


ORIGINAL ARTICLE

Differences in brain changes between adults with childhood-onset epilepsy and controls: A prospective population-based study

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Purpose: To determine the impact of childhood-onset uncomplicated epilepsy (COE) on brain aging over 50-year prospective follow-up.

Methods: A population-based cohort of 41 aging subjects with COE and their 46 matched controls participated in a detailed in-person prospective assessment in 2012 and 2017 to characterize ongoing changes in the aging brain.

Results: The mean age of the COE participants was 63.2 years (SD 4.14, median 63.2, range 55.8–70.6) and 63.0 years (mean, SD 4.13, median 63.3, range 56.0–69.9) years for controls. Neurologic signs were significantly more common in COE participants not in remission ($p = .015$), and the most frequent abnormalities were cerebellar signs ($p < .001$). Neurologic signs in general ($p = .008$) and cerebellar signs in particular ($p = .018$) were significantly more common in focal than in generalized epilepsies. MRI white matter abnormalities were significantly associated with absence of vocational education ($p = .011$), and MRI hippocampal atrophy in COE subjects was associated with arterial hypertension versus normal blood pressure ($p = .017$). In the combined study cohort of COE subjects and controls, presenting neurologic signs increased both in the subjects and in the controls from the 2012 to 2017 study.

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Conclusions: At ultra-long-term follow-up, clinical and neuroimaging findings show tendencies to brain aging that is more accelerated in COE participants with active adult childhood-onset epilepsy, and particularly in focal epilepsy.

KEYWORDS

active epilepsy, brain aging, childhood-onset uncomplicated epilepsy, long-term outcome, population study

1 | INTRODUCTION

Epilepsy can be a life-long disorder, but seizures may also discontinue with time. In fact, 70% of patients with epilepsy will enter remission.¹ The remission rate is related, among other things, to the duration of follow-up. Long-term remission rates are mostly reported on patient cohorts with 10 to 20 years of follow-up. One existing population study with 50-year follow-up² was based on baseline data of patients with “present epilepsy” in 1962–1964, and a subsequent questionnaire mailed in 1976 and 2015. Ninety percent of their surviving subjects were in 5-year terminal remission on or off medications. No outcomes other than remission data were given.

We have previously reported very long-term medical outcomes of subjects with childhood-onset epilepsy (COE) in a unique prospective cohort established in 1961–1964.^{3,4} This is the only prospective, long-term, population-based interval study ever reported with regular follow-up check-ups from onset of childhood epilepsy to older age. While the seizure outcome was excellent, the subjects showed more neurological soft signs, cognitive and imaging abnormalities than controls.^{4–6} However, it is unknown if these findings represent a stable outcome (eg, accumulated during years of active epilepsy) or progressive changes related to faster brain aging that could predispose these individuals to adverse outcomes later in life. In order to answer this question, we had two goals for re-examining the cohort: (1) to characterize the cohort's neurological and seizure status, and (2) the longitudinal trajectory of previously reported findings at 55-year follow-up with focus on the last five years. Our hypotheses were that neurological signs would continue to increase and that brain aging would be accelerating in subjects with childhood-onset epilepsy, particularly in subjects with persisting active epilepsy.

2 | MATERIALS AND METHODS

The study design is previously described in detail.^{3,4,7} In brief, the initial study consisted of all the children who were resident in the catchment area of Turku University Hospital, Turku, Finland, in 1961–1964, were less than 16 years, and had onset of epilepsy (repeated unprovoked seizures) or had a previous diagnosis of epilepsy with one or more seizures, considered as active epilepsy, in 1961–1964. Children were identified on the basis of several data sources: hospital inpatient and outpatient records; primary healthcare records; private offices patient records; and review of the National Health

Service (NHS) records, a register of all patients residing in Finland. Review of the NHS register was of importance from the point of case identification because, according to the rule, all children with epileptic or probable epileptic seizures were to be admitted to hospital care. A total of 245 subjects were identified for a longitudinal, prospective study of outcomes.³ In 1992, age, sex, and domicile matched controls were chosen by the Population Register Centre from the general population of the study area for those 99 still participating subjects, who had uncomplicated epilepsy.⁷

