Impaired social cognition and fine dexterity in patients with Cowden syndrome associated with germline PTEN variants

Clément Desjardins, Frédéric Caux, Bertrand Degos, Djallel Benzohra, Astrid de Liège, Gérôme Bohelay, Michel Longy, Chloé Béreaux, Béatrice Garcin

▶ **To cite this version:**

HAL Id: hal-03511890
https://hal.sorbonne-universite.fr/hal-03511890

Submitted on 5 Jan 2022

Impaired social cognition and fine dexterity in patients with Cowden syndrome associated to germline *PTEN* variants.

Clément Desjardins[1], Frédéric Caux[2], Bertrand Degos[1,3], Djallel Benzohra[5], Astrid De Liège[1], Gérôme Bohelay[2], Michel Longy[4], Chloé Béreaux[1], Béatrice Garcin[1].

1. AP-HP, Hôpital Avicenne, Hôpitaux Universitaires de Paris-Seine Saint Denis (HUPSSD), Department of Neurology, Sorbonne Paris Nord, Bobigny, France.

2. AP-HP, Hôpital Avicenne, Hôpitaux Universitaires de Paris-Seine Saint Denis (HUPSSD), Department of Dermatology, Sorbonne Paris Nord, Bobigny, France.

3. Dynamics and Pathophysiology of Neuronal Networks Team, Center for Interdisciplinary Research in Biology, Collège de France, CNRS UMR7241/INSERM U1050, Université PSL, Paris, France.

4. Cancer Genetics Unit and INSERM U1218, Institut Bergonié, University of Bordeaux, Bordeaux, France.

5. AP-HP, Hôpital Avicenne, Hôpitaux Universitaires de Paris-Seine Saint Denis (HUPSSD), Department of Radiology, Sorbonne Paris Nord, Bobigny, France.

Corresponding Author:

Dr. Béatrice Garcin,

Consultation mémoire, Service de Neurologie,

Hôpital Avicenne, Hôpitaux Universitaires de Paris-Seine Saint Denis (HUPSSD).

125 rue de Stalingrad, 93000 Bobigny, France.

Phone number: +33-1- 48-95-54-01

E-mail: beatrice.garcin@aphp.fr

Abstract:

Purpose: Cowden syndrome (CS) is an autosomal dominant disease related to germline *PTEN* variants and characterized by multiple hamartomas, increased risk of cancers and frequent brain alteration. Since the behavior of CS patients sometimes appears to be inappropriate, we analyzed their neuropsychological functioning.

Methods: This monocentric study was conducted between July 2018 and February 2020. A standardized neuropsychological assessment including an evaluation of social cognition, executive functions, language and dexterity as well as a cerebral Magnetic Resonance Imaging (MRI) were systematically proposed to all CS patients. Moreover, *PTEN* variants were identified.

Results: Fifteen patients from 13 families were included with 6 non-sense (40%), 3 missense (20%), 5 frameshift (33.3%) and 1 splice site (6.6%) variant types. Eleven patients (73%) had altered social cognition: nine patients had a pathological Faux-Pas score and eleven had Ekman's facial emotions recognition impairment. Nearly all patients (93%) had impaired dexterity. Cerebral MRI showed various cerebellar anomalies in seven patients (46.7%).

Conclusion: Altered social cognition and impaired fine dexterity are frequently associated with Cowden syndrome. Further studies are needed to confirm these results and to determine whether dexterity impairment is due to the effect of germline *PTEN* variants in the cerebellum.

INTRODUCTION:

Cowden syndrome (CS, MIM 158350) is a rare autosomal dominant inherited tumor predisposition syndrome,[1] originally named and described by Lloyd and Dennis in 1963 after a patient with multiple hamartomas, fibrocystic breast disease and neurological abnormalities[2] even if some clinical descriptions without giving rise to the individualization of the entity have been previously published.[3–5]

CS is related to germline variants of *PTEN* (Phosphatase and TENsin homolog), a tumor suppressor gene with a documented role in the development of both hereditary and sporadic malignancies. Several syndromes are associated with germline variants of *PTEN*, including CS,[6] and are grouped under the umbrella term « *PTEN* hamartoma tumor syndrome » (PHTS).

CS is characterized by an increased risk of developing numerous cancers particularly female breast cancer, thyroid cancer, melanoma, endometrial cancer and renal cancer.[7] It is associated with macrocephaly and autism spectrum disorders (ASD).[8] Encephalic abnormalities, notably Lhermitte-Duclos disease (hamartoma of the cerebellum), described as pathognomonic of CS in adult, are frequently encountered. Various neuroimaging abnormalities are reported in CS such as meningiomas, multiple venous anomalies, but also white matter abnormalities, prominent perivascular spaces and cortical malformations.[9] There are several genetic variants, mainly nonsense, missense, splice site and frameshift, affecting all exons of the gene.[10]

In our practice of reference center for rare genetic skin diseases, we observed during CS patients' visits, that their behavior was often slightly maladapted to social norms and conventions (see Supplementary Material S1 for clinical vignettes). ~~For example, during his first consultation, a patient with CS asked if the medical doctor could subsidize his wedding. However, most of these patients are professionally well inserted~~. Thus, current data in the literature suggesting a link between ASD in which social cognition is majorly impaired and germline *PTEN* variant, [11] as well as our clinical

observation both suggest a link between impaired social cognition and CS. To date, no study has specifically assessed social cognition in CS.

~~These behaviors can be interpreted as social impairs and thus be linked to impaired social cognition.~~ Social cognition refers to the various cognitive processes that are involved in our interpersonal relationships and that make these relationships adequate and adapted to social norms.[12] There are different approaches of social cognition, and others define social cognition as socially contextualized cognition.[13] Social cognition performances correlate with other cognitive processes notably executive functions[14] and language in its semantic component.[15] As most cognitive domains, it also correlates with mood, social cognition being affected in depressive syndromes.[16]

To date, only one study has focused on the cognitive functioning of adult patients with CS.[17] This study did not evaluate social cognition, but it highlighted an extremely variable intellectual functioning, and an impairment of working memory, executive functions, and fine dexterity. ~~which was suggestive of frontal lobe damage or dysfunction. However, in this study, there were no systematic brain imaging to search for brain lesions which are commonly reported in CS, and no specific evaluation of social cognition. Executive function disorders have also been observed in children with PTEN variant.~~

