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Central nervous system complications in adult cystinosis patients

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Abstract

Little is known about the long-term progression of adult nephropathic cystinosis patients. Our objective was to study central nervous system complications in cystinosis patients in the era of early cysteamine treatment, using advanced neuroimaging techniques. Neurological examination and multimodal brain 3 Tesla MRI were performed in 21 adult cystinosis patients, including 18 infantile cystinosis patients, 20 controls matched for age and renal function, and 12 healthy controls. Differences in gray matter volume and rest cerebral blood flow (CBF) using arterial spin labeling sequence were investigated using whole-brain voxel-based approach. Median age was 33.8 years (18.7-65.8). Seven patients (38.9%) presented with at least one central nervous system clinical abnormality: two (11.1%) with seizures, three (16.7%) with memory defects, five (27.8%) with cognitive defect, and one (5.5%) with stroke-like episode. These patients had a worse compliance to treatment (compliance score 2 vs 1, $P = .03$) and received a lower median cysteamine dose (0.9 g/day vs 2.1 g/day, $P = .02$). Among patients with infantile cystinosis, 13 (72.2%) showed cortical atrophy, which was absent in controls, but it was not correlated with symptoms. Cystinosis patients showed a significant gray matter decrease in the middle frontal gyrus compared with healthy controls and a significant negative correlation between the cystine blood level and rest CBF was observed in the right superior frontal gyrus, a region associated with executive function. Compliance to cysteamine treatment is a major concern in these adult patients and could have an impact on the development of neurological and cognitive complications.

KEYWORDS

arterial spin labeling, central nervous system, cortical atrophy, cysteamine, cystine blood level, cystinosis

1 | INTRODUCTION

Cystinosis is a rare autosomal recessive disease caused by intracellular cystine accumulation.[1,2] Renal transplantation markedly improves the life span of cystinotic patients. However, cystine accumulation continues in nonrenal organs.[3] Although rare, central nervous system complications have been described in adults with cystinosis.[4-6] In these publications, central neurological complications occurrence did not correlate with other extra-renal complications

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of cystinosis, but their frequency did correlate directly with age. Two forms were observed: a cystinosis encephalopathy[4,7] and stroke-like episodes.

More recent clinical studies have shown that patients may have mild neurocognitive abnormalities.[8-10] An increasing discrepancy with age compared to controls was described which may reflect a progressive cognitive impairment, possibly as a result of cystine accumulation in the brain over time.[8]

These central nervous system complications may affect quality of life, academic function, and professional insertion. However, little is known about the long-term neurological complications in adult patients since specific treatment by cysteamine became available. The development of advanced neuroimaging techniques has provided new tools to study the underlying neurophysiopathological mechanisms of metabolic diseases.[11] Therefore, in this study, our objective was to investigate neurological complications and anatomo-functional brain abnormalities in adult patients with cystinosis in the era of early cysteamine treatment. For that purpose, we first studied the neurological clinical profile and brain scans looking for radiological abnormalities. Then, we performed a neuroimaging study to investigate anatomo-functional abnormalities in patients when compared to a control group.

2 | PARTICIPANTS AND METHODS

2.1 | Participants

Eligible patients were male and female, age more than 18 years, with confirmed diagnosis of cystinosis. Twenty-one patients (median age 33.8 years, range 18.7-65.8) and 20 controls matched for age (median age 36.6 years, range 22.7-66.0) and renal function (or dialysis/transplantation) were selected and underwent brain Magnetic Resonance Imaging (MRI). We also included a group of 12 healthy controls matched for age (median age 23.0, range 18.5-24.8).

2.2 | Clinical investigations

Compliance to cysteamine treatment was graded by the investigator according to the patient questioning and the mean leucocyte cystine level using a three-tiered scoring system in which "1" corresponds to good compliance to cysteamine treatment prescribed at optimal dose, four times a day if immediate release cysteamine, with mean cystine level < 2.0 nmol half-cystine/mg protein; "2" to quite good compliance, with leucocyte cystine<3.0 but >2.0 nmol half-cystine/mg protein; and "3" to extended period without treatment and cystine level > 3.0 nmol half-cystine/mg protein. All available cystine values since 1993 were collected. A numerical value of compliance was assigned to each year of age and the median score was calculated for each patient. Median follow-up of cystine dosages was 22 years (range 8-24).