In 2012, a new nested study, the Turku Adult Childhood-Onset Epilepsy study (TACOE-50) was initiated at 50 years following diagnosis of epilepsy in childhood.⁴ All subjects with uncomplicated epilepsy and all controls who had returned their completed study questionnaires during the last 10 years and gave written informed consent to participate were recruited. They underwent an extensive two-day investigation program that included clinical neurological examination by a single neurologist, chemical laboratory examinations, EEG recordings, 3T magnetic resonance imaging (MRI), and neuropsychological testing. For chemical laboratory and neuroimaging results, the assessor was single one per each investigation type and blinded to participants whether subjects or controls. The main results have been published previously.^{4–6}

Fifty-one subjects and 52 controls consented in writing and participated to the complete investigation program in 2012 (Figure 1). Given reasons for decline were mostly personal or family health problems, job barriers, reluctance to attend too many medical visits and claustrophobia. Among subjects, the nonparticipants did not significantly differ from the participants in terms of seizure variables including age at onset, remission status, or medication status. The proportions of nonparticipants were similar in subjects and controls

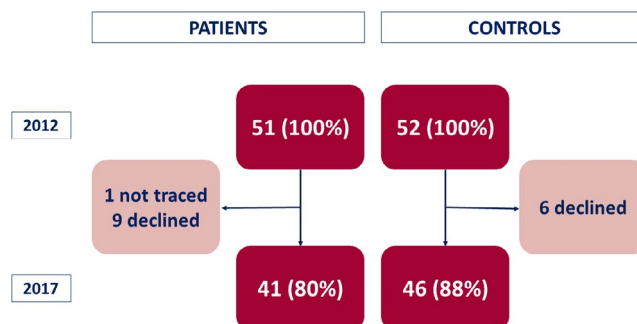


FIGURE 1 Flow chart of the participant enrollment

by sex, sociodemographic factors, academic or vocational education, working status, lifestyle, or chronic disorders.⁴

In 2017, after extended 5-year follow-up, this process was repeated (TACOE-55 study). Of 51 subjects, 41 (80%) participated as did 46 of the 52 controls (88%). Ten (20%) subjects and six (12%) controls declined. None of the subjects or controls died between the years 2012 and 2017 (Figure 1). The main measures for outcomes were findings in structured clinical neurological examination, chronic comorbidity other than epilepsy, and 3T magnetic resonance imaging (MRI). The MRI equipment using a single scanner (Siemens Skyra Fit 3T, Siemens Healthcare) was unchanged from 2012 to 2017, except for an upgrade from Verio to Skyra fit version before 2017 with comparable image quality, and the assessor was blinded to group (COE subjects vs. controls). White matter changes were assessed separately for periventricular and deep white matter regions. For quality control, every fourth month, the physicists checked the homogeneity of the magnetic field and the coil status and the radiologist continuously followed the possible occurrence of external disturbances like motion artifacts. Voxel-based morphometrics were not undertaken.

The TACOE-50 participants were re-studied using the same parameters including three-dimensional T1, T2, and FLAIR sequences, diffusion tensor imaging (DTI) and T2* sequence. MRIs were visually interpreted by a single neuro-radiologist (R.P.) blinded to the group status. Interpretation included assessment of hippocampal atrophy and age-related white matter changes. Hippocampal atrophy was evaluated using Schelten's scale from 0 to 4, and white matter changes were evaluated using Fazekas scale from 0 to 3.^{8,9} The outcomes were compared between subjects and controls, and between subjects with active epilepsy and remitted epilepsy.