Fine dexterity can be defined as the ability to coordinate accurately and rapidly hand and finger movements in an adaptive manner, such as required for fine control in grasping and manipulation of small objects.[18] It is acquired through repetition and experience in motor learning.[19] Fine dexterity overlaps with other cognitive functions notably motor control, limb-kinetic praxis and ideomotor praxis.[20, 21] Additionally, several studies have shown an association between fine dexterity and various cognitive domains, notably executive function, in healthy individuals as well as in Alzheimer's disease and parkinsonian patients.[22, 23] More specifically, fine dexterity was mainly associated with flexibility, fluency and problem solving.[20, 23]

In clinical practice, dexterity can be evaluated by various tests including the Nine Hole Peg Test (9-HPT)[24] which has been previously used in Parkinson's Disease[25] or Multiple Sclerosis.[26] Most manual dexterity tests are timed and require a certain level of accuracy.[27]

The aim of the study was to assess social cognition and fine dexterity in CS by means of a neuropsychological assessment. In this aim, we analyzed 15 patients with *PTEN* variants in order to determine whether the inappropriate behaviors we observed in CS patients relate to impaired social cognition. All patients underwent an extensive neuropsychological assessment, and a brain MRI to verify whether the putative social cognition impairment would be associated with brain lesions and/or other cognitive impairment and/or fine dexterity impairment. Because of previous reports of executive dysfunctions in CS, we proposed a slightly more detailed assessment of executive functions than other cognitive functions. The secondary aim was to assess whether social cognition impairment correlates with impaired mood, dysexecutive syndrome, or language impairment and to search for a correlation between social cognition impairment and cerebral abnormalities on brain MRI.

MATERIAL AND METHODS:

Patients

All CS patients seen by a dermatologist (FC) in the department of Dermatology at Avicenne Hospital (Bobigny, France), whether they had expressed a cognitive complaint or not, have been granted neurological examination, neuropsychological testing, and brain MRI, as part of the follow-up for CS.

Patients seen between July 2018 and February 2020 and fulfilling the following inclusion criteria were included: (i) clinical manifestations of Cowden syndrome; (ii) definite germline *PTEN* variants; (iii) age greater than 18 years. The non-inclusion criterion was a refusal to perform the neuropsychological tests or the brain MRI. We also excluded patients who had a severe comorbidity requiring urgent

care. All the data were obtained from the records of patients. Oral consent was obtained from all participants and written consent was obtained for genetic analysis. The current study obtained the authorization of the Local Ethics Committee of Avicenne Hospital (CLEA-2019-92).

Demographic and clinical information such as gender, age, and history of benign or malignant tumors of skin, breast, thyroid, gastrointestinal tract, and central nervous system were collected.

Neurological examination

All participants had a clinical evaluation by a neurologist (BG or ADL). A systematic interview was performed for each patient to collect personal and family history (notably neurological and psychiatric history), neurological development (dyslexia, psychomotor retardation, and educational difficulties), cognitive complaint and lifestyle (notably education duration and occupation). Neurological examination was carried out in search of focal signs or impairment of cognitive functions (memory, instrumental and executive). Among instrumental functions, praxis was assessed during physical examination of limb-kinetic, ideomotor and ideational praxis. Cranial perimeter was systematically measured; macrocephaly was defined as a cranial perimeter greater than 58 cm for female and 60 cm for male, according to Pilarski et al.[28]

Neuropsychological testing

All participants underwent a systematic and standardized neuropsychological assessment, conducted by a qualified neuropsychologist (CB).

It included an evaluation of ~~the~~ two core aspects of social cognition: theory of mind and facial emotions recognition. The ~~cognitive~~ theory of mind was assessed by the TOM-15[29] and the modified and reduced version of the Faux-Pas test,[30] which are components of the mini Social and Emotional Assessment (MINI-SEA).[31] They assess mentalizing abilities through two different gold-standard paradigms. TOM-15 relies on false-beliefs understanding, and the modified Faux-Pas test relies on both mentalizing and social contexts understanding. Facial emotions recognition was

assessed with Ekman faces test, which is a reduced version of the Pictures of Facial Affect (POFA) test[32] and which is also a component of the MINI-SEA. Dexterity was assessed by the 9-HPT.[24]

Neuropsychological testing included Raven's progressive matrices (PM-38) to assess inductive reasoning capacity,[33] which is a component of global intellectual functioning. It included an assessment of executive functions with Trail Making Test (TMT-A and B) and verbal fluencies for mental flexibility,[34] Stroop for mental inhibition,[34] and memory of WAIS-IV numbers for working memory.[35] Language was assessed with a 40 drawings naming test (DENO-40). A psycho-affective assessment was performed with the Apathy Scale[36] and the HADS Depression and Anxiety Scales.[37]

All tests were interpreted using age-corrected and, when appropriate, educationally corrected standards according to the recommendations of published textbooks (Supplemental material S1). Since all tests were interpreted in the context of age, and/or education, and/or gender that varied across patients we described the results as normal or impaired according to normative data. Results were considered as impaired when the Z-score value was below -1.65.

Brain MRI

All study participants underwent a brain MRI to search for brain abnormalities and tumors associated with CS.

The imaging protocol was developed based on the most frequently described brain abnormalities in CS patients[9]. It included the following imaging sequences: diffusion and Apparent Diffusion Coefficient (ADC), Susceptibility Weighted Imaging (SWI), 3-dimensional Fluid Attenuated Inversion Recovery (3-d FLAIR), time-of-flight (TOF), 3-dimensional Brain Volume T1-weighted (BRAVO) and gadolinium injection with Time Resolved Imaging of Contrast KineticS (TRICKS) and Fast Spoiled Gradient-echo (3d FSGPR).

Genetics analyses

The variant search was carried out on blood DNA by next-generation sequencing according to an Illumina technique on a Myseq device after exon capture of a genes panel including *PTEN* (Agilent SureSelect Target enrichment kit). The detected variants were confirmed by Sanger sequencing on two independent samples. Interpretation of sequence variants was performed using the criteria of the American College of Medical Genetics and the Association for Molecular Pathology (ACMG/AMP).[38]

Statistics

We performed statistical analyses to compare patients' characteristics and neuropsychological results according to the different types of PTEN variants. We also carried statistical analyses to search for correlation between cognitive tests and demographic characteristics. These analyses can be found as Supplementary Material S2.

We used non-parametric tests given the small size of the population sample. We performed Kruskal-Wallis (Chi2) tests followed by Mann Whitney (U) tests to compare patients' characteristics and neuropsychological results according to the different types of *PTEN* variants (nonsense, missense, splice site and frameshift) found in our population.