A complete clinical examination and a neurological examination by a specialized neurogeneticist were performed, including muscular testing and swallowing evaluation (see Appendix S1, Supporting Information).The severity of the myopathy was gauged using a five-tiered scoring system in which "5" indicated normal muscle strength, and "1" indicated severe wasting and weakness. A clinical questionnaire was used to evaluate the patient's swallowing ability adapted from Sonies et al.[12] Mini Mental State (MMS) examination was performed in 12 patients.[13]

Measurement of cystine in leucocytes was performed by liquid chromatography-tandem mass spectroscopy as already described.[14,15]

2.3 | Neuroimaging data

All participants underwent brain multimodal brain MRI and CT scan without injection in the Department of Radiology and Imagine institute, Necker Hospital. Multimodal brain imaging was performed in 3 Tesla MRI (General Electric scanner) and included weighted images in at least three different contrasts (T1, T2, and FLAIR). Echo-short (35 ms) monovoxel spectroscopy sequences were performed to visualize cystine peak.[11]arterial spin labeling (ASL) MRI was used to measure rest cerebral blood flow (CBF).[16] Diffusion tensor imaging (DTI) was used to measure fractional anisotropy (FA), as an index of brain white matter microarchitecture (Appendix S1).

2.4 | Data analysis

2.4.1 | Clinical data

Continuous values are reported as median (range). Dichotomous data are presented as percentages. The Fisher's exact test was applied for dichotomous and categorical data. To compare two continuous variables, we used unpaired Mann-Whitney non-parametric test. Two-tailed P values < .05 were regarded as statistically significant. Statistical analyses were performed using InStat 3 and Prism 4 software.

2.4.2 | Radiological study

All scans were analyzed by an experienced neuroradiologist expert in metabolic diseases brain imaging (NB).

2.4.3 | Neuroimaging study (see Appendix S1)

Images from 21 cystinosis patients, 13 controls with nephropathy and 12 healthy controls were included in the brain imaging study. Whole-brain voxel-wise comparisons between the

three groups for the gray matter and rest CBF images were performed using the framework of the general linear model within SPM12 using a gray matter mask thresholded to 30% and setting *P* values to .05 Family Wise Error (FWE) corrected for multiple comparisons. Voxel-based morphometry (VBM) analysis was performed on normalized gray matter images. Correlation analysis between cystine blood level, brain anatomy and rest CBF was performed.

TABLE 1 Clinical and biological data according to central nervous system complications

