Brain white matter lesions are associated with reduced hypothalamic volume and cranial radiotherapy in childhood-onset craniopharyngioma

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Funding information
This work was supported by the Swedish Children’s Cancer Foundation, and the Medical Faculty, Lund University, Sweden.

Abstract

Context: White matter lesions (WML) are caused by obstruction of small cerebral vessels associated with stroke risk. Craniopharyngioma (CP) patients suffer from increased cerebrovascular mortality.

Objective: To investigate the effect of reduced HT volume and cranial radiotherapy (CRT) on WML in childhood-onset CP patients.

Design: A cross-sectional study of 41 patients (24 women) surgically treated childhood-onset CP in comparison to controls.

Methods: With magnetic resonance imaging (MRI), we analysed qualitative measurement of WML based on the visual rating scale of Fazekas and quantitative automated segmentation of WML lesion. Also, measurement HT volume and of cardiovascular risk factors were analysed.

Results: Patients had a significant increase in WML volume (mL) ($P = .001$) compared to controls. Treatment with cranial radiotherapy (CRT) vs no CRT was associated with increased WML volume ($P = .02$) as well as higher Fazekas score ($P = .001$). WML volume increased with years after CRT ($r = 0.39; P = .02$), even after adjustment for fat mass and age. A reduced HT volume was associated with increased WML volume ($r = -0.61, P < .001$) and explained 26% of the variation ($r^2 = 0.26$). Altogether, 47% of the WML volume was explained by age at investigation, HT volume and CRT. Patients with more WML also had higher cardiovascular risk.

Conclusions: CRT may be associated directly with increased WML volume or indirectly with reduced HT volume associated with higher cardiovascular risk. Risk factors should be carefully monitored in these patients.

KEYWORDS
craniopharyngioma, hypothalamic lesion, hypothalamic volume, radiotherapy, white matter lesions
A craniopharyngioma (CP) is a benign pituitary tumour known for its aggressive behaviour and high recurrence rate. Adult patients with childhood-onset CP have increased cardiovascular risk and particularly increased cerebrovascular mortality. In comparison to radical operation, prior studies have shown positive effect of a more conservative surgery followed by cranial radiotherapy (CRT) in terms of tumour control in CPs. About 50% of CP suffers from hypothalamic obesity, which seems to be the most important link to increased cardiovascular risk. Recently we showed that reduced hypothalamic (HT) volume is a strong predictor of fat mass in these patients.

White matter lesions (WML) are pathological changes caused by obstruction of small cerebral vessels resulting in hypoperfusion of the brain microvasculature and are widely accepted as clinically relevant. WML can be visualized on T2-weighted magnetic resonance images (MRI), corresponding to myelin loss and mild gliosis. These lesions normally start to develop after 60 years of age and baseline severity of WML is perhaps the most consistent predictor of progression. WML has indicated an increased risk for stroke, and these lesions are also prevalent in patients with hypertension, hypercholesterolaemia or diabetes. However, WML are common among patients with brain tumour subjected to CRT, with a significant correlation to the radiation dose and the time interval since completion of CRT. However, among patients with CP comparable information is missing.

The aim of the present study was to analyse WML among CP patients, considering CRT, HT volume and age. Further, possible associations between WML and CV risk factors were analysed.

## METHODS

### Patients

Forty-one (24 women) patients, aged ≥17 years, were recruited from 64 eligible subjects from the South Medical Region of Sweden (population 2.5 million). The patients were surgically treated for a childhood-onset CP between 1958 and 2010. Excluded subjects (n = 23) were either assessed too ill for participation (meningioma n = 1, neuromuscular disease n = 1, living in a home for disabled n = 2), too busy (n = 6), investigations to be stressful according to patients (n = 2), had aneurysm clip (n = 1), no reason given (n = 7), had missing medical record (n = 1), or did not reply (n = 2).