2.1 | Definitions

Epileptic seizures and etiology of seizures were defined according to the guidelines for epidemiological research of the International League Against Epilepsy (ILAE).¹⁰⁻¹² For the present report epilepsy syndromes, classified initially by the ILAE 1989,¹¹ and re-classified in 1999¹³ in accordance with the contemporary ILAE guidelines,¹² were again re-classified to meet the criteria of the current ILAE classification by Scheffer et al. (2017).¹⁴ Generalized syndromes included generalized tonic-clonic seizures alone, childhood absence, juvenile absence, and juvenile myoclonic epilepsy. Those who presented with tonic-clonic seizures and had normal EEG were not classifiable. Remission of seizures ever was defined as a seizure-free period of 10 years (10YRE),¹⁵ and the subject was considered as drug-responsive or a case of self-limited epilepsy. Terminal remission (10YTR) was defined as 10-year remission at last follow-up. Active epilepsy was defined as failure to enter ten-year terminal remission with or without medication during the last five years. High blood pressure was defined as systolic pressure >130 mmHg or diastolic pressure >80 mmHg according to the Finnish Current Care Guidelines (<https://www.kaypahoito.fi/hoi04010>). Obesity

was defined as a body mass index of >30 kg/m² according to the WHO guidelines.¹⁶ Abnormal neurological status was defined as one or more abnormal findings on examination. Abnormal findings, that is clinical signs, included the assessment of consciousness level, behavior, and orientation to time and place; oral communication; cranial nerve, locomotor, and fine-motor functions; balance; muscular tonus, muscular mass, reflexes, and strength; involuntary movements; and sensory functions. Prescribed daily doses (PDD, WHO Collaborating Centre for Drug statistics 2021)¹⁷ of the four most frequently used antiseizure drugs (ASDs), that is, carbamazepine (CBZ), diphenylhydantoin (DPH), phenobarbital (PHB), and valproate (VPA), were calculated and converted to grams for every subject. Life-long ASD load was defined as cumulative sums of all four (CBZ + DPH + PHB + VPA) and separately for diphenylhydantoin and phenobarbital (DPH + PHB).

2.2 | Dropout analysis

The previously reported attrition rates at different stages of follow-up² were low and without any differential dropouts. The attrition rate in the present study from TACOE-50 to TACOE-55 was also low with a non-significant difference between COE subjects and controls (12% vs. 20%, $p = .289$). Dropouts were more often female than male (23% vs. 3%, $p = .004$) for unknown reasons; dropouts were more frequent among those with no or less than weekly versus weekly alcohol consumption (22% vs. 4%, $p = .015$); the effects did not significantly differ between the COE and control subgroups. No other significant differences were found between the participants and nonparticipants. Reasons for dropouts are presented in Figure 1. Of 10 declined subjects, seven reported other diseases (multiple sclerosis, cancer, hearing problems, etc.), one suffered from claustrophobia and two did not present any particular reason. One control person had intensive cancer treatments, and the remaining six did not express any reason for refusal.

2.3 | Statistics

The main outcomes were analyzed first as a function of group (COE subjects and controls) and second within the COE group comparing subjects with (a) active versus remitted epilepsy and (b) focal versus idiopathic generalized epilepsy syndrome. Fisher's exact test was used. The data were given as frequencies. The association of lifetime cumulative ASD load with the main outcomes was analyzed retrospectively using Wilcoxon rank sum tests. The data were given as medians (IQR). To detect possible differences in the pace of brain aging between COE subjects and controls during the 5-year follow-up, repeated measures binary or cumulative logistic regression analyses using general estimation equations (GEE) estimation were done. Due to the modest sample size, multiple comparison corrections were not made. As predictors, the models included study group (subjects vs. controls), time (2017 vs. 2012), and their interaction.

The data were given as odds ratios (OR) with 95% confidence intervals (95% CI). p -values $<.05$ were considered as significant. The analyses were done using SAS version 9.4 (SAS Institute).

2.4 | Ethics

The Institutional Review Board approved the study design (Diary No. T08/044/17, Study No. T286/2017). Written informed consent was given by both the subjects and controls.