	Total	No central nervous system complication	At least 1 central nervous system complication	*P*
N	18	11 (61.1)	7 (38.9)	
Sex (F/M, %)	12/6 (66.7)	7 (63.6)	5 (71.4)	1
Age at visit (y)	30.2 (18.7-39.3)	29.0 (18.7-37.3)	33.4 (21.4-39.3)	.79
Age at diagnosis (y)	1.0 (0.5-2.2)	0.9 (0.5-2.2)	1.2 (0.6-2.1)	.5
Age at cysteamine start (y)	1.7 (0.8-6.0)	1.6 (0.8-4.7)	1.8 (1.2-6.0)	.72
Total duration of treatment (y)	26.7 (9.9-35.8)	26.8 (15.9-35.8)	21.1 (9.9-33.6)	.86
Total duration without treatment (y)	2.2 (0.8-29.5)	2.2 (0.8-18.5)	2.2 (1.2-29.5)	.59
Cysteamine dose (g/day)	1.6 (0.3-2.4)	2.1 (0.3-2.4)	0.9 (0.6-1.6)	**.02**
Leucocyte cystine level (nmol ½ cystine/mg proteins)	2.0 (0.5-8.1)	1.8 (0.5-5.5)	3.2 (1.3-8.1)	.17
Compliance to cysteamine	2 (1-3)	1 (1-3)	2 (2-3)	**.03**
ESRD	16 (88.9)	9 (81.8)	7 (100)	.49
Age at ESRD (y)	17.5 (9.0-22.0)	18 (11.0-21.0)	17.0 (9.0-22.0)	.83
Creatinine (μmol/L)				
Before ESRD	117 (97-138)	117 (97-138)	NA	NA
After RT[a]	113 (71-235)	111 (100-235)	131 (71-175)	.88
eGFR mL/min/1.73m[a]				
Before ESRD	62.4 (42.9-80.2)	62.4 (42.9-80.2)	NA	NA
After RT[a]	51.8 (21.0-88.6)	53.8 (21.0-77.6)	41.7 (39.0-88.6)	.72
Hypothyroidism	7 (38.9)	4 (36.3)	3 (42.8)	1
Diabetes	3 (16.7)	2 (18.2)	1 (14.2)	1
High blood pressure	9 (50)	5 (45.4)	4 (57.1)	1
Myopathy	8 (44.4)	4 (36.3)	4 (57.1)	.63
Swallowing defect	4 (22.2)	2 (18.2)	2 (28.6)	1
Dysarthria	1 (5.5)	0	1 (14.2)	.39
Memory defect	3 (16.7)	0	3 (42.8)	**.04**
Cognitive defect	5 (27.8)	0	5 (45.4)	**.002**
MMS[b]	27 (20-30)	29 (26-30)	24.5 (20-26)	**.018**
Seizures	2 (11.1)	0	2 (28.6)	.13
Stroke	1 (5.5)	0	1 (14.2)	.39
Atrophy	13 (72.2)	9 (81.8)	4 (57.1)	.32
Ventricular dilatation	12 (66.7)	8 (72.7)	4 (57.1)	.62
White matter hypersignals (pyramidal)	9 (50.0)	6 (54.5)	3 (42.8)	1
Chiari	2 (11.1)	2 (18.2)	0	.49

Note: Three patients with late-onset cystinosis are not presented in this table. Median (range), number (percentage).

[a]Three additional patients on hemodialysis.

[b]Twelve patients tested.

Abbreviations: ESRD, end stage renal disease; F, female; M, male; RT, renal transplantation.

3 | RESULTS

3.1 | Clinical presentation

From the 21 cystinosis patients included, 18 patients presented with infantile nephropathic cystinosis, two with adolescent onset and one with adult onset cystinosis. Two of these patients were diagnosed late, in a context of familial screening, at 42.1 and 54.4 years of age, respectively, after renal transplantation in the first one and on ophtalmological signs in the second one. In the third patient, cysteamine treatment was started late, at diagnosis, at 14 years of age and the two others were not treated by oral cysteamine. These three patients were analyzed separately.

In patients with infantile nephropathic cystinosis, median age at diagnosis was 1.0 years (0.5-2.2) and median age at visit was 30.2 years (18.7-39.3) (Table 1).

3.2 | Treatment

In patients with infantile nephropathic cystinosis, median age at cysteamine treatment start was 1.7 years (0.8-6.0) (Table 1). Median life-long duration of treatment was 26.7 years (9.9-35.8) and median cumulative time without specific treatment (before diagnosis or due to non-adhesion) was 2.2 years (0.8-29.5).Compliance to treatment was graded 1 in six patients (33.3%), 2 in eight patients (44.4%), and 3 in four patients (22.2%). Median cysteamine dose was 1.6 g/day (0.3-2.4). Median leucocyte cystine level at visit was 2.0 (0.5-8.1) nmol ½ cystine/mg proteins.

3.3 | Disease complications

Clinical complications are presented in Table 1 and Table S1. In patients with infantile nephropathic cystinosis, 16 patients (88.9%) had reached end stage renal disease and 13 (72.2%) were currently transplanted. Two (11.1%) still had functioning native kidney. One patient with adolescent onset cystinosis was transplanted and the two others had normal renal function (eGFR 76.4 and 79.10 mL/min/1.73m^2) and mild proteinuria (0.3 and 0.2 g/g creatininuria), treated with angiotensin conversion enzyme inhibitor in one.