All 41 patients were included in the cross-sectional investigation of metabolic risk factors but 38 remained as 3 patients were too heavy to perform a dual-energy X-ray absorptiometry (DXA) and none of them were smoking. Five patients had to withdraw from MRI due to presence of either a shunt causing significant MR artefacts (n = 1), pacemaker (n = 1), claustrophobia (n = 2) or weight restrictions (n = 1), thus 36 patients completed the MRI. One patient was excluded from the HT volume analyses due to silver clips and motion artefacts, but this patient was however included in the measurement of WML based on different requirements for that analysis. Thus 35 patients were included in the HT volumetric analysis while data on WML were available for 36 patients.

Patient baseline characteristics and details of tumour treatment modalities are shown in Table 1. Sixteen patients had received CRT, median dose 50 Grey (Gy) (35-55 Gy). Median age at first operation was 12 years in women (3-29) and 9 years in men (3-22), and median age at investigation was 35 years (18-56) in women, and 36 years (20-49) in men. Median time since the first operation was 21 years (6-49) in women, and 23 years (11-42) in men. At the time of this study, the same neurosurgeon graded the tumour location retrospectively based on each patient’s operation records: intrasellar growth, supra-sellar growth, supra-sellar growth towards or into the 3rd ventricle. The latter was a criterion for HT lesion (n = 23). All patients were operated transcranial with the microscope from the right side of the brain and only 5 patients were operated before year 1980.

Thirty-four patients had GH deficiency, thereof 29 patients with pan-hypopituitarism including AVP deficiency. Most patients included in the metabolic analysis (76%, 31/41) as well as in the MRI analysis (75%, 27/36) were receiving GH therapy at the time of the study. Daily GH doses were 0.6 mg (0.4-1.2) in women and 0.5 mg (0.2-0.8) in men with a normalization of serum IGF-I. All pituitary hormone deficiencies were sufficiently supplemented. Further details on the exact hormone supplementations are presented in Fjalldal et al.

### Control subjects

A control group of 32 subjects (18 women) was established. Each patient was matched with a control subject similar in age-, gender, residence (rural/nonrural) and smoking habits randomly selected from a computerized population register as previously described. For each patient, 10 potential control subjects matched for gender and age were selected randomly from the population register. They were contacted by telephone and then also matched for smoking habits. The first eligible control that matched and agreed to participate in the study was selected. Twenty of them were recruited from a pool who participated in our previous studies. Twelve new controls were selected from a computerized population register as previously described. One control terminated MRI due to claustrophobia.

### Study design

The present set-up was performed during a single day in each subject. The ethics committee approved the protocol (DNR 2011/769). All participants gave written informed consent.
| With HT lesion (n = 23) | Without HT lesion (n = 18) |
|------------------------|---------------------------|
| Gender/Age at invest. (y)/Age at first operation (y) | Treatment | Hormone substitution | Gender/Age at invest. (y)/Age at first operation (y) | Treatment | Hormone substitution |
| F/38/20 | S | G/T\(^d\) | F/49/12 | S | AVP\(^d\) |
| F/46/27 | S | GH\(^f\) | F/47/12 | S | T/AVP\(^d\) |
| F/36/12 | S | GH/G/T/C/AVP\(^f\) | F/25/21 | S | T/AVP\(^e\) |
| F/56/7 | S + CRT\(^c\) | GH/G/T/C | F/41/11 | S | None\(^e\) |
| F/33/3 | S + CRT+In | GH/G/T/C/AVP | F/34/15 | S | GH/G/AVP |
| F/33/5 | S + CRT | GH/G/T/C/AVP | F/40/11 | S | GH/G/T/C/AVP |
| F/32/15 | S + CRT | GH/G/T/C/AVP | F/38/9 | S | GH/G/T/C/AVP |
| F/29/13 | S | GH/G/T/C/ADH | F/32/10 | S | GH/G/T/C/AVP |
| F/28/4 | S + CRT | GH/G/T/C/AVP | F/29/17 | S | GH/G/T/C/AVP |
| F/40/22 | S + ln | GH/G/T/C/AVP | F/18/6 | S + ln+SR | GH/G/T/C/AVP |
| F/35/29 | S | GH/G/T/C/AVP | F/30/5 | S + CRT | GH/G/T/C/AVP |
| F/19/7 | S | GH/G/T/C/AVP | M/40/17 | S | ADH\(^f\) |
| F/37/9 | S + CRT | GH/G/T/C/AVP | M/35/14 | S | GH/G/T/AVP |
| M/43/9 | S + CRT+In | GH/G/T/C/AVP\(^f\) | M/47/5 | S | GH/G/T/C/AVP |
| M/20/9 | S + CRT | None\(^e\) | M/46/14 | S | GH/G/T/C/AVP |
| M/33/22 | S + CRT | GH/G/T/C | M/37/3 | S | GH/G/T/C/AVP |
| M/49/12 | S | GH/G/T/C/AVP | M/36/14 | S | GH/G/T/C/AVP |
| M/27/7 | S + CRT | GH/G/T/C/AVP | M/27/4 | S + CRT | GH/G/T/C/AVP |
| M/35/6 | S + CRT+In + SR | GH/G/T/C/AVP |
| M/21/9 | S | GH/G/T/C/AVP |
| M/38/16 | S + CRT | GH/G/T/C/AVP |
| M/37/8 | S + CRT | GH/G/T/C/AVP |
| M/35/16 | S + CRT | GH/G/T/C/AVP |