3 | RESULTS

At baseline (TACOE-50), the COE subjects had been followed for 50 years (mean 50.1, SD 1.06, median 51, range 49–52). The duration of extended follow-up (TACOE-55) was five years for COE subjects and controls. Total person-years of follow-up for subjects up to TACOE-55 were 2404 years. Age at the end of follow-up (TACOE-55) was 63.2 years (mean, SD 4.14, median 63.2, range 55.8–70.6) for COE subjects and 63.0 years (mean, SD 4.13, median 63.3, range 56.0–69.9) for controls. None of the controls had past or present epileptic seizures during follow-up. One fourth (26%) of the COE group had active epilepsy, and three fourths (74%) were in remission. Generalized epilepsies included 12 with generalized tonic-clonic seizures alone, two childhood absence and two juvenile absence epilepsies and one juvenile myoclonic epilepsy. Focal epilepsies were temporal in 15 and extra-temporal or non-localizable focal in five cases.

Compared with COE patients in remission, in 2017, neurologic signs were significantly more common in COE subjects who were not in remission. Of significant neurologic signs, cerebellar signs without visually observable asymmetry were most frequent followed by pyramidal and peripheral signs (Table 1). Neurologic signs in general and cerebellar signs in particular were, not unexpectedly, significantly more common in those with a history of focal than generalized epilepsies. Hypercholesterolemia was also significantly more common in subjects with focal than generalized epilepsy. High lifetime ASD loads for the four most frequently used ASDs (Figure 2) and for the combination of DPH and PHB (Figure 3) were associated with neurologic signs, especially cerebellar signs and peripheral neuropathy.

In COE subjects, there was a significant association between obesity and MRI white matter abnormalities ($p = .006$), but not between obesity and any MRI abnormality ($p = .0827$). MRI hippocampal atrophy was significantly more common in COE subjects with high arterial hypertension versus normal blood pressure (100% vs. 21%; $p = .017$), but did not reach significance in subjects with type 2 diabetes mellitus ($p = .083$). MRI white matter abnormalities were significantly associated with absence of vocational education (100% vs. 60%; $p = .011$), but not with basic education ($p = .181$). None of the MRI abnormalities was significantly more frequent in subjects with continuing seizures than in remitted COE subjects. Subsequent

comparisons of epilepsy syndromes were not indicated given the modest sample sizes.

In the combined study cohort of COE subjects and controls, neurologic signs increased both in the COE subjects and in the controls from the TACOE-50 to TACOE-55 study, except for cranial nerve dysfunction that one control reported to have disappeared. While any neurological signs significantly increased in the combined study from 2012 to 2017, no significant difference was found between the groups or in the pace of change within the two groups (time \times group interaction $p = .8$; not included in the final model. (Table 2). In 2012, cerebrovascular abnormalities in MRI were more common in COE subjects than controls. The difference evened during five-year follow-up due to more, mainly mild (Fazekas scale 1) white matter changes in controls than in COE subjects (group \times time interaction $p < .001$) (Table 3).

4 | DISCUSSION

The present study was based on five additional years of prospective follow-up of a unique population-based cohort that had been actively monitored and studied for the preceding five decades.^{3,4} Our study is unique as the only other 50-year follow-up study² was based on questionnaire data and did not examine cerebral changes.

While there were no *overall* differences between the total COE group and controls over the time interval of 5 years, our results indicated that COE subjects with *active* epilepsy, present in 26% of the sample, were strongly associated with clinical neurologic findings and particularly MRI evident cerebellar atrophy, albeit the association did not quite reach statistical significance, possibly due to a limited sample size. One single cranial nerve sign of one COE subject was no more present in 2017, resulting either from recovery or, more probably, from variability in clinical interpretation. The impact of continuing active epilepsy on the emergence of peripheral neuropathy was also significant. For the majority of the COE subjects who experienced remitted epilepsy (87.4%), the findings are more reassuring.

