abilities and motor function are generally preserved in the juvenile form, and the disease has a milder progression than the infantile form.[12] Ataxia and spasticity, swallowing difficulties and speech problems are frequent.[12,13] In the adult form, dysarthria, dysphagia, dysphonia, and ataxia are experienced.[14] Cognition can be well preserved, and some asymptomatic cases have been reported.[14] However, in adults with AxD, there is evidence of difficulties in concept formation, reasoning, attentional abilities, executive skills, and memory retrieval on neuropsychological testing.[15]

According to Prust et al.,[12] AxD can be classified into two macro-categories: (1) type I, with young age onset (before four years of age) and characterized by seizures, encephalopathy, paroxysmal deterioration, failure to thrive and developmental delay; (2) type II, with later onset, characterized by autonomic dysfunctions, ocular movement abnormalities, palatal myoclonus and no neurocognitive or developmental deficits. As recently suggested by Mura et al.,[16] the type I form can be divided into four subgroups of decreasing severity to better describe the disease evolution over time.

To date, the treatment of AxD is mainly supportive to prevent secondary complications. However, new experimental data suggest that suppressing GFAP with antisense oligonucleotides could provide a therapeutic strategy and these findings need to be further explored.[17]

Most of the studies in the literature on AxD in children have focused on the description of the clinical features and their evolution over time (e.g.[16]) and the description of the neural correlates of AxD (e.g.[11]). However, we are unaware of any studies specifically aimed at describing the neuropsychological features of children with AxD. The present study aimed to describe the developmental profile of children and young adults with AxD, analyzing their adaptive behavior and neuropsychological skills. Considering the wide range of severity in individuals with AxD, we used a multi-method approach to assess their abilities in different domains. In particular, we used a parent report and an interview to evaluate their clinical condition and adaptive behavior. We also administered some neuropsychological tests to assess their memory, language, and praxis skills. Special attention was given to narrative competence since with a single task (i.e. a storytelling task) it is possible to gather information on many aspects of individuals' development[18]: language use (lexicon and syntax), narrative knowledge (story structure and quantity of information told),

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and also abilities to assume other perspectives (mental state lexicon). The study aimed to explore whether particular strengths or fragilities could be identified in the developmental profiles of children and young adults with AxD.

Materials and Methods

Participants

Eight Italian participants with AxD (four females and four males) and their parents were involved in this study. The participants' parents were recruited through the AxD Italian association "Più Unici che Rari odv" (*More Unique than Rare voluntary organization*). No specific inclusion criteria were adopted except for having a son or a daughter with a diagnosis of AxD confirmed by identification of GFAP mutations (in seven cases, the mutation was de novo and in one case, inherited from maternal mosaicism). A summary of the participants' characteristics is reported in Table 1. The participant's mean chronological age was 11 years (SD = 6.86 years; range = 5–23 years). Two children attended kindergarten, two primary school, one middle school, and the remaining three (PART_1, PART_7, and PART_8) were not attending school at the time of the study. Considering the age at symptoms onset, all participants had an AxD infantile form (Type I AxD).

Concerning their parents, the mean maternal age was 40 years (SD = 10.15 years; range = 29–56), and the mean paternal age was 45 years (SD = 7.14 years; range = 37–58). Their educational level was varied: two mothers and one father had a middle school level (19%), three mothers and five fathers had a high school diploma (50%), and three mothers and two fathers had a master's degree (31%). They were biological parents and had a mean of 1.88 children, including the one with AxD (range = 1–3). All parents worked outside the home except for five mothers (63% of the mothers), who were housewives and family caregivers.