Abbreviations: AVP, arginine vasopressin; C, cortisone; CRT, cranial radiotherapy; F, female; G, gonadal steroids; GH, growth hormone; In, installation of yttrium; M, male; S, surgery; SR, stereotactic radiosurgery; T, levothyroxine; y, years.

\(^a\)Hypothalamic lesion according to the neurosurgeon’s retrospective assignment of patients to the nonhypothalamic lesion and hypothalamic lesion group based on operation records.

\(^b\)27 patients had 1 operation (13 hypothalamic lesion), 11 patients had 2 operations (8 hypothalamic lesion), 3 patients had 3 operations (2 hypothalamic lesion).

\(^c\)35 Gy Cobalt three-field’s technique.

\(^d\)Intact GH axis based on insulin tolerance test.

\(^e\)Intact GH axis based on clinical judgement.

\(^f\)GH deficient but stopped GH treatment.
2.4 | Assessments of physical activity and fatigue

The degree of physical exercise during work and spare time was assessed by a self-rating questionnaire in which patients and matched controls classified their physical activity according to a four-grade scale. The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity.

2.5 | Anthropometric measurement, criteria for International Diabetes Federation (IDF) and biochemical assays

BMI (kg/m²) and body composition using DXA were assessed as previously described. Data for body composition are expressed as estimated fat mass (kg and %) and fat-free mass (kg). Metabolic syndrome was defined according to the International Diabetes Federation (IDF) guidelines. Plasma levels of insulin (<25 mIE/L), testosterone (8.0-30 nmol/L), free T4 (12-22 pmol/L) and free T3 (3.6-6.3 pmol/L) were measured with electrochemiluminescence immunoassay. Plasma high-density lipoprotein cholesterol (HDLC) was measured with a homogeneous enzymatic colorimetric assay (females 1.0-2.7 mmol/L, males 0.80-2.1 mmol/L). Low-density lipoprotein cholesterol (LDL-C) measurements were based on the selective solubilization of LDL-C by a nonionic detergent and the interaction between dextran, dextrin and lipoprotein components (≤30 years: 1.2-4.3 mmol/L, 31-50 years: 1.4-4.7 mmol/L, >50 years: 2.0-5.3 mmol/L). Triglycerides (TG), (<0.4-2.6 mmol/L) were measured by an enzymatic method. Analysis of apolipoprotein A (ApoA) (<200 mmol/L) and apolipoprotein B (ApoB) (females: 0.60-1.17 g/L, males: 0.66-1.33 g/L) was carried out by immunochromatography techniques. C-reactive protein (CRP) (<3.0 mg/L) was measured by immunoturbidimetry method.

