CLINICAL/SCIENTIFIC NOTE

Long-term MRI Findings in Patients With Cerebrotendinous Xanthomatosis Treated With Chenodeoxycholic Acid

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Abstract

Objectives

To describe long-term follow-up brain MRI findings in patients with cerebrotendinous xanthomatosis (CTX) treated with chenodeoxycholic acid (CDCA).

Methods

Of a cohort of 79 Dutch patients with CTX, we retrospectively reviewed brain MRI findings of patients at diagnosis (before the start of treatment) and after long-term follow-up (7–27 years) in 12 patients. In addition, we report on 2 families with remarkable brain MRI findings.

Results

MRI abnormalities showed progression in all 7 patients diagnosed at 24 years or older and only in 1 of 5 patients diagnosed younger than 24 years. MRI findings in the other patients diagnosed younger than 24 years were normal at baseline and remained normal even after follow-up of more than 25 years. The total MRI scores at baseline were 2 and 19 and at follow-up 4 and 37, respectively, for patients diagnosed before or after the age of 24 years, despite a comparable number of treatment years.

Discussion

MRI findings are fully in line with our long-term treatment effect article, emphasizing the importance of early diagnosis and treatment in CTX. Expanding the spectrum of brain MRI findings (including the finding of a posterior leukoencephalopathy) leads to a better understanding of the heterogeneity of this treatable disease.

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Cerebrotendinous xanthomatosis (CTX) is a treatable, autosomal recessively inherited inborn error of metabolism, caused by deficiency of sterol 27-hydroxylase (*CYP27A1*).[1] The natural history of CTX starts with chronic diarrhea within the first year, followed by cataract/learning difficulties between the age of 5 and 15 years, another 5–15 years later followed by motor/psychiatric symptoms.[2] Diagnosing CTX may be challenging because of its clinical heterogeneity. As CTX is a treatable disorder, early diagnosis and initiation of adequate treatment with chenodeoxycholic acid (CDCA) is essential, resulting in biochemical and neurologic improvement.[3,4] Previously, we showed that patients diagnosed and treated before the age of 24 years have a significantly better clinical outcome than patients diagnosed at a later age.[4] The absence of signal abnormalities of the dentate nuclei at baseline is suggested to be an indicator of better prognosis.[5]

In this report, we describe brain MRI findings in 12 patients with CTX treated with CDCA at baseline and after long-term follow-up. Furthermore, we report on 2 families with remarkable MRI findings.

Methods

We performed a retrospective cohort study in 79 Dutch patients with CTX, from 46 families, treated at the CTX reference center in the Netherlands (Canisius Wilhelmina Hospital Nijmegen). The study was approved by the Local Ethics Committee, and informed consent was obtained from all participants. Only patients with brain MRI at diagnosis (before the start of treatment) and after a minimum follow-up of 7 years on CDCA therapy were included. Treatment was started directly after diagnosis (biochemically and genetically confirmed in all patients). The clinical condition was assessed with the Modified Rankin Scale and Expanded Disability Status Scale. The MRI protocol included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images. The images were scored by an independent neuroradiologist (G.J.L.N.) and blinded for clinical and treatment status; the age of participant was disclosed. The presence of 9 different MRI abnormalities described in CTX, namely, cortical/cerebellar atrophy, abnormalities in the periventricular white matter, basal ganglia, brainstem, cerebellar white matter, and dentate nuclei (hyperintensity, calcification, and vacuolation) were scored 1 point each, with a maximum score of 9.

Results

Twelve patients had a brain MRI at diagnosis and after long-term follow-up. Follow-up MRI was performed independently of clinical status. Clinical and brain MRI characteristics are summarized in the Table. The mean age at diagnosis was 26 years (range 11–48). The mean time between both MRIs, that is, before the start of treatment and at follow-up, was 18.2 years (range 7–27, with a total of 91 treatment years) in patients diagnosed younger than 24 years and 14.7 years (range 8–22, with a total of 103 treatment years) in patients diagnosed at 24 years or older.

