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Letter to the Editor

Neuropsychological features of adult form of Alexander disease

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Dear Editor,

Alexander disease (AxD) is a rare leukodystrophy caused by autosomal dominant mutations, either *de novo* or inherited, in the glial fibrillary acidic protein (GFAP) gene. The current prevalence of AxD is uncertain, whereas the annual incidence was estimated to be 1/2.7 million in one population study in Japan [1]. Three age-dependent clinical subgroups of AxD can be distinguished: infantile (onset before 2 years of age), juvenile (onset between 2 and 12 years of age) and adult (onset after 12 years of age), which are characterized by a varying combination of cognitive and neurological features [1,2]. In particular, the infantile and juvenile forms of AxD are almost constantly characterized by a varying degree of neuropsychological disorders, whereas they seem to be absent in the adult forms [3] or at most occasional [1–4]. However, there is no study focused on the cognitive performance in the adult form of AxD. For this reason, the purpose of this work was to investigate the neuropsychological features of these patients.

We retrospectively analyzed the neuropsychological performances of eight symptomatic adult Italian patients with AxD (5 males, 3 females; mean age at evaluation: 40 years, range: 21–61 years; eight with the adult forms and one with the juvenile one), assessed at the Fondazione IRCCS Istituto Neurologico “C. Besta” from 2004 to 2018. The diagnosis was confirmed by the presence of a *GFAP* mutation in all patients. The demographic, clinical, genetic features and neuroimaging of all the patients are summarized in Table 1. Given the retrospective nature of our study, the most relevant cognitive domains (language, memory, attentional/executive function, and praxis) were always assessed but using a varying set of neuropsychological tests. Therefore, the results of testing were classified using Standard Deviation (SD): average (± 1 SD), mildly impaired (between -1 and -2 SD) or impaired (lower than -2 SD). Informed consent was obtained from all patients included in the study.

The neuropsychological profile of each patient is summarized in Table 2. In all patients the Mini Mental State Examination (MMSE) score was ≥ 24, but none of them achieved the highest score of 30. Concept formation and reasoning were impaired in six out of eight assessed patients, whereas attentional/executive functions were impaired in five out of eight. Specifically, we detected difficulties in verbal intelligence (proverbs and similarities), visual selective attention (Trail Making Test Part A and Visual Search), set shifting task/sustained attention (Trail Making Test Part B and Stroop Test), or phonemic fluency. With regards to learning and memory functions, four out of seven assessed patients had difficulties in visual and verbal delayed recall abilities (impaired memory retrieval), but normal coding and storage of information (normal *learning curve*). Finally, three patients (out of 8) showed a deficit in visual perception organization (Gestalt Completion and Rey Complex Figure Test), whereas all patients obtained normal performance at language testing (naming, comprehension, and semantic fluency).

Adult leukodystrophies encompass a large number of genetic diseases primarily affecting the brain white matter and characterized by movement disorders and/or a varying degree of cognitive impairment, ranging from severe dementia to mild attention deficit or even normal cognitive profile [5]. Regarding the adult form of AxD, in a comprehensive study of 11 adult AxD subjects, cognitive impairment was considered as to be absent based on global first-level screening tests [3]. Another comprehensive study indicates that cognitive impairment may occur [1], but the degree and type of impairment are not defined. Finally, in a report of only two patients with late-onset AxD, neuropsychological disturbances are reported as to be early and prominent but limited data are provided about their features [4].

In this work, we provide evidence that cognitive impairment is a common feature in adult AxD patients. Indeed, our study suggests that adult AxD patients can present minimal decrements in MMSE, but definite difficulties in concept formation and reasoning, attentional and executive abilities, and memory retrieval on formal neuropsychological testing. This cognitive profile can be framed within the concept of *white matter dementia*, which is characterized by sustained attention deficit, visuospatial and executive dysfunction, memory retrieval deficit, and no language dysfunction [5].

All these functions can be strictly related to WM connection and its integrity, as demonstrated by systematic studies using neuropsychological assessment and neuroimaging correlation [6,7]. The attentional and executive dysfunctions are mediated by a network of

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Table 1
Summary of neurological and neuroradiological findings.