2.6 | Neuroimaging protocol

Images were acquired on a 3-Tesla MR scanner (MAGNETOM Skyra, Siemens healthcare, Erlangen, Germany) using a 20 channel head/neck receive coil. Participants were in the supine position and their head was padded to minimize patient movement. For volumetric measurements, axial T1-weighted MPRAGE images were used (acquisition parameters: 1 mm isotropic resolution, TE 3 ms, TR 1900 ms, flip angle 9). For WML measurements axial T2 FLAIR images (23 slices, slice thickness 5 mm) were acquired.

2.7 | Measurement of the HT volume

The HT volume was estimated manually on coronal T1-weighted images in a rostral to caudal axis (ANALYZE 10.0 software package, Biomedical Imaging Resource, Mayo foundation, Rochester, MN) as described previously.

2.8 | Qualitative and quantitative assessments of WML

For the quantitative measurement, a trained rater assigned a single summary value of WML severity based on the visual rating scale of Fazekas. The scale provides an overall impression on the occurrence of WML for the complete brain and differentiates between periventricular WML and deep WML. The total Fazekas score has a range from 0-3 where 0 = no or a single punctate lesion, 1 = multiple punctate lesions, 2 = beginning confluency of lesions, 3 = large confluent lesions.

A quantitative automated segmentation of WML was performed using the Lesion Segmentation Tool (LST) implemented in SPM8 (http://www.applied-statistics.de/lst.html); this generated a total lesion volume [mL], henceforth named ‘WML volume’, for each individual.

For the descriptive analysis of the study population in relation to increased CV risk the arbitrary limit of WML ≥ 1 mL vs WML < 1 mL was chosen.

2.9 | Radiotherapy techniques

Conventional radiotherapy was delivered with photon-technique with a linear accelerator and typically delivered daily in doses of 1.7-2.0 Gy/fraction over a period of approximately 5-6 weeks with a total dose of 50 or 54 Gy (7 patients received 50 Gy and 5 received 54 Gy). Mostly three-field technique noncoplanar with two temporal portals and one portal from the vertex was used. Two patients received treatment with only 2 fields (temporal). Field sizes were mostly 6 × 5 cm (except 1 patient 11 × 8 cm). The treatment was delivered during 1994-2004 and usually on a modern linear accelerator with multi-leaf collimators dose sculpting, for example by helical tomotherapy and rigid immobilization of the patient.

2.10 | Statistics

Data are presented as median and range (min-max) with the exception of physical activity where the results are presented as mean ± SD. Differences between patients and controls were compared using Mann-Whitney U test. Bivariate correlations were assessed using Spearman rank correlation coefficient. The comparisons between radiated and nonradiated patients regarding WML were investigated.
with Mann-Whitney $U$ test. Despite the relative low number of participants, we performed multivariate linear regression models to investigate whether our associations were confounded by age and fat mass. However, model assumptions were evaluated by analysis of residual. In addition, the fractions of explained variances were presented as adjusted $r^2$. $p$ value < .05 was regarded as statistically significant.

3 | RESULTS

3.1 | Anthropometric, biochemical and hormone measurements in patients vs controls

Anthropometric and hormone measurements between CP patients and controls have already been published elsewhere, but are included here for illustrating the metabolic profile of the study population (Table 2). In all CP patients, significantly higher weight, BMI, waist as well as fat mass were measured. We now provide additional results on no significant differences in HDL-C, LDL-C, TG, ApoB/ApoA-1 ratio levels between all patients and controls. Not previously published is the comparison between patients with HT lesion ($n = 23$) vs controls, where significantly higher weight, BMI, waist and fat mass were measured, as well as lower HDL-C and higher TG and hs-CRP levels (Table 2).

3.2 | Treatment data and CV risk in patients and controls with WML $\geq 1$ mL and those with WML $< 1$ mL

Significantly more patients with WML $\geq 1$ mL had an increased CV risk according to the IDF metabolic syndrome criteria (Table 3) and higher BMI. The size of the study populations did not allow statistical analyses for medication related to CV risk. Although, patients who had cardio-protective medication, also belonged to the patient group with WML $\geq 1$ mL and included antiplatelet (1 vs 0), antihypertensive (2 vs 0), lipid-lowering (2 vs 0) and antidiabetic medications (3 vs 0). This restriction also includes the comparison between radiation dose and number of patients with radiation. Higher number of patients received CRT within the group with WML $\geq 1$ mL and despite having the same year of birth they were operated almost 10 years earlier, but with no difference in the year of CRT. The number of patients with pan-hypopituitarism did not differ between the groups although the presence HT lesion as well as higher Fazekas score was more common among patients with WML $\geq 1$ mL. No differences in physical activity or physical fatigue were recorded in the study population (Table 3).