MRI abnormalities showed progression in all 7 patients diagnosed at 24 years or older and in only 1 of 5 patients diagnosed younger than 24 years. In this patient (patient 2), MRI at baseline already showed abnormalities. MRI in the other patients diagnosed younger than 24 years was normal at baseline and remained normal at follow-up. At baseline, the total MRI score was 2 in the group of patients diagnosed younger than 24 years and 19 in the group of patients diagnosed at 24 years or older. At follow-up, these scores were 4 and 37, respectively, despite a comparable number of treatment years. Figure 1 shows the classic brain MRI findings in CTX.

In addition, we report on 2 families with remarkable brain MRI findings (eAppendix, links.lww.com/WNL/C229). In Family I (patient 3–5, diagnosed <24 years), follow-up MRI showed no abnormalities after a follow-up of more than 25 years (Figure 2, A–C). In Family II, describing 2 siblings, brain MRI at diagnosis showed white matter abnormalities suggesting a prominent posterior leukoencephalopathy, not typically seen in patients with CTX, with only subtle signal abnormalities of the dentate nuclei (Figure 2, D and E).

Discussion

Our study shows that in young patients with a normal MRI at diagnosis, the MRI remained normal even after more than 25 years of follow-up. These MRI findings are fully in line with our long-term treatment effect article,[4] emphasizing the importance of early diagnosis and treatment in CTX. Early diagnosis and treatment depends on early recognition, depending on physicians' awareness of characteristic findings in CTX. Expanding the spectrum of brain MRI findings, including the finding of a posterior leukoencephalopathy, in CTX hopefully leads to a better understanding of the heterogeneity of this treatable disease.

This report describes and evaluates the long-term follow-up MRI data in CTX patients. Limitations of the study are that only 12 of 79 patients had sequential brain MRI's and there was no quantitative imaging assessment that took severity into account.

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Disclosure
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Table Clinical and Brain MRI Characteristics of 12 CTX Patients With Brain MRI at Baseline (Before the Start of Treatment) and at Follow-up

Patient[a]	Sex	Age diagnosis, y	*CYP27A1* sequence variant	Timing of MRI	Neonatal jaundice	Diarrhea	Cataract	Tendon xanthomas	Pyramidal signs	Cerebellar signs	Epilepsy	Polyneuropathy	Parkinsonism	Intellectual disability	Psychiatric symptoms	Cholestanol,[b] µmol/L	mRS score	EDSS score
1	M	11	c.646G>C (p.Ala216Pro)	Baseline	−	+	−	+	−	−	−	−	−	−	+	13.7	1	1
			c.1183C>T (p.Arg395Cys)	7 y after start CDCA		−	−	−	−	−	−	−	−	−	+	NA	1	1
2	M	12	c.646G>C (p.Ala216Pro)	Baseline	−	+	+	−	−	+	−	−	−	+	+	28.6	1	3
			c.1183C>T (p.Arg395Cys)	7 y after start CDCA		−	+[f]	−	−	−	−	−	−	+	+	NA	1	3
3	M	13	c.1263+1G>A	Baseline	+	+	+[f]	−	+	+	−	−	−	+	−	58.1	1	2
			c.1213C>T (p.Arg405Trp)	25 y after start CDCA		−		−	−	−	−	−	−	−	−	11.4	0	0
4[d]	F	17	c.1263+1G>A	Baseline	+	+	+	−	+	−	−	−	−	−	−	41.6	1	1
			c.1213C>T (p.Arg405Trp)	27 y after start CDCA		−	−	−	+	+	−	−	−	−	−	51.1[b]	1	2
5	F	20	c.1263+1G>A	Baseline	+	+	+	−	+	+	−	−	−	−	−	74.2	1	1.5
			c.1213C>T (p.Arg405Trp)	25 y after start CDCA		−	−	−	−	−	−	−	−	−	−	8.5	0	0
6	F	24	c.1016C>T (p.Thr339Met)	Baseline	+	+	+	−	+	+	−	−	−	−	−	54	2	3
			c.1016C>T (p.Thr339Met)	9 y after start CDCA		−	+[f]	−	+	+	−	−	−	−	−	7	3	5
7	F	30	c.776A>G (p.Lys259Arg)	Baseline	−	+	+[f]	+	−	−	−	−	−	−	−	186	0	0
			c.776A>G (p.Lys259Arg)	18 y after start CDCA		−		+	+	−	−	−	−	−	−	NA	4	6