Procedure

This study included three phases: 1. an online parent survey; 2. online semi-structured interviews with the parents; and 3. a direct assessment of the participant's neuropsychological skills completed online. The study was conducted entirely online due to the COVID-19 restrictions in place at the time of the study. Each participant's parents ($n = 8$) completed a 15-item online survey specifically developed for the present study to investigate their child's clinical and developmental history. Then, parents were asked to participate in an interview (Vineland Adaptive Behavior Scales, second edition – VABS-II[19] to assess their child's adaptive behavior. The parents of six children participated in this second study's step. The parents of one participant (PART_1) did not agree to continue the study, and one participant (PART_7) was excluded due to her severe clinical condition; she was bedridden and in a minimally conscious state at the time of the study (i.e. not totally unconscious but retaining only limited behavioral signs of consciousness[20]). Finally, the children who had sufficient attentional skills to participate in an online testing session and who could communicate with at least a few words ($n = 4$) were assessed with a neuropsychological battery. PART_3 and PART_8 were excluded from this phase because they could communicate only using gaze; therefore, they were not assessable by standard neuropsychological tests.

The study was approved by the Ethical Committee of the University of Milano-Bicocca. Parents signed a written informed consent before inclusion in the study. Parental consent was also requested for the two young adults with AxD (PART_7 and PART_8) because they were unable to consent for themselves. In the following paragraphs, we describe the instruments used in the project's three phases.

Online Survey

An online survey was implemented using the Qualtrics platform. Seven mothers and one father filled in the survey. The 15-item survey investigated the following topics: a. Clinical features of AxD; b. Individual's developmental level; and c. Presence of regressions.

(a) Clinical features of AxD:
- Age at symptoms onset;
- Age at clinical AxD diagnosis;
- Type of GFAP mutation;
- Presence of one or more of the typical symptoms of AxD (i.e. epilepsy, hearing or visual problems, breathing difficulties, nutritional disorders, motor impairment, intellectual disability, language or learning difficulties, attentional problems).

(b) Developmental level:
- Motor development (i.e. *"Is your child able to sit without support?," "Is your child able to walk?," "Is your child able to manipulate objects?"*);
- Language and communication (i.e. *"How does your child communicate with other people?"*);
- Learning skills (i.e. *"Is your child able to understand an oral text?"*, *"Is your child able to read (decoding)?"*, *"Is your child able to comprehend a written text?"*, *"Is your child able to write?"*).

Table 1. Participants' description.

	Sex	Age (years)	GFAP Mutation	Age (months) at first symptoms	Age (months) at clinical diagnosis
PART_1	M	5	De novo	18	18
PART_2	F	5	De novo	18	30
PART_3	M	6	De novo	6	9
PART_4	F	9	De novo	5	60
PART_5	F	10	De novo	15	48
PART_6	M	13	Hereditary	12	24
PART_7	F	20	De novo	6	48
PART_8	M	23	De novo	5	36

(c) Presence of regressions:
- Regression in motor development (i.e. *"Did your child show a regression in his/her motor skills?"*);
- Regression in language and communication abilities (i.e. *"Did your child show a regression in his/her communicative or linguistic skills?"*);
- Regression in learning abilities (i.e. *"Did your child show a regression in his/her learning skills (e.g. reading, writing, text comprehension)?"*).

Adaptive Behaviour Assessment

The Vineland Adaptive Behavior Scales second edition (VABS-II[19] were administered online by an expert psychologist to the participating parents. The parents of six individuals with AxD participated in this phase of the project (for three individuals with AxD, the respondent was the mother, for one individual with AxD, the father responded, and for two individuals with AxD, both parents participated in the interview). The VABS-II is a semi-structured interview that evaluates an individual's adaptive behavior in four domains:

(1) Communication. Receptive (i.e. what the individual can comprehend), expressive (i.e. what the child individual can say), and written (i.e. what the individual can write);
(2) Daily living skills. Person (i.e. how the individual takes care of their own body in terms of nutrition and hygiene), Domestic (i.e. how they collaborate in housework), Community (i.e., how the individual uses their time, money and skills);
(3) Social skills. Relationships (i.e. how the individual interacts with other people), Play (i.e. how the individual plays and uses her spare time), Coping skills (i.e. how the individual manifests a sense of responsibility and sensitivity toward others);
(4) Motor skills. Gross motor (i.e. how the individual uses arms and legs for movement and coordination), Fine motor (i.e. how the individual uses hands and fingers to manipulate objects).