	Pt. 1[a]	Pt. 2[a]	Pt. 3[a]	Pt. 4	Pt. 5	Pt. 6	Pt. 7[a]	Pt. 8
Demographic, clinical and genetics features								
Gender (M/F)	F	M	F	F	M	M	M	M
Education (YEARS)[b]	8	13	13	13	13	8[b]	8	8
Age at onset (years)	33	57	34	43	49	~15	13	late-childhood
Age at neuropsychological testing (years)	35	61	39	50	59	30	26	21
GFAP mutation	p.Ser393Ile	p.Glu332Lys	p.Arg70Gln	p.Asn386Ser	p.Leu359Pro	p.Met432ArgfsTer12	p.Arg416Trp	p.Arg416Trp
Neurological examination								
Walking ability	Ambulatory without aid	Ambulatory without aid	Fully ambulatory	With bilateral assistance	Ambulatory without aid	Wheelchair-bound	Ambulatory without aid	With unilateral assistance
Cerebellar ataxia	−	+	−	+	−	+	+	+
Lower brainstem signs	+	+	+	+	+	+	+	+
Pyramidal signs/spasticity	+	+	−	+	+	+	+	±
Bladder dysfunction	+	−	+	+	−	+	+	+
Sleep apnea	Unknown	+	−	±	+	−	−	Unknown
Brain MRI changes								
Supratentorial WM	± (PV)	−	+ (PV)	± (PV)	± (PV)	+ + (PV; dWM; CCA; T1-w hypo)	+ + (PV; dWM; CCA; T1-w hypo)	+ + (PV; dWM; CCA; T1-w hypo)
Cerebellar (DN-SCPs)	+	+	+	+	±	+	+	+
Bulbar (atrophy and WM changes)	+	+	+	+	+	+	+	+

Abbreviations: CCA, corpus callosum atrophy; DN, dentate nuclei; dWM, deep White Matter; PV, periventricular; SCPs, superior cerebellar peduncles; T1-w hypo, T1-weighted hypointensity; WM, white matter.

[a] Patients 1, 2, 3, −, and − 7 have been previously reported [3].

[b] Among the patients with low education, only the patient 6 had poor school performance, suggesting intellectual disabilities since childhood.

Table 2
Neuropsychological results of eight patients test.

	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7	Pt. 8
Global assessment								
Mini mental state examination (score)[a]	Average (25)	Average (24)	Average (25)	Average (28)	Average (27)		Average (24)	Average (24)
Concept formation and reasoning								
Verbal intelligence (Proverbs and Similarities)	Impaired	Impaired	Mildly Impaired			Impaired	Impaired	Average
Brixton test				Impaired				
Attentional/executive functions								
Digit span backward				Mildly Impaired	Average			Average
Visual search	Average	Average	Mildly Impaired	Average	Average		Mildly Impaired	Average
Trail making test part A				Average	Average	Impaired		Mildly Impaired
Trail making test part B				Average	Average			Impaired
Trail making test B – A				Average	Average			Impaired
Stroop test				Mildly Impaired	Average			
Phonemic fluency	Average			Average	Average		Mildly Impaired	Average
Memory								
Digit Span	Average		Average	Average	Average	Impaired	Average	Average
Story recall test	Average	Average	Average				Average	
RVLT immediate recall	Average		Average	Average	Average		Mildly Impaired	Average
RVLT delayed recall	Average		Impaired	Average	Average		Mildly Impaired	Average
Corsi span	Average			Impaired	Average			Impaired
Complex figure test (Delayed Recall)				Impaired	Average		Average	Average
Visual perceptual organization								
Gestalt completion test	Average	Impaired	Average				Average	
Complex figure test (copy)	Average	Average	Average	Impaired	Average	Impaired	Average	Average
Language								
Naming				Average	Average			Impaired
Comprehension	Average	Average	Average				Average	Average
Semantic fluency	Average	Average	Average	Average	Average		Average	Average

[a] Mini Mental State Examination's (MMSE) scores have been calculated with correction for age and education.

interconnected structures that include the frontal areas and their connections to posterior ones [8] and the corpus callosum, while visual and verbal retrieval depends also on connections between the frontal and temporal areas through the uncinate fasciculus [9,10].

In our study, the MRI findings show that almost all patients (7 out of 8) present supratentorial WM lesions and three of them have overt

corpus callosum atrophy (Table 1), but these supratentorial changes are definitely less marked than in the early-onset, severe forms of AxD [1]. Therefore, it is reasonable to suppose that the cognitive impairment is related to the degree of supratentorial WM involvement, including corpus callosum atrophy, rather than to the infratentorial abnormalities.

Finally, a practical consequence of our work is that the presence of cognitive impairment should be regularly evaluated in late-onset AxD when planning rehabilitation interventions. Indeed, physiotherapy plays a key role in AxD treatment, and cognitive impairment could negatively impact on the patient's compliance to physiotherapy, thus limiting its efficacy.

Our study has some limitations, mainly resulting from its retrospective design and from the small sample size due to the rarity of the disease. Nevertheless, by revealing the common presence of cognitive impairment in late-onset AxD, it encourages the systematic, longitudinal assessment of a greater number of neuropsychological skills on a larger sample of patients, as well as their precise correlation with neuroimaging findings, disease duration and genotype.

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Ethics

The patients provided written informed consent for the scientific publication of their clinical data in anonymized form.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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