Continued

Table Clinical and Brain MRI Characteristics of 12 CTX Patients With Brain MRI at Baseline (Before the Start of Treatment) and at Follow-up *(continued)*

Patient[a]	Sex	Age diagnosis, y	*CYP27A1* sequence variant	Timing of MRI	Neonatal jaundice	Diarrhea	Cataract	Tendon xanthomas	Pyramidal signs	Cerebellar signs	Epilepsy	Polyneuropathy	Parkinsonism	Intellectual disability	Psychiatric symptoms	Cholestanol,[b] µmol/L	mRS score	EDSS score
8	F	31	c.1183C>T (p.Arg395Cys)	Baseline	NA	−	+[f]	−	−	+	−	+	−	−	−	36	1	2
			1263+1G>A	22 y after start CDCA		−		−	−	−	−	+	−	−	−	8.2	1	2
9	F	32	c.776A>G (p.Lys259Arg)	Baseline	−	+	+[f]	+	+	−	−	+	−	+	−	46	4	6.5
			c.776A>G (p.Lys259Arg)	18 y after start CDCA		−		−	+	+	−	+	−	+	−	8.7	5	8
10	M	37	c.1016C>T (p.Thr339Met)	Baseline	+	+	+	−	−	−	−	+	−	+	−	102	2	3.5
			c.1016C>T (p.Thr339Met)	13 y after start CDCA		−	+[f]	−	−	+	−	+	−	+	−	NA	3	6
11[e]	M	37	c.1183C>T (p.Arg395Cys)	Baseline	NA	+	+[f]	−	+	+	−	+	−	+	−	104	1	2.5
			1263+1G>A	15 y after start CDCA		−		−	−	+	−	+	+	+	−	14	3	3.5
12	M	48	c.844+1G>A	Baseline	−	−	+[f]	+	+	−	−	−	−	−	+	43	2	2
			c.1183C>T (p.Arg395Cys)	8 y after start CDCA		−		+	+	−	−	−	−	+	+	NA	NA	NA

Patient[a]	Treatment	Timing of MRI	Cortical atrophy[c]	Cerebellar atrophy[c]	Cerebral/periventricular hyperintensities (T2W/FLAIR)	Basal ganglia hyperintensities (T2W/FLAIR)	Brainstem hyperintensity (T2W/FLAIR)	Cerebellar hyperintensity (T2W/FLAIR)	Dentate nuclei hyperintensity (T2W/FLAIR)	Dentate nuclei calcification	Cerebellar vacuolation	Total MRI score (max 9)
1	CDCA 15 mg/kg adjusted to body weight until 750 mg/d	Baseline	0	0	−	−	−	−	−	−	−	0
		7 y after start CDCA	0	0	−	−	−	−	−	−	−	0
2	CDCA 15 mg/kg adjusted to body weight until 750 mg/d	Baseline	0	1	+	−	−	−	−	−	−	2
		7 y after start CDCA	1	1	+	−	−	−	+	−	−	4

Continued

Table Clinical and Brain MRI Characteristics of 12 CTX Patients With Brain MRI at Baseline (Before the Start of Treatment) and at Follow-up *(continued)*