Our results also inform the longstanding debate concerning the complicated etiology of cerebellar pathology in epilepsy, especially so given the childhood-onset epilepsy of this cohort and the life-span follow-up. Significant interest and research in the cerebellum continues in the general neuroscience community, especially so during the past several years,¹⁸ as well as in epilepsy community where not only atrophy but even cerebellar hypertrophy in temporal lobe epilepsy has been reported in some¹⁹ but not in all studies.²⁰ The association between epilepsy and cerebellar atrophy is well-known,²¹ but what is cause, what is effect, and what is coincidence remain areas of research.^{22,23} Our COE subjects did not initially present with cerebellar signs. The association with cerebellar atrophy might suggest that this is a consequence of the epileptic seizures and/or medical treatment.²⁰ We cannot discriminate between the relative impact of epilepsy per se, seizures or ASD therapy on cerebellar dysfunction and atrophy,

TABLE 1 Clinical neurologic and MRI findings in 37 adult subjects with remitted versus non-remitted childhood-onset epilepsy, or with focal versus genetic generalized epilepsy syndrome

Epilepsy	Active ¹	Remitted	<i>p</i> ²	Focal	Generalized	<i>p</i> ²
	<i>n</i> (%)	<i>n</i> (%)		<i>n</i> (%)	<i>n</i> (%)	
<i>Neurologic signs</i>						
Total <i>n</i>	9	28		20	17	
Any signs ³	9 (100)	15 (54)	.015	17 (85)	7 (41)	.008
<i>CNS signs</i>						
Cerebellar	9	6	<.001	12	3	.018
Pyramidal	3	0	.011	2	1	>.99
Cognitive	2	3	.577	4	1	.350
Extrapyramidal	1	4	>.99	3	2	>.99
Cranial nerve	1	4	>.99	3	2	>.99
Peripheral signs	7	8	.017	11	4	.092
<i>Non-neurologic somatic disorders⁴</i>						
High BP ⁵	9	24	.554	16	17	.109
Hypothyroidism	2	4	.620	4	2	.667
Hypercholesterolemia	2	9	.695	9	2	.037
Obesity ⁶	4	10	.705	10	4	.173
<i>MRI abnormalities</i>						
Total	8	28		19	17	
Any abnormalities ³	7 (89)	20 (71)	.648	14 (74)	11 (65)	.721
Atrophy	4	7	.214	4	4	>.99
Cerebellar ⁷	3	2	.062	0	2	.216
Cerebral	3	3	.109	3	1	.605
Hippocampal ⁸	0	3	>.99	1	1	>.99
Markers of cerebrovascular disease ²	6	14	.257	5	4	>.99
White matter changes, Fazekas scale			.345			.695
Score 1	2	10		5	3	
Score 2	1	2		0	0	
Score 3	1	0		0	1	
Infarcts	3	3	.109	5	1	.182

¹Seizures during last 10 years and/or ASD medication during last 5 years.

²Fisher's exact test.

³Number of participants: An individual may present several signs/disorders.

⁴All participants had 1 or more non-neurologic somatic disorder.

⁵High blood pressure: systolic >130 mmHg or diastolic >80 mmHg.

⁶BMI > 30 kg/m².

⁷Assessed on scale 0–3: All participants with observed abnormalities were on grade 1.

⁸Scheltens scale 0–4; all participants with observed abnormalities were on grade 1.

but the association of cerebellar atrophy and the calculated lifetime drug load of the four most frequent ASDs (carbamazepine, diphenylhydantoin, phenobarbital, and valproate) was highly significant ($p < .001$). Our COE subjects, whose ASD treatment was initiated in the early 1960s, had all been administered one or several of the four abovementioned ASDs, except for two patients, who had only been on succinimide or trimethadione for childhood

absence seizures. We also excluded benzodiazepines prescribed as add-on drugs in small dosages to two participants. While many of our participants had been on combined DPH and PHB therapy and their effects could not be separated in drug load analysis, the strongest impact could be ascribed to DPH therapy in line with the previous reports.^{24,25} The review by Strick et al.²⁴ showed the percentage of patients affected by cerebellar pathology to be