We performed Mann Whitney (U) tests to compare quantitative data between two groups and Spearman (Rho) correlations analyses to search for correlations between quantitative data. The degree of significance p was set at 0.05, after correction for multiple comparisons by Bonferroni method. All statistics were performed using SPSS IBM v24 software.

Results are expressed as mean ± standard deviation (SD).

RESULTS:

A total of 16 patients were assessed between July 2018 and February 2020. One patient was excluded because of a psychiatric disorder requiring emergency hospitalization. Data of 15 patients from 13 families were analyzed (Table 1).

Mean age was 43.3 ± 14.4 years old (range: 18 to 67 years) with a mean education duration of 12.7 ± 2.6 years (range: 8 to 17 years). The sex ratio was nine women and six men (9:6).

	Gender	Age (range in years)	Occupation	CP (cm)	Education (years)	Cognitive complaint	Neurological history	Neurodev. Disorder	Tumoral history
Patient 1	M	45-50	Computer scientist	63°	14	No	No	No	Gingival papillomatosis, thyroid nodule, melanoma
Patient 2	M	50-55	Teacher	65°	17	No	No	No	Gingival papillomatosis, GI polyposis, thyroid nodule
Patient 3	F	65-70	Child care assistant	58°	10	No	No	No	Breast adenocarcinoma, acrokeratoses, thyroid nodule
Patient 4	M	35-40	Employee	61°	15	No	Focal epilepsy	No	Oligodendroglioma, gingival papillomatosis, thyroid nodule
Patient 5	F	30-35	Caregiver	62°	11	Yes	No	No	Breast adenocarcinoma, gingival papillomatosis, thyroid nodule
Patient 6	M	30-35	Human resources	62°	15	No	No	No	Acrokeratoses, thyroid nodule
Patient 7	F	50-55	Secretary	60°	14	No	No	No	Meningioma, gingival papillomatosis, thyroid nodule
Patient 8	F	45-50	Public official	59°	15	No	No	No	Breast adenocarcinoma, acrokeratoses, thyroid nodule
Patient 9	F	45-50	Specialized Helper in pre-school	59.5°	12	Yes	Focal epilepsy	No	Thyroid nodule, acrokeratoses
Patient 10	M	15-20	Student	59.6	10	No	No	Yes (language, motor)	Arnold-Chiari, acrokeratoses, thyroid nodule
Patient 11	M	20-25	Automobile inspector	64°	12	No	No	No	Cerebellar DVA, gingival papillomatosis
Patient 12	F	25-30	Dog handler	60°	12	No	No	No	Meningioma, gingival papillomatosis, thyroid nodule
Patient 13	F	55-60	Director of company	61°	16	No	Focal epilepsy	No	Gingival papillomatosis, breast adenocarcinoma, thyroid nodule
Patient 14	F	40-45	Public official	62°	14	No	No	No	Gingival papillomatosis, breast adenocarcinoma, thyroid nodule
Patient 15	F	45-50	Public official	62°	8	Yes	No	Yes (language)	GI polyposis, papillary thyroid carcinoma
Mean (SD)	6M/9F	43.3 (14.4)		61.9 (1.96)	12.7 (2.6)				

Table 1. Demographical features. DVA: Developmental Venous Anomaly, CP: Cranial Perimeter, GI: Gastrointestinal SD: Standard Deviation. Patients with macrocephaly are marked with °.

Genetic features

All patients had an identified germline *PTEN* mutation. Variant types included 6 non-sense (40%), 3

missense (20%), 5 frameshift (33.3%) and 1 splice site (6.6%). These are truncating mutations (all but

missense) responsible for a loss of function of PTEN in most of cases and missense mutations in three

cases classified as probably pathogenic (class 4) according to the ACMG/AMP criteria. The identified

variants are summarized in Table 2.

Patient	Exon	cDNA (NM_000314.8)	Protein	Consequence	Pathogenicity
Patient 1	Exon 2	c.103A>G	p.(Met35Val)	missense	Class 4
Patient 2	Exon 5	c.388C>T	p.(Arg130*)	nonsense	Class 5
Patient 3	Exon 5	c.463T>A	p.(Tyr155Asn)	missense	Class 4
Patient 4	Exon 7	c.675 T>A	p.(Tyr225*)	nonsense	Class 5
Patient 5	Exon 5	c.352dupC	p.(His118Profs*8)	frameshift	Class 5
Patient 6	Exon 7	c.733C>T	p.(Gln245*)	nonsense	Class 5
Patient 7	Exon 7	c.722_723dupTT	p.(Glu242Leufs*15)	frameshift	Class 5
Patient 8	Exon 5	c.477G>T	p.(Arg159Ser)	missense	Class 4
Patient 9	Exon 8	c.955_958delTACT	p.(Thr319*)	nonsense	Class 5
Patient 10°	Exon 8	c.955_958delTACT	p.(Thr319*)	nonsense	Class 5
Patient 11	Exon 5	c.352dupC	p.(His118Profs*8)	frameshift	Class 5
Patient 12	Exon 1	c.48T>A	p.(Tyr16*)	nonsense	Class 5
Patient 13	Intron 7	c.801+1delG		splice	Class 5
Patient 14	Exon 8	c.820 delT	p.(Trp274Glyfs*2)	frameshift	Class 5
Patient 15	Exon 7	c.659dupT	p.(Val222Glyfs*21)	frameshift	Class 5

Table 2- List of the PTEN variants involved in the 15 Cowden syndrome patients. Patient with proven autistic spectrum disorder is marked with °.

Clinical features

The two most frequent benign tumors in this cohort were skin tumors (n=15; 100%) with gingival papillomatosis in 10 patients (66.7%), and thyroid tumors (n=13; 86.7%) with thyroid nodules in 8 patients (53%). The most frequent malignant tumor was adenocarcinoma of the breast in 5 patients (33.3%). Macrocephaly was present in 14 out of 15 patients (93.3%) and mean cranial perimeter was 61.9 ± 1.96 cm, (range: 58-64 cm).

One patient had a history of neurosurgery for a brain tumor during childhood (oligodendroglioma; patient 4), and two patients (13.3%) had a neurodevelopmental abnormality: a ~~proven~~ confirmed autistic spectrum disorder (ASD) associated with a delay in language acquisition for one patient (patient 10), a delay in writing and reading learning for the other patient (patient 15). Diagnosis of ASD was confirmed by a multidisciplinary examination, including a specialized psychiatrist, psychologist and neuropsychologist and following the diagnosis criteria of the DSM-5.[39] In addition, 3 patients (20%) had a history of focal epileptic seizure.