Patient[a]	Treatment	Timing of MRI	Cortical atrophy[c]	Cerebellar atrophy[c]	Cerebral/periventricular hyperintensities (T2W/FLAIR)	Basal ganglia hyperintensities (T2W/FLAIR)	Brainstem hyperintensity (T2W/FLAIR)	Cerebellar hyperintensity (T2W/FLAIR)	Dentate nuclei hyperintensity (T2W/FLAIR)	Dentate nuclei calcification	Cerebellar vacuolation	Total MRI score (max 9)
3	CDCA 15 mg/kg adjusted to body weight until 750 mg/d	Baseline[g]	0	0	–	–	–	–	–	–	–	0
		25 y after start CDCA	0	0	–	–	–	–	–	–	–	0
4[d]	CDCA 15 mg/kg adjusted to body weight until 750 mg/d	Baseline[g]	0	0	–	–	–	–	–	–	–	0
		27 y after start CDCA	0	0	–	–	–	–	–	–	–	0
5	CDCA 750 mg/d	Baseline[g]	0	0	–	–	–	–	–	–	–	0
		25 y after start CDCA	0	0	–	–	–	–	–	–	–	0
6	CDCA 750 mg/d + statin	Baseline	0	0	–	–	–	–	–	–	–	0
		9 y after start CDCA	0	0	–	–	–	–	+	–	–	1
7	CDCA 750 mg/d + statin[h]	Baseline	0	2	+	–	–	+	+	–	+	5
		18 y after start CDCA	2	2	+	–	–	+	+	–	+	6
8	CDCA 750 mg/d + statin	Baseline	0	0	–	–	–	–	+	–	–	1
		22 y after start CDCA	1	1	–	–	–	–	+	+	+	5
9	CDCA 750 mg/d + statin[h]	Baseline	1	0	–	–	–	–	+	–	–	2
		18 y after start CDCA	3	3	+	–	–	–	+	–	–	4
10	CDCA 750 mg/d + statin	Baseline	0	0	–	–	–	–	–	–	–	0
		13 y after start CDCA	3	3	+	–	+	+	+	+	+	8

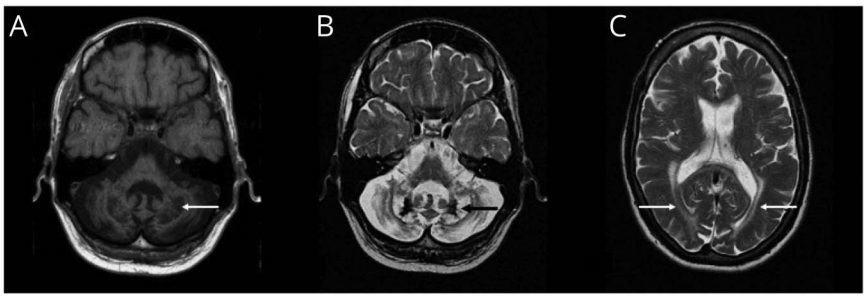
Continued

Table Clinical and Brain MRI Characteristics of 12 CTX Patients With Brain MRI at Baseline (Before the Start of Treatment) and at Follow-up *(continued)*

Patient[a]	Treatment	Timing of MRI	Cortical atrophy[c]	Cerebellar atrophy[c]	Cerebral/periventricular hyperintensities (T2W/FLAIR)	Basal ganglia hyperintensities (T2W/FLAIR)	Brainstem hyperintensity (T2W/FLAIR)	Cerebellar hyperintensity (T2W/FLAIR)	Dentate nuclei hyperintensity (T2W/FLAIR)	Dentate nuclei calcification	Cerebellar vacuolation	Total MRI score (max 9)
11[e]	CDCA 750 mg/d + statin	Baseline	1	3	−	+	+	+	+	+	+	8
		15 y after start CDCA	2	3	+	+	+	+	+	+	+	9
12	CDCA 750 mg/d + statin	Baseline	2	2	−	−	−	−	+	−	−	3
		8 y after start CDCA	2	2	−	−	−	−	+	+	−	4