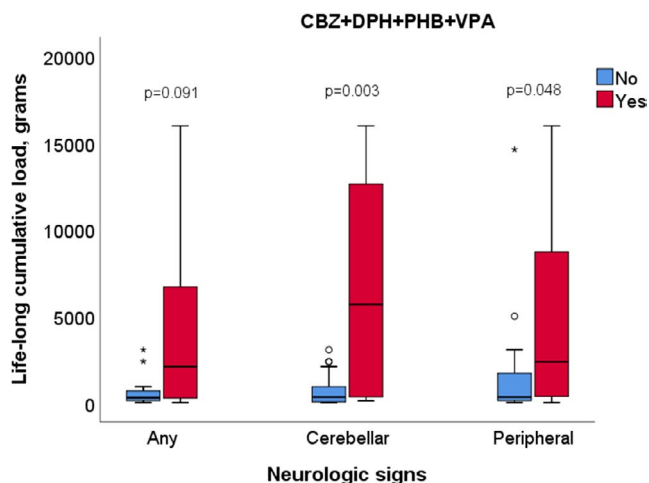


FIGURE 2 Life-long cumulative ASD load of CBZ, DPH, PHB, and VPA after 55 years of follow-up in 39 adult patients with childhood-onset epilepsy. *p*-values from Wilcoxon rank sum tests

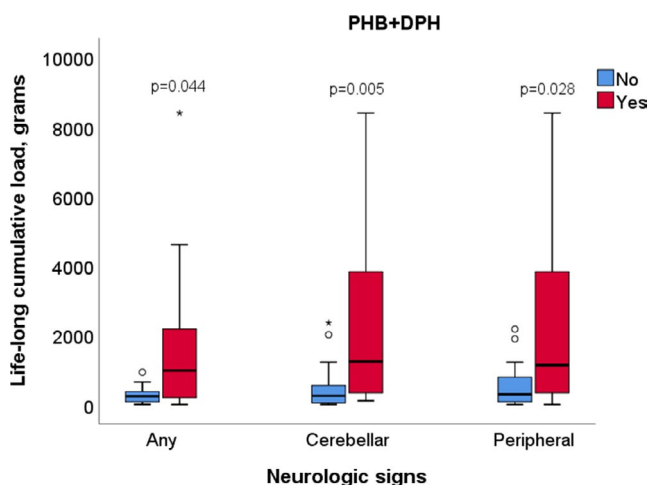


FIGURE 3 Life-long cumulative ASD load of PHB and DPH after 55 years of follow-up in 39 adult patients with childhood-onset epilepsy. *p*-values from Wilcoxon rank sum tests

38% for diphenylhydantoin, but only 1.3%–8.7% for other ASDs. Clonazepam was an outlier (50%) in the review and very seldom administered to our subjects before the 1980s and hardly at all involved in the cerebellar effects.

Clinical and neurophysiological signs of peripheral neuropathy were associated with epilepsy in 17% of patients treated with any “older” antiseizure drugs,²⁶ but the reports on a greater short-term risk on phenytoin-treated patients are controversial.^{26,27} Long-term therapy of children with phenytoin increased the risk up to 71%.²⁸ None of these studies examined differences between subjects not in remission versus in remission. Of our subjects, 56% had a peripheral neurologic sign that occurred significantly more often on phenytoin-treated and in those not in remission.

The cerebellum has been demonstrated to have an inhibitory effect on the occurrence of epileptic seizure.²⁹ The previous literature

suggests the failure of a damaged cerebellum to inhibit epileptic seizures.²³ As a consequence, epilepsy is often, but not always,³⁰ drug-resistant.

Contemporary antiseizure medications administered to the present patients may be considered more or less outdated. However, it would be misleading to believe that currently used “new” ASDs, after tens of years of use, would not cause adverse effects in the same way as the older drugs did after tens of years of launching. Thus, we are warranted to expect antiseizure drug effects of the “modern” drugs as well in the course of years.

Previous information on cerebellar changes is mostly based on data from patients with focal or pooled data on focal and generalized epilepsy. In our study, neurologic and particularly cerebellar signs became obvious in subjects with focal epilepsy significantly more frequently than in those with generalized epilepsy. To our knowledge, no previous inter-comparative studies exist. One report,³¹ in fiber tractography analyses, observed significantly decreased fractional anisotropy images in the cerebellum of patients in comparison with controls. Hagemann et al.²⁰ found a significant association between cerebellar atrophy and epilepsy with generalized tonic-clonic seizures. Overall, our study confirms the conclusions drawn by Ibdali et al.,³² in their systematic review, that focal (in the majority temporal lobe) epilepsy, poor seizure control, and phenytoin drug therapy are predictors of cerebellar deterioration in patients with epilepsy.