Parents completed this assessment, which took 40 to 60 min., answering the questions addressed by the psychologist about their child's adaptive behavior. Considering the parents' responses, the psychologist rated how frequently a parent reported a specific behavior was demonstrated by the individual on a three-point scale (0 = never, 1 = sometimes, 2 = usually). Lower scores indicate greater impairment in adaptive functioning. The scores were then converted into a five-level adaptive scale: (1) Low adaptive level; (2) Moderately low adaptive level; (3) Adequate adaptive level; (4) Moderately high adaptive level; and (5) High adaptive level.

Neuropsychological Assessment

The four individuals (PART_2, PART_4, PART_5, and PART_6) between the ages of 5 and 13 who showed the ability to participate in an online assessment session (i.e. who showed a sufficient attention level and were able to respond to standard tests) were administered two neuropsychological tests: (1) a selection of subtests of the Batteria di Valutazione Neuropsicologica per l'Età Evolutiva (Neuropsychological Assessment Battery for Developmental Age, BVN 5–11[21]) and (2) the Narrative Competence Task (NCT[22]).

From the BVN 5–11, we selected ten subtests assessing the following areas:

(1) Memory
   a. Verbal Short Term Memory (STM) forward (i.e. a forward digit span test);
   b. Verbal STM backward (i.e. a backward digit span test);
   c. Word recall (i.e. the participant is asked to recall some words after seeing the images and labeling them).
(2) Language
   a. Labeling (i.e. the participant is asked to label some pictures);
   b. Syntactic comprehension (i.e. the participant is asked to select the picture depicting a sentence);
   c. Phonemic fluency (i.e. the participant is asked to list words beginning with a specific phoneme);
   d. Categorical fluency (i.e. the participant is asked to list words belonging to a particular category).
(3) Motor praxis
   a. Meaningful praxis (i.e. the participant is asked to do some movements with cultural meaning, e.g. "military salute");
   b. Meaningless praxis (i.e. the participant is asked to do some movements without a codified meaning, e.g. "put your fist on your forehead");
   c. Face praxis (i.e. the participant is asked to do facial expressions, e.g. "whistle").

Raw data were converted into Z scores to compare the children's performances. Since BVN normative data are available from 5 to 11 years of age, we used the norms of 11-year-old children to computing Z scores for older children (i.e. one 13-year-old child).

Narrative skills were assessed using the NCT, a storytelling task. The test consists of an 18-picture storybook about a familiar situation (i.e. a ball thrown by kids on a tree). First, participants were asked to look carefully at the pictures and then tell a story in their own words by looking at the pictures (for a detailed description of the test, see[18,23]). Both macrostructural (i.e. quantity of information and story structure) and microstructural (i.e. the language used) characteristics of the participant's narrative competence were considered:

(1) Macrostructural aspects
   a. Events, which are the number of things that happened in the story;
   b. Structure, which is the ability to tell a well-structured story, assessed by considering how many key passages of the story a participant was able to tell;
   c. Agents, which are the characters that act in the story;
   d. Anaphoric use of the article, which is a measure of story cohesion. The first time a person or an object is

nominated, it is typically preceded by an indefinite article. Then, when it is again nominated in the story, it is preceded by a definite article;
e. Mental state lexicon, which is a measure reflecting the participant's ability to assume the characters' point of view.

(2) Microstructural aspects
a. Tokens, which is the total number of words used by the participant in his narration;
b. Mean length of utterance in words (MLU), calculated by dividing the total number of words uttered by the total number of utterances;
c. Subordinate clauses, which is the total number of dependent clauses produced by the child;
d. Implicit subordinate clauses, which is the number of non-finite dependent clauses produced (i.e. clauses with infinitive tense verbs);
e. Explicit subordinate clauses, which is the number of finite dependent clauses produced (i.e. clauses with finite tense).