Three patients had a psychiatric history (20%), dominated by depressive syndrome (n=2) and anxiety disorder (n=1).

Neuropsychological testing

Three of the 15 patients (20%) expressed a cognitive complaint before the neuropsychological testing. These complaints were about attention (1 patient) and memory (2 patients).

All patients presented at least one pathological score at the neuropsychological assessment (Table 3).

	PM-38 (max. 55)	TMT-A (seconds)	TMT-B (seconds)	TMT B-A (seconds)	*Stroop Interference	Faux-Pas (/15)	Emotion Recognition (/15)	TOM-15 (0-15)	9-HPT DH (seconds)		9-HPT NDH (seconds)		HADS anxiety (0-21, abnormal > 8)	HADS depression (0-21, abnormal > 8)
									1	2	1	2		
Patient 1	41	34	99	65	34	12.4	13.7	13	28°	19	26	26	9	4
Patient 2	46	17	55	38	98°	9''	10.7°'	14	27,9°	22	26,2	20,8	6	5
Patient 3	35	40	121	81	NC°	10.9°'	11.1°	14	23,5°	20,7	23,6	24,2	11°	10°
Patient 4	45	40	151°	111°	107°	8.2°'	8.1°'	13	30,5°	25°	31,2°	29°	2	5
Patient 5	51	41	134°	93°	43	9.4°'	13.3	14	24,4°	19,8°	31,8°	23,3	5	2
Patient 6	47	22	58	36	36	13.1	12	13	23,4°	18,7	26,4°	19,2	5	2
Patient 7	54	18	42	24	49	13.1	9.4°'	13	21,7°	19,7	19	17,3	8	5
Patient 8	50	26	80	54	71	11.2'	12.9	14	23,9°	20,9°	23,4°	21,03	9°	4
Patient 9	44	30	65	35	58	13.1	9.4°'	11	23,7°	19,6	19,5	19,2	11°	4
Patient 10	31°	35	104	69	49	5.2°'	10.3°'	6°	26,9°	26,06°	25,31°	27,8°	9°	7
Patient 11	48	27	65	38	51	15	13.7	11°	26,63°	20,9°	23,7°	20,5	10°	3
Patient 12	42	29	85	56	73	8.2°'	12°	13	25,7°	22,2°	23,5°	21,5°	8	4
Patient 13	47	32	83	51	NC°	10.9°'	11.1°	9°	26°	26,4°	27,5°	32,5°	7	5
Patient 14	36	37	60	23	44	8.2°'	11.5°	3°	23,8°	20,8	25°	22,7°	12°	11°
Patient 15	34	19	82	63	52	8.2°'	12°	9°	19,2	20,9	18,6	18,3	15°	11°
Mean	43.4	29.8	85.6	55.8	58.8	12.1	11.4	13.3	25.0	21.5	24.7	22.9	8.5	5.5

Table 3- Results of neuropsychological assessment. Abnormal results (according to age-appropriate standards) are highlighted in bold and with °. Abnormal results according to recent French norms of MINI-SEA[40] are marked with '.*This score corresponds to the score obtained on the third part of Stroop test. DH: Dominant Hand, NDH: Non Dominant Hand, NC: Not Completed.

Overall inductive reasoning, assessed with the PM-38, was preserved in all but one patient (Patient 10 who suffered from ASD).

Social cognition

Five patients (33.3%) were impaired at the TOM-15, which assesses false-beliefs understanding. These five patients were not able to move away from their own beliefs to put themselves in someone else's shoes. Nine patients (60%) had a pathological modified Faux-Pas test, which assesses mentalizing and social contexts understanding. These nine patients judged social missteps to be intentional or did not understand or perceive social missteps. Eleven patients (73%) were impaired on facial emotion recognition test. More precisely, fear (n=13; 86.6%), anger (n=9; 60%) and sadness (n=8; 53.3%) were the least recognized emotions. On the contrary, all participants identified joy and neutral emotions.

New French norms of the mini-SEA that take into account age and education have been published after the end of the study.[40] Using these new norms showed slightly different results, with ten patients (instead of 9) having abnormal modified Faux-Pas test scores and five patients (instead of 11) having abnormal facial emotion recognition scores.

Executive functions

Regarding flexibility assessment, two patients had a pathological score (13.3%) at the TMT-B and at the TMT-B-A, 4 patients (26.7%) were impaired at semantic verbal fluency with animals and 2 patients (13.3%) at verbal fluency with the letter "P".

Four patients had a pathological score (26.7%) at the interference part of the Stroop test, which assesses cognitive inhibition. Four patients (26.7%) had a pathological score at the digit span subscore of the WAIS IV, which assesses working memory.

Dexterity

Fourteen patients had a pathological score with the dominant hand at first trial (93.3%) and ten had a pathological score with the non-dominant hand (66.7%). Performances were slightly improved at second try, with 8 pathological scores with the dominant hand (53.3%) and 8 pathological scores with the non-dominant hand (53.3%).

Language

Only one patient had a naming disorder on the DENO-40 scale (6.7%).

Mood

Nine patients (60%) had a pathological score on the HADS anxiety scale and three (20%) on the HADS depression scale. Three patients (20%) had a pathological score at the Apathy scale.

Statistical analyses (Supplementary Material S2)

Statistical analyses showed no genotype-phenotype correlations: results in social cognition tests, dexterity, as well as the whole neuropsychological assessment were not different according to the type of germline *PTEN* variants or according to the nature of variants (truncating versus non-truncating). Additionally, there was no correlation between any cognitive scores, dexterity and/or demographic characteristics.

Statistical analyses

Neuropsychological testing according to the type of mutation

There were no significant differences in TOM-15 results (Chi2 = 4.216, p = 0.239), Faux-Pas score (Chi2 = 1.206, p = 0.752) and recognition of facial emotions (Chi2 = 4.156, p = 0.245) according to the type of *PTEN* variant. Furthermore, there was no significant difference between results of social cognition tests according to the presence of truncating or non-truncating *PTEN* variants (TOM-15: U = 6.00, p = 0.087; Faux-pas: U = 12.00, p = 0.421; facial emotion recognition: U = 9.00, p = 0.217).