Cerebrovascular abnormalities were more common in our subjects than controls at 50-year follow-up. The difference was no longer present at 55-year follow-up due to more, mainly mild white matter changes in controls than in subjects, suggesting that cerebrovascular abnormalities in the subjects were masked by white matter lesion burden increasing with aging.³³ However, the number of subjects with more severe white matter changes and brain infarcts still (non-significantly) outnumbered that of controls, which could suggest accelerated cerebrovascular aging. Overall, emerging of the abovementioned changes during a relatively short time period of five years suggests the possibility of an ongoing and maybe accelerating process of deterioration, brain aging, with increasing age in subjects with childhood-onset epilepsy.

Our COE subjects had significantly more frequent MRI white matter abnormalities in the absence of vocational education than vocationally educated in 2017 (100% vs. 60%; $p = .011$), but the association was not significant for basic education ($p = .095$). The causality is an open issue. According to Dufouil et al.,³⁴ a high education may provide a degree of resilience to the consequences of MRI/-obesity white matter changes on cognition and be a protective factor for the cognitive deterioration related to vascular insults of the brain. Also, in our subjects, MRI white matter abnormalities were significantly associated with BMI obesity, which, in turn, is associated with accelerated cognitive decline and dementia.³⁵ Abnormal cholesterolemia may explain, at least in part, the association.³⁶

MRI hippocampal atrophy was significantly more common in our subjects with high arterial hypertension versus normal blood pressure (100% vs. 21%; $p = .017$), but did not reach significance in subjects with type 2 diabetes mellitus ($p = .083$). High blood pressure

TABLE 2 Presenting neurologic and other somatic comorbidity in older adults with childhood-onset epilepsy in 2012 and 2017, and in controls

	2012		2017		Between subjects and controls		Between 2012 and 2017	
	Subjects	Controls	Subjects	Controls	OR	95% CI	OR	95% CI
	n (%)	n (%)	n (%)	n (%)				
<i>Neurologic signs</i>								
Total	37	39	37	39				
Any signs ¹	13 (35)	10 (26)	24 (65)	19 (49)	1.67	0.76–3.67	3.22	1.90–5.45 ^a
<i>CNS signs</i>								
Cerebellar	3	2	15	6				
Extrapyramidal	3	0	5	0				
Cognitive	0	0	5	0				
Pyramidal	1	0	3	1				
Cranial nerve	6	4	5	6				
Peripheral signs	3 (8)	5 (13)	15 (41)	16 (41)				
<i>Neurologic disorders</i>								
Total	37	39	37	39				
Any disorders ¹	7 (19)	3 (8)	8 (22)	5 (13)	2.30	0.77–6.84	1.34	0.73–2.47
Migraine headache	2	3	1	3				
Brain tumor	1	0	1	0				
Peripheral neuropathy	1	0	2	2				
Parkinsonian syndromes	1	0	1	0				
Spastic torticollis	1	0	1	0				
Mild ataxia	1	0	1	0				
Hemisindrome	1	0	1	0				
<i>Non-neurologic somatic disorders</i>								
Total	37	41	37	41				
Any disorders ¹	37 (100)	36 (88)	37 (100)	38 (93)	NA ²		NA ²	
Hypothyroidism	6 (16)	1 (2)	6 (16)	4 (10)	2.03	0.59–6.94	1.29	0.77–2.15
T2DM ³	1 (3)	5 (12)	1 (3)	6 (15)	0.27	0.05–1.52	1.12	0.72–1.74
Obesity ⁴	11 (31)	10 (24)	13 (36)	11 (27)	1.45	0.63–3.33	1.15	0.73–1.81
High BP ⁵	34 (97)	33 (85)	31 (89)	35 (90)	2.40	0.82–7.00	0.99	0.37–2.70
Hypercholesterolemia	6 (16)	5 (12)	11 (30)	8 (20)	1.53	0.58–4.09	1.85	1.10–3.09 ^b

Abbreviation: OR, odds ratio.