3.4 | Neurological complications

Among the patients with infantile nephropathic cystinosis, eight patients (44.4%) presented with distal myopathy and four (22.2%) with swallowing defects (Table 1 and Table S1).

Seven patients (38.9%) presented with at least one central nervous system clinical abnormality: two (11.1%) with seizures, three (16.7%) with memory defects, and five (27.8%) with cognitive defect. One patient (5.5%) presented with stroke-like episode. MMS examination was assessed in 12 patients and median score was 27 (20-30). Three patients had central nervous system complication without myopathy and three patients had myopathy without central nervous system complication.

One patient with adolescent onset cystinosis developed seizures during a period when she had stopped treatment. One patient with adult onset cystinosis, not treated by cysteamine, developed extrapyramidal syndrome at 54 years of age.

3.5 | Risk factors for the development of central nervous system complications

Patients who developed at least one central nervous system complication had a worse compliance to treatment (compliance score 2 vs 1, $P = .03$) and received a lower median cysteamine dose (0.9 g/day vs 2.1 g/day, $P = .02$) (Table 1). Age at diagnosis and age at visit were not statistically different between patients with and without central nervous system complications.

3.6 | Impact of compliance to treatment

We then analyzed the impact of compliance to treatment on central nervous system complications (Table 2). Patients with a poor compliance to treatment (score 2 or 3) had a higher median cystine level (3.05 vs 0.75 nmol ½ cystine/mg protein, $P = .02$), as expected. They had a lower MMS score (25.5 vs 29, $P = .009$). All patients with at least one central nervous system symptom had poor compliance to treatment.

3.7 | Neuroimaging study

3.7.1 | Brain structure

CT scan found brain calcification located on left hippocampus in one patient who presented with a stroke like episode.

Magnetic resonance spectroscopy sequences did not visualize any cystine peak or any other abnormal peak. Chiari malformation was observed in two patients (9.5%) without any clinical manifestation.

Among patients with infantile cystinosis, 13 (72.2%) showed evidence of cortical atrophy, mild to moderate in 11 and severe in two, 12 patients (66.7%) showed central atrophy (ventriculomegaly), mild to moderate in 10 and severe in two, and nine (50.0%) demonstrated both (Table 1 and Table S2, Figure 1A). Only two patients with infantile cystinosis had normal brain MRI, both being the youngest patients included in this study (ages 18.4 and 21.7 years). The three patients with adolescent and adult onset cystinosis had no atrophy even if they were older than the other patients. Controls with nephropathy and normal controls did not show such atrophy. Nine patients (50.0%) had marked white matter hypersignals, mild to moderate in six and

TABLE 2 Clinical and biological presentation according to compliance to treatment