Neuropsychological testing according to demographical and psychological parameters. Performance at the Raven progressive matrices (PM-38) correlated negatively with HADS depression score (Rho = - 0.638, p = 0.010), HADS anxiety score (Rho = - 0.546, p = 0.035) and the apathy scale (Rho = - 0.553, p = 0.033). There was a significant negative correlation between the Faux-Pas score and the HADS depression score (Rho = -0.544, p = 0.036). Education duration also negatively correlated with anxiety (Rho = - 0.566, p = 0.028).

There was no correlation between scores on the HADS anxiety scale and scores of social cognition tests (TOM-15: Rho = -0,449, p = 0,093; Faux-Pas score: Rho = 0,035, p = 0,903; facial emotion recognition: Rho = 0,249, p = 0,371) and no correlation between scores on tests exploring executive functions and scores of social cognition tests (Supplemental material S1).

Additionally, neuropsychological tests did not differ according to gender, age, or cranial perimeter. Nor did they differ according to the presence of a memory complaint, nor according to the presence of a cerebellar abnormality (Supplemental material S1).

MRI (Supplementary Material S3)

Thirteen patients (86.7%) had at least one brain abnormality, when dilatation of Virchow-Robin spaces was considered abnormal. The most frequent abnormality was the presence of dilated perivascular spaces (PVS) or Virchow-Robin present in 13 patients (86.7%). Eight patients (53.3%) presented developmental venous anomalies and 5 (33.3%) had periventricular and semi-oval centers nonspecific leukopathy, which rated at 2 on the Fazekas scale, corresponding to moderate impairment. In addition, 7 patients out of the 15 (46.7%) had various cerebellar abnormalities and among them, 2 patients (13.3%) presented a Lhermitte-Duclos disease.

The other observed abnormalities were meningioma (n=3; 20%), microbleeds (n=3; 20%), ptosis of the cerebellar tonsils (n=4; 26.7%) and cavernoma (n=2; 13.3%).

Main MRI findings are presented in Figure 1.

DISCUSSION:

We examined social cognition in patients with CS and *PTEN* variants using a standardized neuropsychological assessment and showed impaired social cognition especially in facial emotion recognition and affective theory of mind. Fine dexterity was impaired in almost all patients. All patients underwent a clinical neurological evaluation and a standardized brain MRI, which showed various brain abnormalities.

This study has several limitations. First, the size of our patient group was small since CS is a rare disorder, with estimated prevalence of 1:200.000.[41] However, the results were clear-cut showing that the majority of patients were impaired on at least one of the social cognition tests. This suggests a strong link between social cognition impairment and germline *PTEN* variants. Secondly, there might have been a selection bias because participation was based on willingness and the most affected patients may have refused to take the tests. The cognitive assessment was systematically proposed to all patients during a follow-up dermatological consultation whether they had expressed a cognitive complaint or not, to limit this bias as much as possible. ~~Thirdly, the tests used for social cognition assessment may be partly outdated, notably regarding the Ekman's faces. This test, developed by Ekman and Friesen in 1976, was one of the first tools available for the evaluation of facial emotion recognition. It only takes primary emotions into account and therefore does not provide information on the patient's ability to perceive more complex emotional states.~~ Thirdly, we showed here a significant impairment of social cognition by comparing the test results to validated norms, but controlled studies with age, gender and pathological context-matched controls group would be necessary to confirm these results. Finally, patients had significant anxiety and depressive symptoms on the HADS scale, which may confound and distort the results of neuropsychological tests and thus be responsible for a confusion bias. However, we found no correlation between HADS scores and social cognition scores.

The majority (73%) of patients were impaired on facial emotion recognition. Fear was the most affected emotion, followed by anger and sadness. On the contrary, joy and neutral emotions were relatively preserved. Ekman faces test analyses primary emotions. Thus, impairment on this test may indicate a non-subtle impairment of primary emotions, which may have significant impact on daily activities. However, these results should be interpreted with caution, since an additional analysis in the light of the latest published norms showed less significant results with only 5 patients having impaired scores on facial emotion recognition.

Regarding the theory of mind assessment, we found that the modified and reduced version of the Faux-Pas test, assessing social context understanding, was abnormal in the majority of patients (60%), while the TOM-15 scores, assessing false-beliefs understanding, were relatively preserved in most patients. The different degree of impairment between these two tests might be explained by several factors such as more possibilities for subjective interpretation, higher variance in the responses and the greater differential importance of socials norms in the modified Faux-Pas test that in the TOM-15.

The different degree of impairment between the two components of the theory of mind might be explained by their possible functional independence. Impairment of the cognitive theory of mind might relate to diffuse lesions of the lateral prefrontal cortex while impairment of the affective theory of mind would relate to lesions of the orbito-medial prefrontal cortex and the fronto-striatal limbic system. The predominant impairment of negative emotions, particularly fear, can be compared to other pathological situations, notably in patients with behavioral variant Fronto-Temporal Dementia (bv-FTD). Indeed, the deficit in the treatment of negative-valued emotions (sadness, fear, anger, disgust) in bv-FTD, is usually attributed to lesions of the orbito-medial prefrontal cortex and the amygdala. Our results suggest a possible involvement of the orbito-medial prefrontal cortex and the amygdala (anteromedial region of the temporal lobe): notably because the recognition of negative emotions and the theory of affective mind rely on both structures. There was

no brain anomaly detected to explain social cognition impairment, but microstructural and molecular modifications may be involved. At a molecular level, it has been recently shown that synaptic actions of PTEN in mice's amygdala interferes with their social behavior : decrease in activity at synapses was associated with less sociability whereas an increase in activity was associated with increased social behavior.[42] In parallel, the cerebellum might be involved in the social cognition impairment of our patients. Several arguments support this hypothesis. First, almost half of the patients had a cerebellar abnormality on brain MRI and all but one had an impaired dexterity that was compatible with cerebellar dysfunction. Second, there is a demonstrated link between germinal *PTEN* variants and the existence of structural abnormalities of the cerebellum (Lhermitte-Duclos disease). Third, it has been shown that the cerebellum plays an important role in social cognition by assisting in learning and understanding social actions and by supporting optimal predictors about social interactions.[43] Social cognition testing was not different in patients with cerebellar abnormalities when compared to patients without cerebellar abnormalities. However, microstructural changes undetected by brain MRI might be involved. Further studies, including functional MRI, will be necessary to determine the anatomical correlates of social cognition impairment of CS patients.