Five controls had WML $\geq 1$ mL together with higher CV risk according to IDF criteria and with higher BMI, compared to other controls of the same age.

3.3 | WML according to Fazekas visual scale and the quantitative measurement of WML volume in patients and controls as the anatomical distribution of WML

On total Fazekas score no significant differences were found between all CP patients ($n = 36$) and controls ($n = 31$) $0 (0-6)$ vs $0 (0-4)$. A significant difference was recorded on total Fazekas score between CP patients with ($n = 12$) and without CRT ($n = 24$). $[2 (0-6) vs 0 (0-4), P = .001]$, but not between CP patients without CRT ($n = 24$) and controls ($n = 31$), $0 (0-4)$ vs $0 (0-4)$. The CP patients ($n = 36$) had a significant increase in total WML volume compared to matched controls ($n = 31$) $1.00 (0.00-18.32)$ vs $0.38 (0.00-2.14)$ mL, ($P = .001$). Patients with CRT ($n = 12$) had a significant increase in WML volume compared to patients without CRT ($n = 24$); $1.52 (0.35-18.32)$ mL vs $0.64 (0.00-2.72)$ mL, ($P = .02$). Among the radiated patients the presence of WML were recorded in the right and left frontal region and in the parieto-occipital region (vertex). No WML was recorded in the temporal lobes or basal ganglia of the brain.

3.4 | Associations between HT volume, age at investigation and years since CRT vs WML volume among CP patients and controls

Among patients a reduced HT volume was associated with increased WML volume ($r = -0.61, P < .001$, Figure 1) and explained 26% of the variation ($r^2 = 0.26$). For every 200 unit decrease in HT volume (mm³), WML volume increased by 1 mL (CI: 0.4-1.6; $P = .001$). Among patients exposed to CRT, a positive association with WML volume ($r = 0.39; P = .02$) was recorded, which explained 15% of the variation in WML volume ($r^2 = 0.15$). In a linear regression these results continued to be significant after adjustment for age at investigation and fat mass (kg).

Among radiated patients, age at study investigation was significantly associated with increased WML volume by 0.41 mL for each year (Figure 2). No such association was recorded among patients without CRT or among controls nor did the linear regression show any significant effect of age on the variation in WML volume.

However, without significance was the correlation between number of years since CRT and WML volume ($P = .12$; Figure 3).

When HT volume, CRT and age at investigation where included in the multiple linear regression model simultaneously they explained 47% of the variation in WML volume (Table 4). For each $100 \text{mm}^3$ increase in HT volume, the WML volume decreases with 0.4 mL. The patients who received CRT had 2.7 mL higher WML volume, whereas each year of age older at investigation corresponded to an increase in WML volume of 0.15 mL. In other words, having received CRT corresponded to the similar effect as being 18 years older (2.7/0.15). Two outliers were identified in the data. Excluding the outliers from the analyses did not change the results.
TABLE 2  Anthropometry, body composition and hormone assessment in (1) 41 CP patients and controls (2) 23 CP patients with HT lesion (HL) and controls