Raw scores were converted into Z scores to compare the narrative performance of children of different ages. Since NCT's normative data are available for children from 3 years and six months to 8 years and six months, the Z scores of older children (i.e. three children with 9, 10, and 13 years) were computed using the norms of eight years and six months.

Results

Description of Clinical Features, Individuals with AxD Developmental Level, and Regressions

Participants with AxD's characteristics and their clinical problems, as collected by the online survey completed by parents, are summarized in Table 2.

One-half of the participants (four out of eight) experienced epileptic seizures. The problems more frequently reported by parents were motor impairment in 88% of the participants (seven out of eight) and intellectual disability and language or specific learning disabilities in 75% of the participants (six out of eight). Nutritional disorders were shown by 63% of participants (five out of eight) and breathing difficulties by 25% (two out of eight). Attentional difficulties were experienced by 50% of the individuals (four out of eight). A minority of participants showed sensory impairments, with 25% (two out of eight) having hearing impairments and 25% (two out of eight) having visual impairments.

Concerning motor development, five out of eight participants with AxD (PART_1, PART_2, PART_4, PART_5, and PART_6) could sit without support and walk, although three of them (PART_1, PART_2, and PART_5) needed aid devices or adult help to walk. Six out of eight participants (PART_1, PART_2, PART_3, PART_4, PART_5, and PART_6) were able to manipulate objects. Concerning language development and communication skills, three individuals (PART_3, PART_7, and PART_8) could communicate only using gaze, one (PART_1) could produce a few words, one (PART_2) could produce simple sentences, and three (PART_4, PART_5, and PART_6) used fluent conversational language. Concerning learning skills, only one participant (PART_6) showed the ability to read (decoding) and write some simple words, and three (PART_4, PART_5, and PART_6) showed the ability to understand simple oral texts.

The parents were asked to report if their children had a regression in one of the investigated areas. According to the parent report, six participants with AxD (PART_2, PART_3, PART_4, PART_5, PART_7, and PART_8) showed a regression over time in motor development, four (PART_3, PART_5, PART_7, and PART_8) showed a regression in language and communication skills, and three (PART_4, PART_7, and PART_8) showed a regression in their learning skills. Only PART_1 and PART_6 did not show any developmental regression at the time of the study.

Participants with AxD Adaptive Behaviour

The VABS-II semi-structured interview was conducted with six parents (as reported above, the parents of PART_1 did not agree to continue the study, whereas PART_7 was excluded from this phase due to her minimally conscious state). Data from the VABS-II showed a generally poor level of adaptive behavior or high level of support needs (see Figure 1). All the communication area scores indicated a low or moderately low level of adaptive behavior, except for the adequate for chronological age receptive skills of PART_5. Within daily living skills, the domestic skills were those better preserved, with four participants with AxD (PART_2, PART_4, PART_5, and PART_6) reaching an adequate for chronological age adaptive level. Only PART_2 reached an adequate for chronological age level of socialization skills considering interpersonal relationships and play skills. Finally, only two participants (PART_4 and PART_6) reached an adequate level for

Table 2. Clinical features reported by parents in the parent survey.

	PART_1	PART_2	PART_3	PART_4	PART_5	PART_6	PART_7	PART_8
Epileptic seizure	+	+	+	+	-	-	-	-
Hearing difficulties	+	-	-	-	-	-	+	-
Visual disorders	-	-	-	-	+	-	+	-
Breathing difficulties	-	-	-	-	-	-	+	+
Nutritional disorders	-	-	+	+	+	-	+	+
Motor difficulties	+	+	+	-	+	+	+	+
Intellectual disability	-	+	+	+	-	+	+	+
Language or learning difficulties	-	+	+	+	-	+	+	+
Attentional difficulties	-	-	+	-	-	+	+	+

Note. + = present; - = absent.

