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FOOD FOR THOUGHT

Cognitive impairment in women with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type

Carolina Baeza-Velasco[1] · Caroline Bourdon[2] · Roberto Polanco-Carrasco[3] · Marie de Jouvencel[4] · Marie-Christine Gely-Nargeot[5] · Anne Gompel[6] · Claude Hamonet[7]

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To the Editor,

The Ehlers-Danlos syndrome hypermobility type (EDS-HT) is the most frequent hereditary disorder of connective tissue. EDS-HT is clinically indistinguishable from the rheumatic clinical condition named joint hypermobility syndrome (JHS/EDS-HT) [1, 2], which is characterized by fragility of tissues and joint hypermobility. The prevalence of JHS/EDS-HT is estimated to be around 3% being more common among women [3]. The clinical picture of JHS/EDS-HT encompasses symptoms in multiple body systems, that is, musculoskeletal, mucocutaneous, gastrointestinal, cardiovascular, uro-gynecological, ocular, olfactory, oral, and neuropsychiatric problems [4]. Such multifaceted symptoms can be understood by the wide distribution of collagen in the body. Among them, cognitive impairments constitute a frequent complaint among patients in clinical setting. However, they have been poorly investigated systematically [5]. Some studies explored concentration [6] or cognitive problems [7] in JHS/EDS-HT, but these are based on self-reports. To our knowledge, no studies exist on cognitive performance using a more specific tool to screen difficulties on different neuropsychological domains in this pathology. To address this concern, we carried out a controlled observational study comparing the performance on neuropsychological tasks between patients with JHS/EDS-HT and healthy controls. A secondary objective was to explore the relationship between cognitive performance, pain, and fatigue in JHS/EDS-HT patients. For this, women with JHS/EDS-HT according to Villefranche [8] and Brighton criteria [1], and matched healthy controls were recruited in a specialized unit and from the general population, respectively. Exclusion criteria for all subjects included: problems in understanding the French language, history of head trauma and substance abuse, current clinical depression, or other comorbid somatic condition considered affecting the cognitive status. Cognitive performance was assessed with the French version of the Barrow Neurological Institute Screen (BNIS) for higher cerebral functions [9]. The BNIS explores different cognitive domains, such as speech/language, orientation, attention/concentration, visuospatial problem-solving, learning and memory as well as meta-cognitive aspects (awareness of performance) and affect. In addition, we assessed pain and fatigue intensity with a verbal rating scale. This instrument proposes a set of hierarchized qualifiers for pain and fatigue experienced at the present moment, and ranging from absent to severe. The cognitive assessment was performed by an experienced neuropsychologist.

✉ Carolina Baeza-Velasco
carolina.baeza-velasco@parisdescartes.fr

1 Laboratoire de Psychopathologie et Processus de Santé (EA4057), Institut de Psychologie, Université Paris Descartes, 71 Av. Edouard Vaillant, Boulogne-Billancourt cedex, 92100 Sorbonne-Paris Cité, France

2 Centre de Rééducation Fonctionnelle, Hôpital Privé d'Evry, Evry, France

3 Asociación Chilena de Revistas Científicas de Psicología, Santiago, Chile

4 Cours d'Appel de Versailles, Versailles, France

5 Laboratoire Epsylon (EA 4556), Université Paul Valéry Montpellier 3, Montpellier, France

6 Unité de Gynécologie-Endocrinienne, APHP, Hôpitaux Universitaires Paris Centre, Université Paris Descartes, Sorbonne-Paris Cité, France

7 Service de Médecine Physique et Réadaptation, APHP, Hôpitaux Universitaires Paris Centre, Université Paris-Est Créteil, Hôtel Dieu, Paris, France

Twenty-eight patients (mean age = 36.1, SD = 13) and 21 healthy women (mean age = 33.6, SD = 9.3) were enrolled at the time of preliminary data presentation. The groups did not differ in terms of age and years of education (Table 1).

A significantly higher proportion of women with cognitive impairment was observed in the patients group (74.4 vs. 23.8%; $p < 0.05$). Patients scored significantly lower on visuospatial problem-solving, attention, memory, and awareness of performance that control subjects (Table 2). No significant relationship was observed between cognitive performance (BNIS total score) and pain intensity dichotomized as severe versus absent/mild ($U = 50.5$, $p = 0.133$). Nevertheless, a non-significant trend toward lower scores on cognitive performance was observed in patients with severe fatigue ($U = 36$, $p = 0.061$).

Despite limits, these results confirm clinical observations concerning cognitive impairment in women with JHS/EDS-HT, especially on visuospatial problem-solving, attention, and memory. These problems cannot be attributable to depressive mood, because patients were previously screened for depression. Difficulties in the identification of visual and spatial relationships among objects observed in the JHS/EDS-HT group at the assessment of visuospatial problem-solving (which also includes eye–hand coordination tasks) are likely related to impairments in proprioceptive precision [10], hand–wrist hypermobility, and vestibular problems which could impact visual competences, including tracking issues [11]. Although non-significant in this study (probably due to the small sample size), the potential relationship between fatigue and cognitive performance especially on attention and memory merits further