| n          | Patients (F = 24) | Controls (F = 18) | P value | Patients with HL (F = 13) | Controls (F = 18) | P values |
|------------|-------------------|-------------------|---------|--------------------------|-------------------|----------|
| n          | Patients (F = 24) | Controls (F = 18) | P value | Patients with HL (F = 13) | Controls (F = 18) | P values |
| Age        | 35 (18-56)        | 37 (19-56)        | ns      | 35 (19-56)               | 37 (19-56)        | ns       |
| Weight (kg)| 92 (56-203)       | 72 (53-149)       | <.001   | 111 (74-203)             | 72 (53-149)       | <.001    |
| Height (cm)| 174 (153-191)     | 172 (161-188)     | ns      | 174 (157-191)            | 172 (161-188)     | ns       |
| BMI (kg/m²)| 30 (20-66)        | 24 (20-49)        | <.001   | 35 (27-66)               | 24 (20-49)        | <.001    |
| Waist (cm) | 102 (69-150)      | 82 (69-120)       | <.001   | 111 (85-150)             | 82 (69-120)       | <.001    |
| **Anthropometric measurements** |               |                   |          |                          |                   |          |
| Age        | 35 (18-56)        | 37 (19-56)        | ns      | 35 (19-56)               | 37 (19-56)        | ns       |
| Weight (kg)| 92 (56-203)       | 72 (53-149)       | <.001   | 111 (74-203)             | 72 (53-149)       | <.001    |
| Height (cm)| 174 (153-191)     | 172 (161-188)     | ns      | 174 (157-191)            | 172 (161-188)     | ns       |
| BMI (kg/m²)| 30 (20-66)        | 24 (20-49)        | <.001   | 35 (27-66)               | 24 (20-49)        | <.001    |
| Waist (cm) | 102 (69-150)      | 82 (69-120)       | <.001   | 111 (85-150)             | 82 (69-120)       | <.001    |
| **Body composition (DXA)** |             |                   |          |                          |                   |          |
| Fat mass (kg) | 38³ (13-75)     | 23³ (10-50)       | <.001   | 46³ (25-75)              | 23³ (10-50)       | <.001    |
| Fat mass (%) | 43³ (15-57)      | 33³ (14-51)       | <.001   | 47³ (30-57)              | 33³ (14-51)       | <.001    |
| Fat free mass (kg) | 51³ (32-70) | 44³ (29-64)      | ns      | 54³ (38-70)              | 44³ (29-64)       | .008     |
| Fat free mass (%) | 54³ (41-83) | 63³ (46-83) | <.001   | 51³ (41-67)              | 63³ (46-83)       | <.001    |
| **Biochemical measurements** |             |                   |          |                          |                   |          |
| S-Insulin (mIU/L) | 14.0 (1.0-64.0) | 7.0 (3.0-62.0) | .002    | 17.0 (5.0-64.0)          | 7.0 (3.0-62.0) | <.001    |
| S-Insulin/kg fat mass | 0.30³ (0.08-1.58) | 0.33³ (0.12-0.64) | ns      | 0.35³ (0.12-1.58)       | 0.33³ (0.12-0.64) | ns       |
| P-glucose (mmol/L) | 5.0 (3.6-9.9) | 4.9 (3.7-6.1) | ns      | 5.0 (3.7-9.9)           | 4.9 (3.7-5.1) | ns       |
| P-HDL-C (mmol/L) | 1.30 (0.59-2.00) | 1.50 (0.75-2.40) | ns      | 1.10 (0.59-2.00)       | 1.50 (0.75-2.40) | .004     |
| P-LDL-C (mmol/L) | 2.8 (0.6-4.2) | 2.7 (1.4-5.7) | ns      | 2.5 (0.6-4.2)          | 2.7 (1.4-5.7) | ns       |
| P-TG (mmol/L) | 1.0 (0.4-4.0) | 0.9 (0.5-2.4) | .069    | 1.2 (0.5-4.0)          | 0.9 (0.5-2.4) | .030     |
| ApoB/ApoA-1 ratio | 0.61 (0.17-1.06) | 0.51 (0.34-1.62) | ns      | 0.70 (0.17-1.06)       | 0.51 (0.34-1.62) | ns       |
| P-CRP (mg/L) | 1.4 (0.6-20) | 0.6 (0.6-6.1) | <.001   | 3.0 (0.6-20.0)          | 0.6 (0.6-6.1) | <.001    |