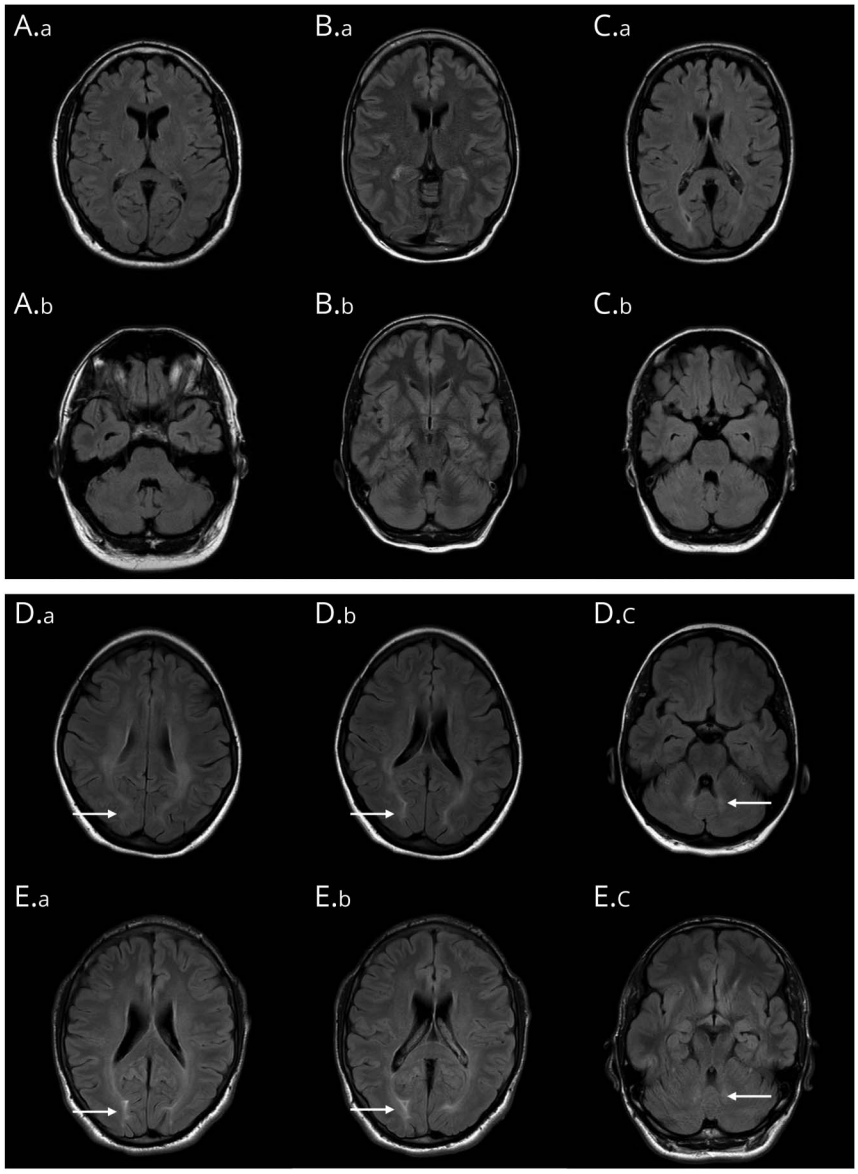
Abbreviations: CDCA = chenodeoxycholic acid; EDSS = Expanded Disability Status Scale; FLAIR = fluid-attenuated inversion recovery; mRS = Modified Rankin Scale; + = present; − = absent; NA = not available; T2W = T2-weighted.
[a] Related (patient 1 + 2; patient 3–5; patient 7 + 9; patient 8 + 11).
[b] Reference value: (3.3–12.5 μmol/L).
[c] 0 = no abnormalities; 1 = minor abnormalities; 2 = moderate abnormalities; 3 = severe abnormalities.
[d] Poor treatment compliance.
[e] Treated with Ursofalk for 1 year because of the unavailability of CDCA.
[f] Cataract extraction.
[g] The images of the brain MRI at baseline were not available, but were reported as normal.
[h] During follow-up, dose was adjusted to 1,000 mg/d based on a high cholestanol level.

Figure 1 Classic Brain MRI Findings in Patient 11, at the Age of 52 Years, 15 Years After the Start of Chenodeoxycholic Acid



(A) Axial FLAIR images show low signal intensity of the dentate nuclei and surrounding white matter consistent with cerebellar vacuolation. (B) Axial T2W images show bilateral hyperintensity of the cerebellar white matter with dentate nuclei involvement with calcification and (C) periventricular hyperintensity with posterior predominance. FLAIR = fluid-attenuated inversion recovery; T2W = T2-weighted.

Figure 2 Family I (A: Patient 3; B: Patient 4; and C: Patient 5)



Axial FLAIR images show no supratentorial white matter abnormalities (A.a–C.a) or cerebellar white matter/dentate nuclei abnormalities (A.b–C.b) at 25–27 years of follow-up after the start of CDCA treatment. Family II (D, E). Axial FLAIR images show white matter hyperintensities with prominent occipital involvement (D.a–D.b, E.a–E.b), with only subtle signal abnormalities at the dentate nuclei (D.c, E.c). FLAIR = fluid-attenuated inversion recovery.

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