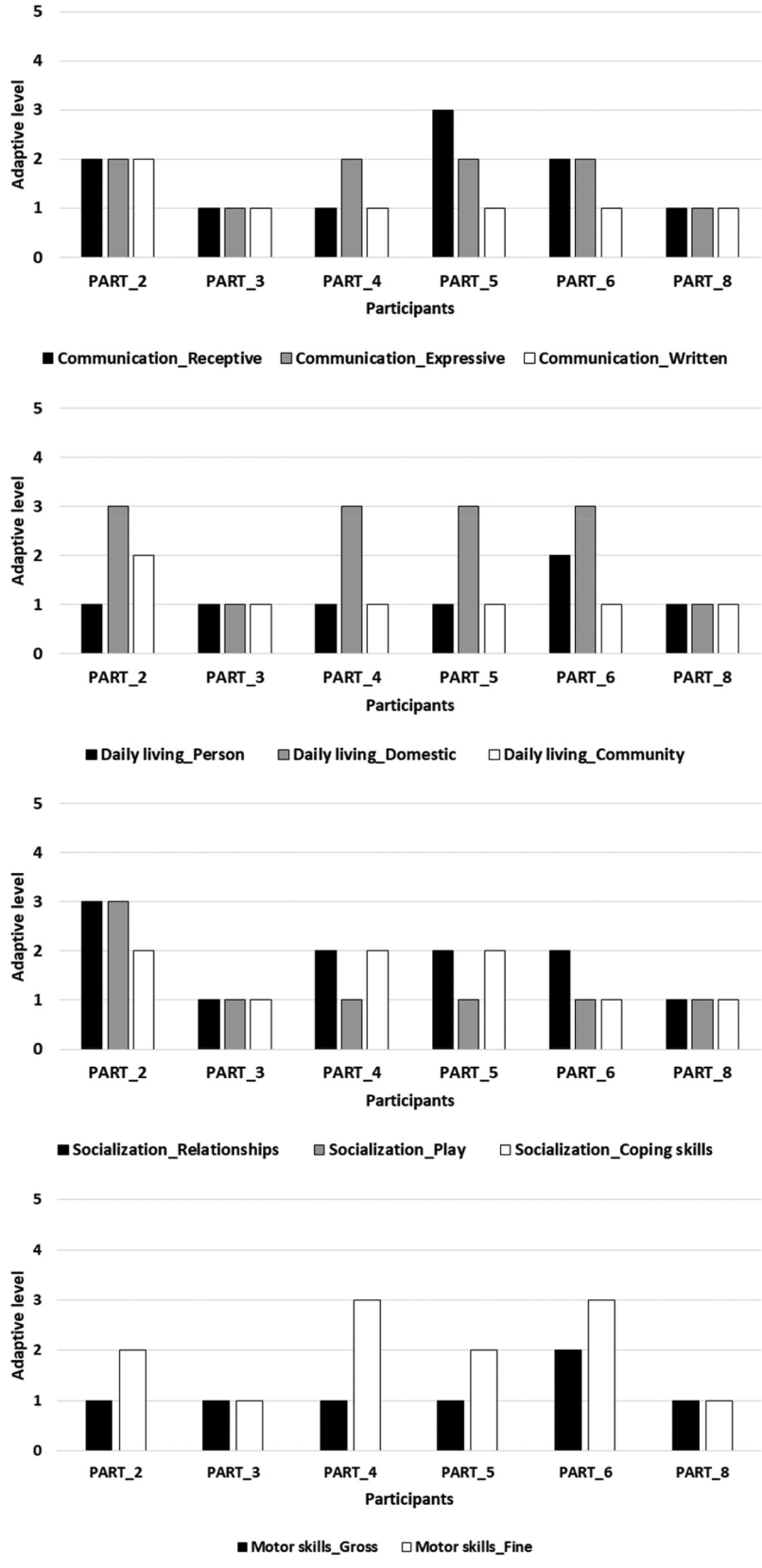

Figure 1. VABS-II Adaptive levels. 1 = Low adaptive level; 2 = Moderately low adaptive level; 3 = Adequate adaptive level; 4 = Moderately high adaptive level; 5 = High adaptive level

chronological age in fine motor skills, whereas no one reached an adequate level in gross-motor skills.