Note: Data are presented as median (range). Apo, apolipoprotein; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; F, female; HDL-C, high-density lipoprotein cholesterol; HL, hypothalamic lesion; hs-CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ns, not significant; P, plasma; S, serum; TG, triglycerides.
³n = 38 as three patients could not perform DXA due to weight.
²n = 31 as one control could not perform DXA due to weight.
²²n = 20 as three patients could not perform DEXA due to weight.
This is the first study showing increased WML in childhood-onset CP. Particularly patients treated with CRT had a significant increase in WML. Importantly, this association continued to be significant after adjustment for confounders as age and fat mass. In addition, among the radiated patients WML volume increased by 0.41 mL for each year of age older at investigation. CRT was provided with photon therapy with 3-field technique on the vertex and temporal...

| TABLE 3 Characteristics for patients and controls with WML volume ≥ 1 mL versus WML volume < 1 mL |
|-----------------------------------------------|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Patients with WML volume ≥ 1 mL n = 18        | Patients with WML volume < 1 mL n = 18        | Controls with WML volume ≥ 1 mL n = 5 | Controls with WML volume < 1 mL n = 26 | P value |
| F/M                                           | F/M                                           | ns                            | ns                            | ns              |
| 12/6                                          | 10/8                                          | 1/4                           | 17/9                          | ns              |
| Age at diagnosis (years)                      | Age at diagnosis (years)                      | .016                          | -                             | -               |
| 9 (3-29)                                      | 14 (4-27)                                     | -                             | -                             | -               |
| HT lesion/no HT lesion (n)                    | HT lesion/no HT lesion (n)                    | .046                          | -                             | -               |
| 12/6                                          | 6/12                                          | -                             | -                             | -               |
| Body mass index (kg/m²)                       | Body mass index (kg/m²)                       | .008                          | 33 (27-49)                    | .001            |
| 34 (24-46)                                    | 28 (20-39)                                    | 23 (20-34)                    |                                |                 |
| IDF metabolic syndrome (n)                    | IDF metabolic syndrome (n)                    | ns                            | ns                            |                 |
| 9                                             | 2                                             | 2                             | 0                             | .001            |
| Year of birth                                 | Year of birth                                 | ns                            | ns                            |                 |
| 1976 (1957-1994)                              | 1976 (1957-1994)                              | 1976 (1971-1977)              | 1977 (1957-1995)              |                 |
| Year of first operation                       | Year of first operation                       | .02                           | -                             | -               |
| 1984 (1964-2008)                              | 1994 (1982-2004)                              | -                             | -                             | -               |
| Irradiation (n)                               | Irradiation (n)                               | na                            | -                             | -               |
| 8 + 1 yttrium                                 | 4 + 1 gammaknife                              | -                             | -                             | -               |
| Irradiation—Gy                                | Irradiation—Gy                                | na                            | -                             | -               |
| 50 (35-55)                                    | 54 (54-55)                                    | -                             | -                             | -               |
| Year of first irradiation                     | Year of first irradiation                     | ns                            | -                             | -               |
| 1991 (1966-1995)                              | 1997 (1990-2004)                              | -                             | -                             | -               |
| >1 op (n)                                     | >1 op (n)                                     | ns                            | -                             | -               |
| 7                                             | 4                                             | -                             | -                             | -               |
| Pan-hypopituitarism (n)                       | Pan-hypopituitarism (n)                       | na                            | -                             | -               |
| 14                                            | 9                                             | -                             | -                             | -               |
| Total Fazekas score                           | Total Fazekas score                           | .04                           | 2 (0-2)                       | ns              |
| 1.5 (0-6)                                     | 0 (0-3)                                       | 0 (0-4)                       |                                |                 |
| Physical activity during work (mean)          | Physical activity during work (mean)          | ns                            | 2.8 (2-4)                     | ns              |
| 1.73 (1-3)                                    | 1.89 (1-4)                                    | 1.96 (1-3)                    |                                |                 |
| Physical activity during leisure time (mean)  | Physical activity during leisure time (mean)  | ns                            | 2.4 (2-3)                     | ns              |
| 1.83 (1-3)                                    | 2.22 (1-4)                                    | 2.38 (1-4)                    |                                |                 |
| Physical fatigue (median)                     | Physical fatigue (median)                     | ns                            | 8.5 (4-18)                    | ns              |
| 13 (4-19)                                     | 10.5 (4-16)                                   | 13 (4-16)                     |                                |                 |

Abbreviations: F, female; Gy, Grey; HT, Hypothalamus; IDF, International Diabetes Federation; M, male; na, not applicable due to low number; ns, non significance; Op, Operation; WML, White matter lesion.