Statistical analyses showed no genotype-phenotype correlations: results in social cognition tests as well as the whole neuropsychological assessment were not different according to the type of germline *PTEN* variants or according to the nature of variants (truncating versus non-truncating variants). However, this analysis should be interpreted cautiously because of the small size of the subgroups tested. Previous mutation analyses of patients with PHTS have shown an over-representation of missense type mutations in patients with a proven ASD,[44] but other authors showed no phenotype-genotype correlation.[45] This highlights the complexity of the genotype-phenotype relationship, the need for a better understanding of the natural history of PHTS via longitudinal studies and suggests the existence of inter- and intra-individual variability factors.

Only a small proportion of CS patients had altered cognitive inhibition, flexibility, lexical fluency and/or working memory. In a previous study, the authors described an impairment of executive functions in CS.[17] In this study, four tests were proposed to assess executive functions. Although results were under the normative mean at the group level, only 13-26% of the 25 participants were impaired in these tests when impairment is defined by a Z-score of -1.65. These figures are strictly comparable to 13 to 26% of participants in the current study. A previous study showed an impairment of all of these executive functions in 25 CS patients. This discrepancy may be explained by a lack of statistical power of our study due to a smaller sample size. Alternatively, the high number of tests used in Busch's study might have led to false positive results due to multiple comparisons.

Most of our patients (93%) had an impaired fine dexterity predominant on the dominant hand or on both hands. This impairment tended to improve at second try. Dexterity assessed by the 9-HPT test was impaired in almost all patients. Processing speed might also be involved in this test and a decreased processing speed may induce altered score at the 9-HPT. However, The TMT-A, which is a test that highly relies on processing speed, was not altered in our patient group. Moreover, the 9-HPT is supposed to assess dexterity more than speed because the test consists of grasping small sticks and inserting them into holes. This requires a certain precision and therefore good fine motor skills. Surprisingly, none of the patients presented any complaint concerning dexterity and no abnormality was observed on clinical neurological examination, in particular no cerebellar syndrome and no apraxia. Thus, the significance of this impairment from a neuroanatomical and pathophysiological point of view remains unclear. Indeed, it could be linked to a pure motor disorder, to a cerebellar dysfunction, to a cognitive slowness and/or to a praxis disorder. The improvement during the second trial would be in favor of a praxis disorder but this improvement is not present in all patients. A similar impairment of fine dexterity has been described previously in CS patients.[17] It might be considered as an endophenotype of *PTEN* variants, and further studies will help to determine the relation between *PTEN* variants, dexterity and the cerebral and cerebellar bases of this dexterity impairment in CS.

All but one patient had a normal score at the inductive reasoning task, suggesting that intellectual functioning, defined as the ability to obtain and use knowledge in adaptive situations, was preserved in most patients, as described previously.[17] It is consistent with the normal professional integration of CS patients. ~~Furthermore, there was a significant negative correlation between anxiety, depressive features, apathy and inductive reasoning task. Although some authors have shown the negative impact of anxiety and depressive symptoms over intellectual functioning, other have shown that the higher an individual's Intellectual Quotient (IQ), the higher the risk of developing psychiatric comorbidities.~~

ASD is part of the clinical symptoms of CS,[28] and may relate to *PTEN* variants.[44] *PTEN* variant seams to lead to a particular cognitive phenotype in patients diagnosed with ASD (*PTEN*-ASD). A recent study has shown that pediatric population *PTEN*-ASD had a distinct neurobehavioral phenotype compared to *PTEN* variant without ASD and to idiopathic ASD: in *PTEN*-ASD, cognitive deficits are more severe and appears to involve several domains such as executive functions, language and intellectual functioning.[46] As social cognition is the most impaired cognitive function in ASD,[11] similar mechanisms might be involved in our CS patient group. In the present study, the patient who was diagnosed with ASD (patient 10) belongs to the same family and carries the same variant as patient 9, emphasizing the intra-familial variability of expression for *PTEN* variants, specifically in the constitution of the autistic phenotype. This observation highlights the need for additional factors associated with *PTEN* variants in the genesis of ASD, which may involve modifier genes. However, the precise pathophysiological involvement of the *PTEN* variants in ASD remains unclear. Anomalies in the hippocampal and cerebellar structures have been reported in CS patients with ASD,[47] including neuronal hyperproliferation, migration and lamination defect, anomalies of synaptic plasticity and axonal myelination, but further studies will be necessary to determine whether similar mechanisms are involved in patients presenting with minor social cognition impairment such as our patient population.

Analysis of cerebral MRI scans revealed various abnormalities in our patients, similar to what has been previously reported for CS.[9] The most frequent brain anomaly was the dilated Virchow-Robin spaces. This lesion is common in the general population (50-100% of patients after the age of 60 years depending on the measurement scales)[48] and it is found in many neurological pathologies such as small vessel disease.[49] According to recent data, it does not appear to be associated with cognitive decline or increased risk of cognitive impairment,[50] although this is still debated. It is questionable whether there is a link between this abnormality and impaired social cognition, especially as our patients had a mean age of 43.3 years, whereas dilated Virchow-Robin spaces are usually reported in older populations with a significant increase of prevalence after the age of 65 years. Finally, most of our patients had developmental venous anomalies, in line with previous studies showing that CS had more central nervous system vascular abnormalities such as venous angiomas and cavernous angiomas.[51]

In conclusion, fine motor dexterity impairment was observed in almost all patients, and social cognition impairment was observed in 73% of the 15 CS patients included in this study. Social cognition impairment might explain some of the awkward behaviors of these patients. Impairment in facial emotion recognition and social context understanding could lead to a shift in social relations and could explain the discomfort of clinicians during consultations. In view of these results, it seems important to recognize the social cognition disability of patients suffering from CS, as it may have important functional implications for patients and their relatives. This study also raises the question of a specific treatment of social cognition impairment. Although not yet validated, specific rehabilitation approaches may be proposed notably with cognitive remediation and social skills training.[52, 53] Recognition of disability, development of specific treatments and rehabilitation for social cognition might improve the quality of life of patients with CS. Finally, this study relied on a small number of patients, and further controlled studies will be necessary to confirm these results.

ACKNOWLEDGMENTS

DISCLOSURE

The authors declare no conflicts of interest.

ETHICS DECLARATION

We conducted a retrospective study, which complied with the Declaration of Helsinki. French law requires neither ethics committee approval nor informed consent for studies of retrospective data. However, all data were anonymized and compiled as required by the Commission Nationale de l'Informatique et des Libertés (the French data protection authority).