	Total	Good compliance (score 1)	Poor compliance (score 2 or 3)	*P*
N	18	6	12	
Sex (F/M, %)	12/6 (66.7)	4/2 (66.7)	8/4 (66.7)	1
Age at visit (y)	30.2 (18.7–39.3)	30.5 (18.7-37.3)	31.2 (21.4-39.3)	.99
Age at diagnosis (y)	1.0 (0.5–2.2)	0.9 (0.6-2.2)	1.1 (0.5-2.1)	.8
Total duration of treatment (y)	26.7 (9.9–35.8)	28.3 (17.3-35.8)	23.3 (9.8-33.6)	.2
Total duration without treatment (y)	2.2 (0.8–29.5)	1.5 (0.8-2.8)	2.4 (1.2-29.5)	**.03**
Leucocyte cystine level (nmol ½ cystine/mg proteins)	2.0 (0.5–8.1)	0.75 (0.5-3.8)	3.05 (0.8-8.1)	**.02**
ESRD	16 (88.9)	4 (66.7)	12 (100.0)	.09
Age at ESRD (y)	17.5 (9.0–22.0)	17.5 (11.0-21.0)	17.5 (9.0-22.0)	.9
Creatinine(μmol/L)[a]				
Before ESRD	117 (97–138)	117 (97-138)	NA	NA
After RT	113 (71–235)	141 (113-235)	107 (71-175)	.07
eGFR(mL/min/1.73m^2)				
Before ESRD	62.4 (42.9–80.2)	62.4 (42.9-80.2)	NA	NA
After RT	51.8 (21.0–88.6)	36.8 (21.0-63.3)	55.9 (39.0-88.6)	.07
Hypothyroidism	7 (38.9)	5 (83.3)	2 (16.7)	.01
Diabetes	3 (16.7)	0	3 (25.0)	.51
High blood pressure	9 (50.0)	3 (50.0)	6 (50.0)	1.3
Myopathy	8 (44.4)	1 (16.7)	7 (58.3)	.11
Swallowing defect	4 (22.2)	0	4 (33.3)	.24
Dysarthria	1 (5.5)	0	1 (8.3)	.67
Memory defect	3 (16.7)	0	3 (25.0)	.51
Cognitive defect	5 (27.8)	0	5 (41.7)	.11
MMS[b]	27 (20-30)	29 (29-30)	25.5 (20-28)	**.009**
Seizures	2 (11.1)	0	2 (16.7)	.53
Stroke	1 (5.5)	0	1 (8.3)	.67
Total central nervous system symptoms	7 (38.8)	0	7 (58.3)	**.03**

Note: Three patients with late-onset cystinosis are not presented in this table. Median (range), number (percentage).

[a]Three additional patients on hemodialysis.

[b]Twelve patients tested.

Abbreviations: F, female; M, male; ESRD, end stage renal disease; RT, renal transplantation.

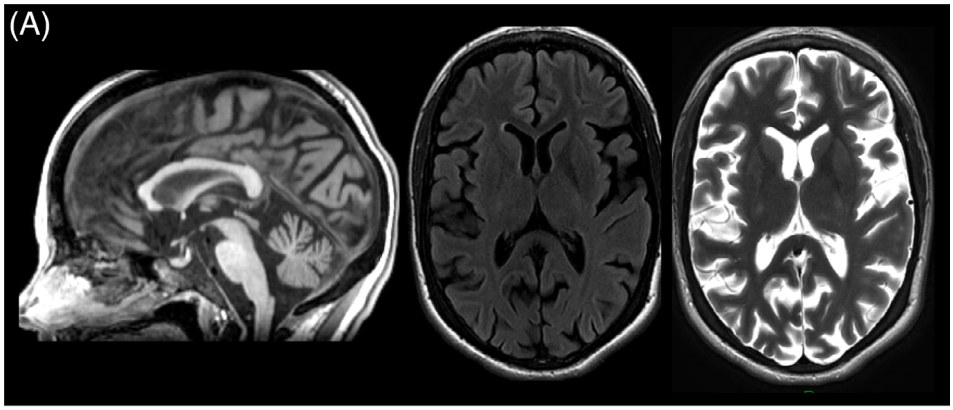
severe in three (Figure 1B and Figure S1A), also found in the two patients with adolescent onset cystinosis. Six controls with chronic renal failure (31.5%) also had these hypersignals (Figure S1B). There was no correlation between clinical manifestations and MRI finding (Table 1). Compliance to treatment had no impact on MRI results.

3.7.2 | Group analysis

Whole-brain VBM analysis showed significantly decreased gray matter in the left middle frontal gyrus in cystinosis patients compared to healthy controls, (t = 5.70; $z_{(score)}$ = 4.88; $P_{(corr)}$ = .012; MNI coordinates: $x = -38$, $y = 14$, $z = 33$) (Figure 2A). A significant decrease in gray matter in the same cluster was observed in controls with nephropathy compared to healthy controls. No significant difference was observed between cystinosis patients and controls with nephropathy.