Participants with AxD Neuropsychological Profile

The neuropsychological tests were administered to PART_2, PART_4, PART_5, and PART_6 (chronological age: $M = 9$; SD = 3.30; range = 5–13). Considering memory skills (Figure 2), almost all the scores were lower than two SD from the mean. Only backward short-term memory and word recall were within two SD below the mean for two participants (PART_2 and PART_4) and one participant (PART_2), respectively. Linguistic skills (Figure 3) appeared less impaired than the memory ones: labeling abilities were above two SD below the mean for all the participants; syntactic comprehension was significantly impaired for two participants (PART_4 and PART_6); phonemic and categorical fluency was significantly impaired for three participants out of four (PART_4, PART_5, and PART_6). Considering motor praxis (Figure 4), one participant (PART_5) performed in the normal range, but the other participants showed at least a score lower than two SD below the mean. It should be emphasized that we used the 11-year-old normative scores to compute Z scores for PART_6 (13 years of age) because BVN normative scores are available from 5 to 11 years of age.

Participants' narrative competence appeared more impaired in macrostructural features (Figure 5) than in microstructural features (Figure 6). Each of the four participants completing the assessment obtained scores under the mean, but PART_2 showed a performance within two SD below the mean in both macro-and microstructure. Concerning narrative macrostructure, the most affected indices were the number of events introduced in the story and the ability to tell a well-structured story. Concerning narrative microstructure, which is the language used in the narrative task, two individuals performed within two SD below the norm (PART_2 and PART_4). In contrast, the number of tokens, the MLU, and the use of subordinate clauses were lower than two SD below the mean for the other two participants. Since NCT normative scores are available from 3.5 to 8.5 years, we used the

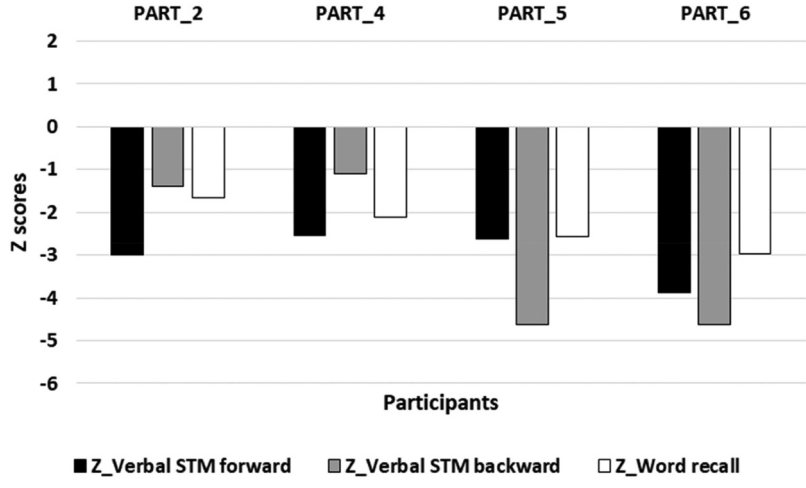

Figure 2. Participants' Z scores in BVN memory subtests.