The current study obtained the authorization of the Local Ethics Committee of Avicenne Hospital (CLEA-2019-92). Oral consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

All the data supporting in Table 1, 2, 3 and Figure 1 are publicly available.

REFERENCES:

1   Uppal S, Mistry D, Coatesworth AP. Cowden disease: a review: Cowden disease. *Int J Clin Pract* 2007;**61**:645–52.

2   Lloyd KM. Cowden's Disease: A Possible New Symptom Complex with Multiple System Involvement. *Ann Intern Med* 1963;**58**:136.

3   Costello MJ. A case for diagnosis (keratosis follicularis?). *Arch Dermatol Syphilol* 1941;:109–10.

4   Witten VH, Kopf AW. A CASE FOR DIAGNOSIS-VERRUCAE PLANAE-ADENOMA SEBACEUM-EPIDERMODYSPLASIA VERRUCIFORMIS. In: *ARCHIVES OF DERMATOLOGY*. AMER MEDICAL ASSOC 515 N STATE ST, CHICAGO, IL 60610 1957. 799–800.

5   Brownstein MH, Wolf M, Bikowski JB. Cowden's disease: a cutaneous marker of breast cancer. *Cancer* 1978;**41**:2393–8.

6   Zbuk KM, Eng C. Cancer phenomics: RET and PTEN as illustrative models. *Nat Rev Cancer* 2007;**7**:35–45.

7   Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, Edery P, Bottani A, Layet V, Caron O, Gilbert-Dussardier B, Delnatte C, Dugast C, Fricker J-P, Bonneau D, Sevenet N, Longy M, Caux F, French Cowden Disease Network. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *J Med Genet* 2013;**50**:255–63.

8   Hobert JA, Embacher R, Mester JL, Frazier TW, Eng C. Biochemical screening and PTEN mutation analysis in individuals with autism spectrum disorders and macrocephaly. *Eur J Hum Genet EJHG* 2014;**22**:273–6.

9   Dhamija R, Weindling SM, Porter AB, Hu LS, Wood CP, Hoxworth JM. Neuroimaging abnormalities in patients with Cowden syndrome: Retrospective single-center study. *Neurol Clin Pract* 2018;**8**:207–13.

10   Yehia L, Keel E, Eng C. The Clinical Spectrum of PTEN Mutations. *Annu Rev Med* 2020;**71**:103–16.

11   Fernández M, Mollinedo-Gajate I, Peñagarikano O. Neural Circuits for Social Cognition: Implications for Autism. *Neuroscience* 2018;**370**:148–62.

12   Frith CD. Social cognition. *Philos Trans R Soc B Biol Sci* 2008;**363**:2033–9.

13   Smith ER, Collins EC. Contextualizing person perception: distributed social cognition. *Psychol Rev* 2009;**116**:343–64.

14   Ziv I, Leiser D, Levine J. Social cognition in schizophrenia: cognitive and affective factors. *Cognit Neuropsychiatry* 2011;**16**:71–91.

15   Apperly IA, Samson D, Humphreys GW. Studies of adults can inform accounts of theory of mind development. *Dev Psychol* 2009;**45**:190–201.

16   Hirschfeld RM, Montgomery SA, Keller MB, Kasper S, Schatzberg AF, Möller HJ, Healy D,

Baldwin D, Humble M, Versiani M, Montenegro R, Bourgeois M. Social functioning in depression: a review. *J Clin Psychiatry* 2000;**61**:268–75.

17   Busch RM, Chapin JS, Mester J, Ferguson L, Haut JS, Frazier TW, Eng C. Cognitive characteristics of PTEN hamartoma tumor syndromes. *Genet Med* 2013;**15**:548–53.

18   Makofske B. Manual Dexterity. In: Kreutzer JS, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology*. New York, NY: : Springer New York 2011. 1522–3.

19   Poirier F. Dexterity as a valid measure of hand function. *Occup Ther Health Care* 1988;**4**:69–83.

20   Vanbellingen T, Kersten B, Bellion M, Temperli P, Baronti F, Müri R, Bohlhalter S. Impaired finger dexterity in Parkinson's disease is associated with praxis function. *Brain Cogn* 2011;**77**:48–52.

21   Leiguarda RC, Marsden CD. Limb apraxias: higher-order disorders of sensorimotor integration. *Brain J Neurol* 2000;**123 (Pt 5)**:860–79.

22   de Paula JJ, Albuquerque MR, Lage GM, Bicalho MA, Romano-Silva MA, Malloy-Diniz LF. Impairment of fine motor dexterity in mild cognitive impairment and Alzheimer's disease dementia: association with activities of daily living. *Braz J Psychiatry* 2016;**38**:235–8.

23   Menon V, Hegde S, Pratyusha PV, Kamble N, Yadav R, Bhattacharya A, Pal PK. Motor Speed Matters! Cognitive Profile of Parkinson's Disease Patients With and Without Deficits in Motor Speed. *Neurol India* 2021;**69**:604.

24   Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole peg test of finger dexterity. *Occup Ther J Res* 1985;**5**:24–38.

25   Earhart GM, Cavanaugh JT, Ellis T, Ford MP, Foreman KB, Dibble L. The 9-hole PEG test of upper extremity function: average values, test-retest reliability, and factors contributing to performance in people with Parkinson disease. *J Neurol Phys Ther JNPT* 2011;**35**:157–63.

26   Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, Hudson LD, Rudick R, Multiple Sclerosis Outcome Assessments Consortium. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl* 2017;**23**:711–20.

27   Berger MAM, Krul AJ, Daanen HAM. Task specificity of finger dexterity tests. *Appl Ergon* 2009;**40**:145–7.

28   Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst* 2013;**105**:1607–16.

29   Desgranges B, Laisney M, Bon L, Duval C, Mondou A, Bejanin A, Fliss R, Beaunieux H, Eustache F, Muckle G. TOM-15 : Une épreuve de fausses croyances pour évaluer la théorie de l'esprit cognitive. *Rev Neuropsychol* 2012;**4**:216.

30   Baron-Cohen S, O'Riordan M, Stone V, Jones R, Plaisted K. Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. *J Autism Dev Disord* 1999;**29**:407–18.

31   Bertoux M, Volle E, de Souza LC, Funkiewiez A, Dubois B, Habert MO. Neural correlates of the mini-SEA (Social cognition and Emotional Assessment) in behavioral variant frontotemporal dementia. *Brain Imaging Behav* 2014;**8**:1–6.