No significant rest cerebral blood flow difference was observed between groups.

Tract-based spatial statistics analysis revealed a significant fractional anisotropy (FA) decrease in cystinosis patients compared to healthy controls in clusters within the corpus callosum's body ($P < .05$) (Figure 2B). A significant



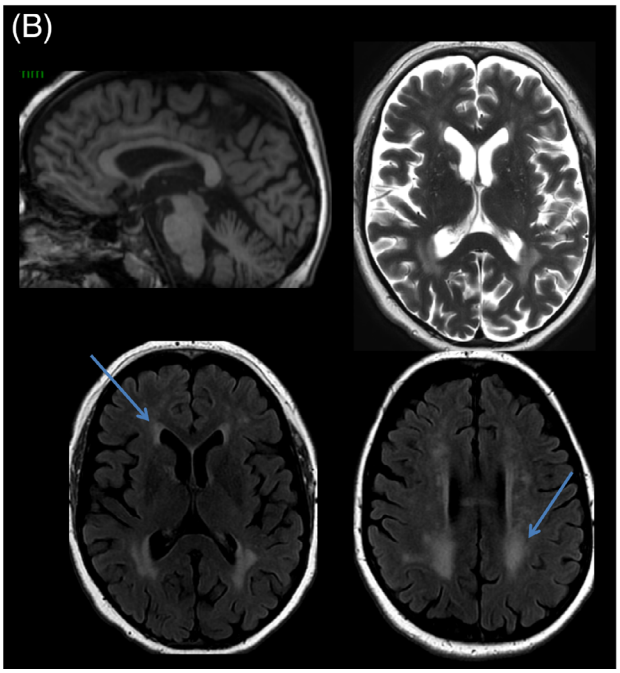


FIGURE 1 Brain magnetic resonance imaging in cystinosis patients. A, Cortical atrophy. B. major white matter hypersignals

decrease of FA in the same clusters was also observed in controls with nephropathy compared to healthy controls. No difference in FA values was observed between cystinosis patients and controls with nephropathy.

3.7.3 | Correlation analysis

In cystinosis patients, whole brain voxel-by-voxel analysis showed a significant negative correlation between the cystine blood level and rest cerebral blood flow measured by ASL in the right superior frontal gyrus (t = 8.43; $z_{(score)}$ = 4.95; $P_{(corr)}$ = .009; MNI coordinates: x = 10, y = 50, z = 40) (Figure 2C). Patients with higher levels of cystine in the blood were those presenting lower rest cerebral blood flow values in this region. No significant correlation was observed between level of cystine and gray matter volume or FA.

4 | DISCUSSION

This study provides evidence of high prevalence of clinical and radiological central nervous system (CNS) defects in adult cystinosis patients. Thirty-eight percent of adult patients have at least one central nervous system complication and 88.9% have a radiological abnormality. Moreover, neuroimaging study showed brain anatomical abnormalities in cystinosis patients compared to healthy controls. Finally, cystine blood level in patients is associated with brain functional abnormalities.

The high prevalence of CNS complications is a major concern since long-term prognosis of adult cystinosis patients appears to be primarily related to neuromuscular complications.[17] Indeed, in the French cohort, neuromuscular disorders were globally reported in 37.2% of patients and included paresis in 75.0%, stroke in 37.5%, mental function deterioration in 56.3%, and seizures in 31.3%. The cause of