¹Number of participants: An individual may present several signs/disorders.

²Logistic model not analyzable due to no variability among subjects with epilepsy.

³Type 2 diabetes mellitus.

⁴BMI > 30 kg/m².

⁵High blood pressure: systolic >130 mmHg or diastolic >80 mmHg.

^a $p < .001$.

^b $p = .020$.

is reportedly associated with hippocampal atrophy and stroke and increases the risk of cognitive decline and dementia.^{37,38}

The population-based prevalence of epilepsy is relatively low. A limitation of the present study is the relatively small source population for very long-term follow-up and a small sample size.³ Notwithstanding, we could show several significant associations that were in line with the data previously reported in the literature.

The strengths of this investigation include the uniqueness of our population-based cohort and the long interval of study with 55-year prospective follow-up. We still had available a sample that can be regarded as representative of the original cohort; dropout analyses showed no significant biases in relevant factors between the participants and nonparticipants. Despite previous 10 occasions of data collection, including two very intensive 2-day investigations in the course of recent follow-up, a vast majority still showed excellent

TABLE 3 MRI abnormalities in older adults with childhood-onset epilepsy in 2012 and 2017, and in controls

	2012		2017		Between subjects and controls		Between 2017 and 2012	
	Subjects	Controls	Subjects	Controls	OR	95% CI	OR	95% CI
	n (%)	n (%)	n (%)	n (%)	OR	95% CI	OR	95% CI
MRI abnormalities								
Total	35	40	35	40				
No abnormalities	11 (31)	29 (72)	8 (22)	15 (38)				
Any abnormalities ^{1,2}	24 (69)	11 (28)	27 (77)	25 (62)	5.49	2.07–14.6 ^a	1.32	0.80–2.19
Congenital	14 (40)	6 (15)	14 (40)	6 (15)	1.61	0.57–4.37	4.49	2.28–8.82 ^a
Atrophy	8 (23)	6 (15)	11 (31)	9 (23)	3.71 ³	1.24–11.1 ^b	NA ³	1.12–2.31 ^c
Hippocampal, Scheltens scale 0–4					1.58	0.56–4.42	1.61	1.12–2.31 ^c
Grade 1	2	3	3	2				
Grade 2	0	0	0	3				
Cerebral	4	2	6	3				
Cerebellar ⁴	2	2	5	2				
Markers of cerebrovascular disease	9 (26)	4 (10)	20 (57)	19 (48)	1.83	0.78–4.31	5.34	3.01–9.45 ^d
White matter changes, Wahlund scale 0–3								
Score 1	8	2	12	16				
Score 2	0	0	3	1				
Score 3	1	0	1	0				
Brain microbleeds	0	2	2	3				
Brain infarcts	1	1	6	2				

Abbreviation: OR, odds ratio.

¹Number of participants: An individual may present several signs/disorders.²Study group*time interaction $p < .001$.³2012 data only.⁴Assessed on scale 0–3: All participants with observed abnormalities were on grade 1.^a $p < .00$.^b $p < .019$.^c $p < .01$.^d $p < .001$.

adherence and participated in the 2017 study. Overall, this dedicated cohort has contributed greatly to our understanding of the prognosis and outcomes of childhood-onset epilepsies.

In conclusion, at ultra-long-term follow-up, clinical and neuroimaging findings show tendencies to brain aging that is more accelerated in COE subjects with active adult childhood-onset epilepsy, and particularly in focal epilepsy. Risk factors include cerebellar atrophy, white matter abnormalities, hippocampal atrophy, hypertension, obesity, and hypercholesterolemia. If our observations can be confirmed, they would have impact on the treatment of epilepsy, prevention research into aging and preclinical dementia, and the alignment of the field of epilepsy with the larger clinical and research community.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PEER REVIEW

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