Table 1 Comparison of socio-demographic characteristics between the groups

	Patients, $n = 28$		Controls, $n = 21$		p
	Median	[IntQ]	Median	[IntQ]	
	%	(n)	%	(n)	
Age	38.0	[24; 47]	30.0	[27; 38]	0.58[a]
Years of education	5.5	[4.0; 6.2]	6.0	[6.0; 6.5]	0.08[a]
Marital status					
Married/living with partner	48.0	(12)	83.3	(15)	0.26[b]
Single/separated/widowed	52.0	(13)	16.6	(3)	
Number of children	0.5	[0.0; 2.0]	0.0	[0.0; 2.0]	0.910[a]
Professional situation					
Active	60.9	(14)	90.5	(19)	0.36[b]
Inactive	39.1	(9)	9.5	(2)	

IntQ InterQuartil (Q25–Q75)

[a]Mann–Whitney test

[b]χ^2 test

Table 2 Comparison between groups on cognitive performance

BNIS	Patients, $n = 28$		Healthy controls, $n = 21$		p
	Median	[IntQ]	Median	[IntQ]	
Total score	36.0	[32.0; 37.7]	39.0	[37.5; 41.0]	<0.001[a]
Cognitive impairment (BNIS total score <47)	71.4%	($n = 20$)	23.8%	($n = 5$)	0.001[b]
Speech and language	15.0	[14.0; 15.0]	15.0	[15.0; 15.0]	0.114[a]
Orientation	3.0	[3.0; 3.0]	3.0	[3.0; 3.0]	0.074[a]
Attention	2.0	[1.0; 2.0]	3.0	[2.0; 3.0]	0.001[a]
Visuospatial problem-solving		[6.0; 7.0]	8.0	[6.5; 8.0]	0.010[a]
Memory	5.0	[4.0; 6.0]	7.0	[6.0; 7.0]	<0.001[a]
Affect	4.0	[4.0; 4.0]	4.0	[4.0; 4.0]	0.126[a]
Awareness versus performance	1.0	[0.0; 1.0]	1.0	[1.0; 1.0]	0.006[a]

BNIS Barrow Neurological Institute Screen for higher cerebral functions, *IntQ* InterQuartil (Q25–Q75)

[a]Mann–Whitney U test

[b]χ^2 test

investigation. It has been postulated that fatigue plays a role in the development of concentration problems [12]. A factor contributing to fatigue in JHS/EDS-HT is the malfunction of the autonomic nervous system or dysautonomia [13], which in turn has been reported as affecting cognitive performances in clinical and non-clinical populations [14–16]. Thus, dysautonomia may underlie some cognitive problems in JHS/EDS-HT patients. Further studies are needed to elucidate the nature and clinical significances of cognitive impairment in this population.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethical approval Ethical approval was obtained from the CERES (Comité d'évaluation éthique des projets de recherche) of the University Paris Descartes. All subjects included in the study gave written informed consent.

References

1. Grahame R, Bird HA, Child A (2000) The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 27:1777–1779
2. Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D (2009) The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet A 149A:2368–2370
3. Hakim AJ, Grahame R (2014) Recognising the scale of joint hypermobility burden: comment on the article by Mulvey et al. Arthritis Care Res 66:496–498
4. Colombi M, Dordoni C, Chiarelli N, Ritelli M (2015) Differential diagnosis and diagnostic flow chart of joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type compared to other heritable connective tissue disorders. Am J Med Genet 169 C:6–22
5. Bourdon C, de Jouvencel M, Baeza-Velasco C, Hamonet C (2016) Trastornos cognitivos y discapacidad, aplicación al síndrome de Ehlers-Danlos. Cuadernos de Neuropsicologia/Panamerican. J Neuropsychol 10(4):71–77
6. Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG (2010) Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. Semin Arthritis Rheum 40:267–274
7. Rombault L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, Calders P (2011) A Impairment and impact of pain in female patients with Ehlers-Danlos syndrome. A comparative study with fibromyalgia and rheumatoid arthritis. Arthritis Rheum 63:1979–1987
8. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ, Ehlers-Danlos National Foundation (USA), Ehlers-Danlos Support Group (UK) (1998) Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Am J Med Genet 77:31–37
9. Truelle JL, Marinescu M, Rusina R (2004) A fast clinical screening of higher functions: from MMSE to BNIS. Barrow Q 20:19–20
10. Clayton HA, Jones SAH, Henriques DYP (2015) Proprioceptive precision is impaired in Ehlers-Danlos syndrome. Springerplus 7:323
11. Guibellini G, Brancati F, Castori M (2015) Neurodevelopmental attributes of joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: update and perspectives. Am J Med Genet C 169C:107–116
12. Castori M, Morlino S, Celleti C, Celli M, Morrone A, Colombi M, Camerota F, Grammatico P (2012) Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type): principles and proposal for a multidisciplinary approach. Am J Med Genet A 158A:2055–2070
13. Hakim AJ, Grahame R (2004) Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? Rheumatology (Oxf) 43:1194–1195
14. Bassi A, Bozzali M (2015) Potential interactions between the autonomic nervous system and higher level functions in neurological and neuropsychiatric conditions. Front Neurol 6:182
15. Saint Martin M, Sforza E, Thomas-Anterion C, Barthélémy JC, Roche F, PROOF Study Group (2013) Baroreflex sensitivity, vascular risk factors, and cognitive function in a healthy elderly population: the PROOF cohort. J Am Geriatr Soc 61:2096–2102
16. Shanks L, Jason LA, Evans M, Brown A (2013) Cognitive impairments associated with CFS and POTS. Front Physiol 4:113