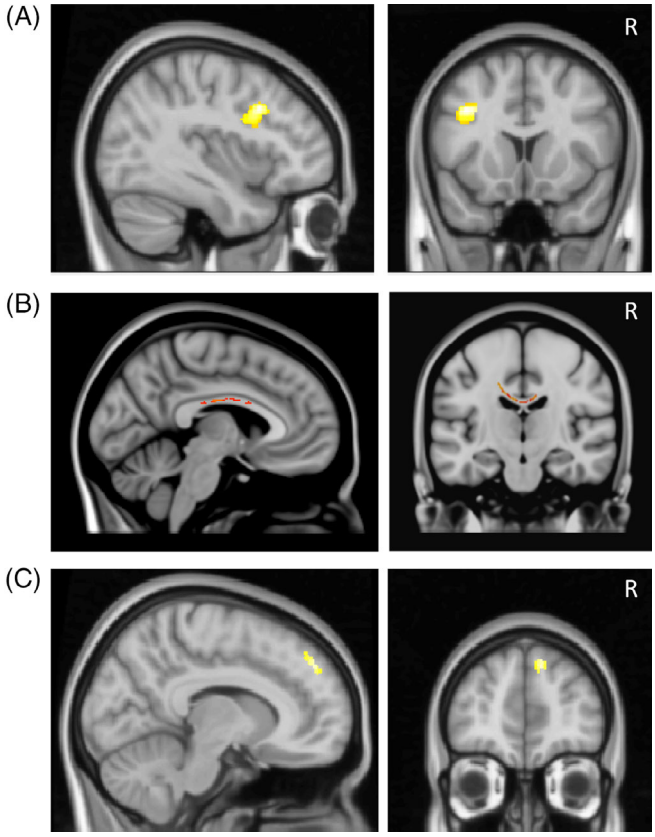


FIGURE 2 Brain Imaging results. A, Significant gray matter decrease in cystinosis patients compared to healthy controls ($P < .05$ FWE corrected). Results were overlaid on the MNI-152 template average brain. The significant cluster (in yellow) is located in the left middle frontal gyrus (peak voxel: $x = -38$, $y = 14$, $z = 33$). B, Significant fractional anisotropy decrease in cystinosis patients compared to healthy controls ($P < 0.05$ FWE and TFCE corrected). Results were overlaid on the MNI 152 average template brain. The significant cluster (in red) is located in the body of corpus callosum (peak voxel: $x = -17$, $y = -31$, $z = 35$). C, Significant positive correlation between cystine blood level and rest cerebral blood flow, measured by arterial spin labeling-magnetic resonance imaging, in cystinosis patients (p < FWE corrected). Results were overlaid on the MNI-152 template average brain. The significant cluster (in yellow) is located in the right superior frontal gyrus (peak voxel: $x = 10$, $y = 50$, $z = 40$). R, right; FEW, family wise error; MNI, Montreal Neurological Institute; TFCE, threshold free cluster enhancement

death was linked to neurological reason in 33.3% of cases. In the series of Gahl et al, two patients out of 33 (6%) died of central nervous system complication.[18]

Our results indicate a strong link between cysteamine treatment and CNS complications. Compliance to treatment and daily cysteamine dose were lower in patients having at least one CNS complication compared to those without complication. None of the patients with a good compliance to the treatment had a CNS complication. However, the groups are too small to demonstrate differences for individual characteristics. Compliance to treatment is a major challenge, particularly in adults.[19] Indeed, overall median cystine level in this study is high at 2.0. In our French historical cohort, we also found a clinical effect of cysteamine on the incidence of neurological complications: the incidence of neuromuscular disorders was significantly reduced when cysteamine was started before 5 years in comparison with the absence of treatment. Furthermore, survival curves indicated that a treatment started before 5 years of age was associated with a significant delay in the occurrence of neuromuscular disorders compared to untreated patients. However, myopathy and CNS complications were analyzed together and specific effect of cysteamine on central nervous system complications has not been studied. The effect of treatment on already existing neurological complications is less clear, but early detection of abnormalities could help adjustment of treatment and early referral to specialized neurologist.[4]

We also found a very high prevalence of abnormalities on clinical scans since 88.9% of patients had an abnormal exam. Chiari malformation was less frequent than previously reported,[20,21] but two third of the patients had cortical atrophy, ventricular dilatation and/or white matter hypersignals. Interestingly, the frequency of these abnormalities was not different between symptomatic and asymptomatic patients. In a previous study, we already observed cortical atrophy by standard tomodensitometry or resonance magnetic imaging in 66.7% of asymptomatic patients.[17] In other studies, cerebral atrophy was also reported in patients without gross central nervous system clinical abnormality[22] and in patients with minor alterations in cognitive performance.[23] In the series by Broyer et al, cortical atrophy was observed in all patients with CNS symptoms.[4]