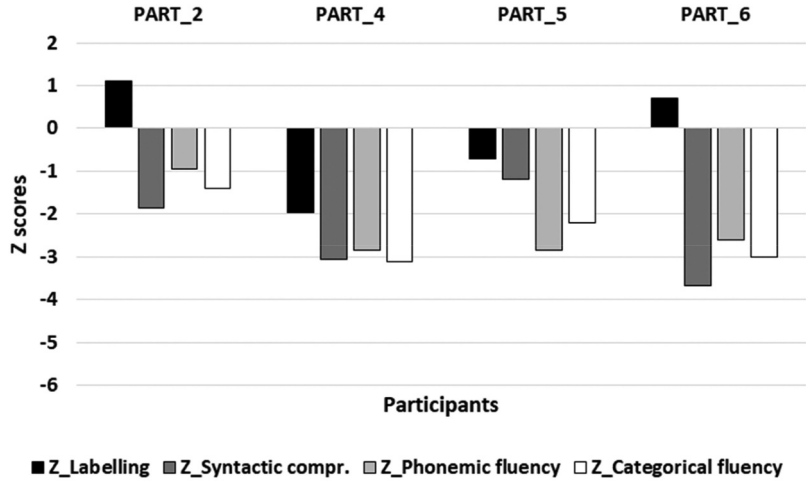

Figure 3. Participants' Z scores in BVN language subtests.

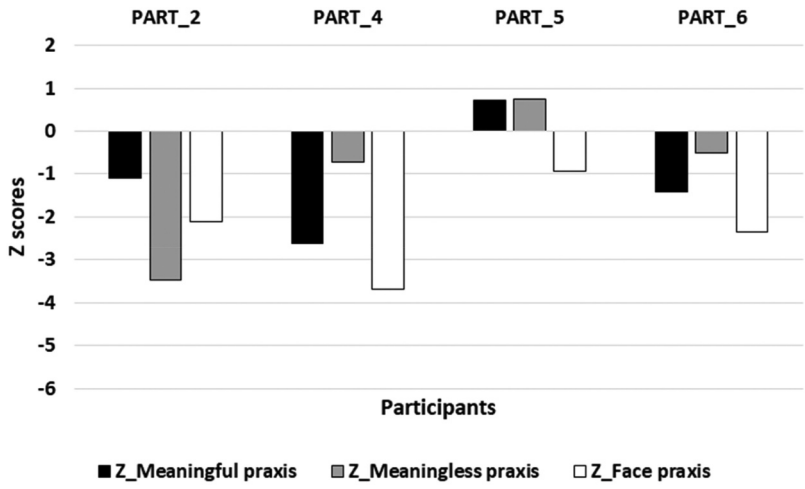

Figure 4. Participants' Z scores in BVN motor praxis subtests.

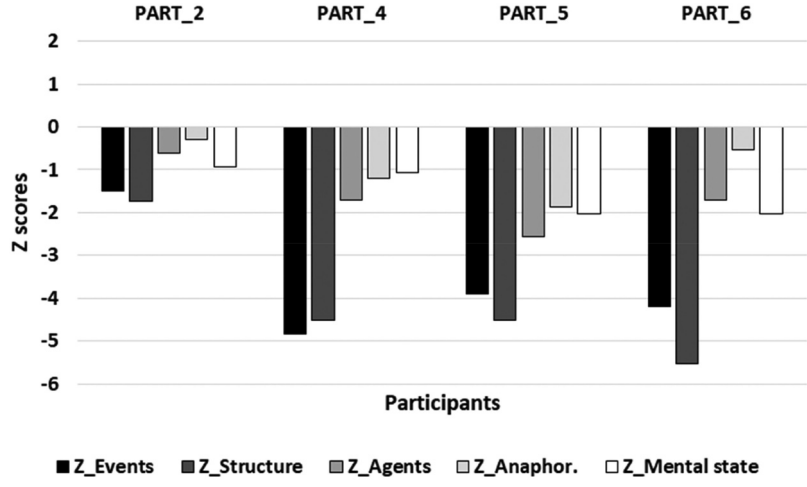

Figure 5. Participants' Z scores in narrative macrostructure.