32   EKMAN P. Pictures of Facial Affect. *Consult Psychol Press* Published Online First: 1976.https://ci.nii.ac.jp/naid/10011335061/ (accessed 15 Jul2021).

33   Raven CP. �ber die Potenz von Gastrulaektoderm nach 24st�ndigem Verweilen im �usseren Blatt der dorsalen Urmundlippe. *Wilhelm Roux Arch F� Entwicklungsmechanik Org* 1938;**137**:661–713.

34   Godefroy O, Azouvi P, Robert P, Roussel M, LeGall D, Meulemans T, Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group. Dysexecutive syndrome: diagnostic criteria and validation study. *Ann Neurol* 2010;**68**:855–64.

35   Suwartono C, Halim MS, Hidajat LL, Hendriks MPH, Kessels RPC. Development and Reliability of the Indonesian Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV). *Psychology* 2014;**05**:1611–9.

36   Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;**4**:134–9.

37   Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;**67**:361–70.

38   Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–23.

39   American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. American Psychiatric Association 2013. doi:10.1176/appi.books.9780890425596

40   Quesque F, Michalon S, Blanc F, Bertoux M. Validation de la mini-SEA dans une population française variée : données de référence pour la pratique clinique. *Rev Neuropsychol* 2020;**12**:367–75.

41   Nelen MR, Kremer H, Konings IB, Schoute F, van Essen AJ, Koch R, Woods CG, Fryns JP, Hamel B, Hoefsloot LH, Peeters EA, Padberg GW. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. *Eur J Hum Genet EJHG* 1999;**7**:267–73.

42   Sánchez-Puelles C, Calleja-Felipe M, Ouro A, Bougamra G, Arroyo A, Diez I, Erramuzpe A, Cortés J, Martínez-Hernández J, Luján R, Navarrete M, Venero C, Chan A, Morales M, Esteban JA, Knafo S. PTEN Activity Defines an Axis for Plasticity at Cortico-Amygdala Synapses and Influences Social Behavior. *Cereb Cortex N Y N 1991* 2020;**30**:505–24.

43   Van Overwalle F, Manto M, Cattaneo Z, Clausi S, Ferrari C, Gabrieli JDE, Guell X, Heleven E, Lupo M, Ma Q, Michelutti M, Olivito G, Pu M, Rice LC, Schmahmann JD, Siciliano L, Sokolov AA, Stoodley CJ, van Dun K, Vandervert L, Leggio M. Consensus Paper: Cerebellum and Social Cognition. *The Cerebellum* Published Online First: 7 July 2020. doi:10.1007/s12311-020-01155-1

44   Frazier TW, Embacher R, Tilot AK, Koenig K, Mester J, Eng C. Molecular and phenotypic

abnormalities in individuals with germline heterozygous PTEN mutations and autism. *Mol Psychiatry* 2015;**20**:1132–8.

45   Waite KA, Eng C. Protean PTEN: Form and Function. *Am J Hum Genet* 2002;**70**:829–44.

46   Busch RM, Srivastava S, Hogue O, Frazier TW, Klaas P, Hardan A, Martinez-Agosto JA, Sahin M, Eng C. Neurobehavioral phenotype of autism spectrum disorder associated with germline heterozygous mutations in PTEN. *Transl Psychiatry* 2019;**9**. doi:10.1038/s41398-019-0588-1

47   Rademacher S, Eickholt BJ. PTEN in Autism and Neurodevelopmental Disorders. *Cold Spring Harb Perspect Med* 2019;**9**:a036780.

48   Laveskog A, Wang R, Bronge L, Wahlund L-O, Qiu C. Perivascular Spaces in Old Age: Assessment, Distribution, and Correlation with White Matter Hyperintensities. *Am J Neuroradiol* 2018;**39**:70–6.

49   Brown R, Benveniste H, Black SE, Charpak S, Dichgans M, Joutel A, Nedergaard M, Smith KJ, Zlokovic BV, Wardlaw JM. Understanding the role of the perivascular space in cerebral small vessel disease. *Cardiovasc Res* 2018;**114**:1462–73.

50   S H, Cs T, Hhh A, M H, V M, N V, E H, Mk I, J A, Mw V, C C, N H, H V, Hj G, R S, Ma I. Enlarged perivascular spaces and cognition: A meta-analysis of 5 population-based studies. Neurology. 2018;**91**. doi:10.1212/WNL.0000000000006079

51   Lok C, Viseux V, Avril MF, Richard MA, Gondry-Jouet C, Deramond H, Desfossez-Tribout C, Courtade S, Delaunay M, Piette F, Legars D, Dreno B, Saïag P, Longy M, Lorette G, Laroche L, Caux F, Cancerology Group of the French Society of Dermatology. Brain magnetic resonance imaging in patients with Cowden syndrome. *Medicine (Baltimore)* 2005;**84**:129–36.

52   Kurtz MM, Gagen E, Rocha NBF, Machado S, Penn DL. Comprehensive treatments for social cognitive deficits in schizophrenia: A critical review and effect-size analysis of controlled studies. *Clin Psychol Rev* 2016;**43**:80–9.

53   Bon L, Lesur A, Hamel-Desbruères A, Gaignard D, Abadie P, Moussaoui E, Guillery-Girard B, Guénolé F, Baleyte J-M. Cognition sociale et autisme : bénéfices de l'entraînement aux habiletés sociales chez des adolescents présentant un trouble du spectre de l'autisme. *Rev Neuropsychol* 2016;**Volume 8**:38–48.

Fig 1. Main associated MRI findings involved in the 15 Cowden syndrome patients. (A) Axial T2 weighted imaging demonstrates classic striated aspect of Lhermitte-Duclos disease (arrows) - patient 7. (B) Axial T1 postcontrast MRI depicts a left anterior frontal developmental venous anomaly (arrow) - patient 4. (C) Axial SWAN sequence MRI illustrates a left frontal focus of magnetic susceptibility (circle) in the cerebral white matter, which is suggestive of a cavernoma - patient 7. (D) Ptosis of cerebellar tonsils (arrowhead) shown on sagittal T2-weighted fluid-attenuated inversion recovery sequence - patient 10. (E) Axial T1 postcontrast MRI illustrates a small left posterior parietal dural-based extra-axial mass (arrow) which is very suggestive of a meningioma - patient in 12. (F) As seen on axial T1-weighted MRI, multiple prominent vascular spaces or Virchow-Robin (arrows) are present in the cerebral white matter - patient 1.