In the era of early cysteamine treatment, we did not observe as severe radiological defects as in historical cohorts. In some patients with profound neurological deficits, brain imaging or post mortem examination revealed multifocal cystic necrosis, dystrophic calcifications of the basal ganglia and periventricular areas, extensive demyelination of the internal capsule, spongy changes in the brachium pontis, and vacuolization.[24-26] More recently, Gahl et al observed a 22% incidence of cerebral calcifications in a large retrospective cohort[18] and we also identified 38% of cerebral calcifications in symptomatic patients in the French historical cohort.[17] However, in the present study only one patient with a very poor compliance to treatment presented cerebral calcifications.

Cystinosis-associated central nervous system anomalies could be due to progressive cystine accumulation. Indeed, our results showed that they were less frequent in well treated patients, absent in two young well treated patients and also absent in late onset cystinosis patients who have

lower cystine levels. Accordingly, cystinosin knockout mice (C57BL/6*Ctns*$^{-/-}$) have elevated cystine levels in the hippocampus, cerebellum, forebrain and brainstem which increase with age.[27]

A major strength of our study is the use of advanced neuroimaging techniques. Indeed, whole brain voxel-by-voxel analysis allowed identifying decreased gray matter in cystinosis patients localized in the frontal brain region compared to healthy controls. Interestingly, brain abnormalities within this region could be associated with executive function deficits clinically described in these patients.[9,10] In addition, investigation of white matter microstructure in cystinosis patients compared to healthy controls showed reduced fractional anisotropy in the body of the corpus callosum. This bundle, that plays a central role in interhemispheric communication, has also recently been associated with cognitive process.[28,29]The fact that these abnormalities were also observed in controls with nephropathy compared to healthy controls, however, suggests they may not be specific of cystinosis patients and encourage brain imaging and neurocognitive investigations in a broader range of renal diseases.

A main result from this study lies in the significant negative correlation between cystine level and rest cerebral blood flow, measured with ASL-MRI. Indeed, the patients with the higher levels of cystine were those presenting with the lower rest cerebral blood flow values in the superior frontal cortex, which reinforces the link between cystinosis disease and abnormalities within frontal brain regions. Importantly, superior frontal cortex is associated with executive functions, and the described abnormalities could be associated with neurocognitive deficits described in cystinosis patients, such as memory defects or further cognitive impairments.

Only two previous studies used MRI to investigate brain abnormalities in cystinosis patients but they involved children or adolescents and not adults.[21,30] Trauner et al focused on volume loss in 46 cystinosis children and adolescents, and found mild volume loss in 11 patients and moderate to severe volume loss in five.[21]Bava et al studied cerebral white matter microstructure in 24 young children with cystinosis.[30] Children with cystinosis evidenced diminutions in mean fractional anisotropy and corresponding elevation in mean diffusivity in component areas of the dorsal visual pathway suggesting that changes in brain white matter were present early on in the development.[30]

5 | CONCLUSION

Cortical or central atrophy are observed in more than two thirds of cystinosis patients, but are not correlated with symptoms. Leucocyte cystine levels are associated with decreased rest cerebral blood flow in the frontal cortex, which could be associated with the neurocognitive deficits described in cystinosis patients. Compliance to cysteamine treatment is a major concern in these adult patients and could be one of the determinants of cognitive and neurological complications.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

A.S., C.A., B.F., and N.B. conceived the overall research questions. A.S., J.B., H.L., and N.B. performed radiological and neuroimaging studies analysis. A.S., A.H., A.S., R.S., R.S., C.L., D.A. and, B.F. contributed substantially to the conduct of the study and enrollment of patients. C.P. contributed to cystine dosages. All authors contributed to drafting the manuscript and interpreting results.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study (CPP Ile de France, number 2015-AOO413-46).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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