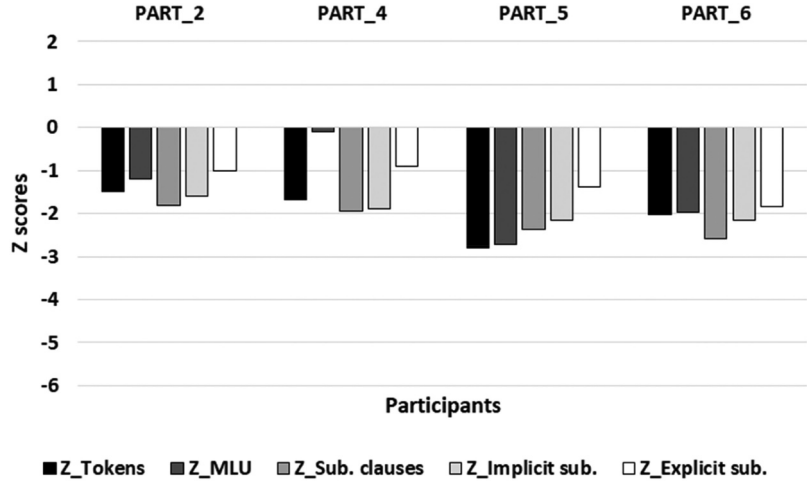

Figure 6. Participants' Z scores in narrative microstructure.

normative scores of 8.5-year-old children to compute Z scores for PART_4 (9-year-old), PART_5 (10-year-old), and PART_6 (13-year-old).

Discussion

The present study aimed to describe the developmental profile of a small group of Italian children with AxD infantile form. After collecting parent reports on the clinical features of AxD, the developmental level of the participants, and the parent-reported presence of regressions, we investigated the adaptive behavior of individuals with AxD using a semi-structured parental interview and their neuropsychological skills using a selected standardized set of tests.

As reported by parents, the clinical features of the individuals with AxD were consistent with the diagnosis of infantile form of AxD, with all participants showing at least motor or cognitive impairments.[8–10] Moreover, most parents reported a regressive trend in at least one area among motor, language or learning skills. A generally poor level of adaptive behavior emerged. The most preserved area appeared to be daily living skills, particularly domestic abilities, such as collaborating in simple housework. In contrast, the most impaired area was gross motor skills, with all participants showing a low adaptive level.

The neuropsychological profile of the few individuals with AxD completing our administered battery appeared to be characterized by high individual variability. The small number of participants did not allow delineating a common trend. However, memory appeared as a particularly impaired area, as also found in formal testing of adults with AxD.[15] Considering both the BVN subtests and the narrative task, language development appeared to be less impaired than other areas (e.g. memory, motor praxis, and narrative macrostructure). In particular, lexical skills (i.e. labeling and fluency) and syntactic skills (i.e. sentence comprehension, MLU, and use of subordinate clauses) appeared to be less impaired than the ability to tell a well-structured and complete story. This could be explained considering that narratives are complex tasks: to tell a story, an individual must master and integrate language, cognitive skills, and social competencies.[23]

Clinical Implications

Individuals with the infantile form of AxD experience substantial difficulties in adaptive behavior, memory, motor development, and language development. Although a common developmental profile could not be identified due to the small number of participants, the study showed a significant impairment in gross-motor skills, memory and narrative macrostructure.

Although the sample size is small, the high individual variability highlights the need for an accurate assessment of each individual's developmental profile before planning rehabilitation treatment. Moreover, the regressive trend found in most participants with AxD in this study highlights the need for a periodical assessment to point out the specific skills that require strengthening. Since there is a lack of published data on the performance on specific tasks by individuals with the infantile AxD form, these findings could hopefully guide clinicians in selecting assessment and rehabilitative tools for children, adolescents and young adults with this genetic condition.

Study Limitations and Future Directions

The small number of participants was the main limitation of the present study. Another limitation was the difficulty in finding adequate neuropsychological tests for this population, standardized with individuals from a wide range of ages and abilities. For this reason, in some cases, we had to compare our participants' performance with normative data collected on younger children.

Future studies will aim to increase the number of participants and to assess their adaptive behavior and neuropsychological skills longitudinally. A longitudinal perspective, which is fundamental in studying child development, will be crucial in investigating developmental trajectories in this progressive disease.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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