FIGURE 2 Correlation between white matter lesion volume (mL) and age at study participation among 12 patients with cranial radiotherapy

4 | DISCUSSION

This is the first study showing increased WML in childhood-onset CP. Particularly patients treated with CRT had a significant increase
regions and WMLs were recorded in the frontal and vertex regions, but not in the temporal regions. When interpreting the present data it is important to bear in mind that it is only representative in CP patients who were radiated in childhood and who were investigated at 18-56 years of age. The exact time when WML starts to develop seems to be around 20 years after CRT (Figure 3), although this is only based on a small group (n = 12) of CP patients and no large assumptions should be drawn from these numbers alone. The association between WML volume and years since CRT was insignificant. The most plausible explanation is low power due to the small sample size. In addition, CRT is only one part of the explanation to WML, other contributing factors are HT volume and age of the patient. Altogether these variables explain 47% of WML volume.

The young age of this patient group when receiving CRT, is also very important as according to Table 3, patients with WML ≥ 1 mL were younger at diagnosis, having their first operation almost 10 years earlier as compared to patients with WML < 1 mL. No difference was found regarding the year when CRT was provided. The threshold level of WML volume when it may start to have a significant effect on CV risk is unknown, but Table 3 illustrates that patients who have WML ≥ 1 mL indeed have a higher BMI and more often fulfill the criteria for metabolic syndrome.

The presence of reduced HT volume is hitherto unexplored in relation to WML and we found a negative association where HT volume explained 26% of the variation in WML volume. For each 100 mm$^3$ increase in HT volume, the WML volume decreases with 0.4 mL (Table 4). Including CRT and age at investigation in the model did not change the results more than marginal. Recently, we showed that a decrease in HT volume in CP was associated with an increase in both fat mass and leptin. Indeed, HT lesion results in hypothalamic obesity together with major metabolic risk factors among these patients. In addition, we have shown that patients with HT lesion are estimated to have a HT volume of approximately 400 mm$^3$ while in comparison healthy controls have around 800 mm$^3$. Based on these results, we suggest that a radical operation of a CP may result in a HT volume somewhere around 400 mm$^3$. According to the linear regression, radical operation of the patient may cause at least 1.6 mL (4 × 0.4 mL) increase in WML volume and if the patient receives CRT this may result in a 2.7 mL increase in WML volume (Table 4). It is well known that WML volume increases with age and from Table 4 it can be estimated that as the patient gets 10 years older the WML volume increases by 1.5 mL (10 × 0.15 mL). Thus, having received CRT corresponded to the similar effect as being 18 year older (2.7/0.15). Table 4 highlights that the late effects of CRT should not be underestimated. This is an issue that needs to be verified in a larger study population in a patient group which is currently increasing in prevalence following the shift in treatment to a subtotal tumour excision + CRT. Finally, we would like to highlight the fact that all together the three variables (CRT, HT volume and age at investigation) explain 47% of the variation in WML volume. To rank the mentioned variables based on importance is not relevant as they are so interrelated. Indeed CRT is more often provided to patients with recurrent tumour and thus with the risk of HT lesion.

**FIGURE 3** Correlation between White matter lesion volume (mL) and years since cranial radiotherapy (CRT) ($P = .12$)

**TABLE 4** Estimated effects ($\beta$) of hypothalamic volume, radiation and age at investigation on WML volume (mL) obtained from linear regression analyses. For the multivariate model, the fractions of explained variances (adjusted $r^2$) are presented

|                               | Univariate models | Multivariate model |
|-------------------------------|-------------------|--------------------|
| Hypothalamic volume (per 100 mm$^3$ increase) | $-0.5 (-0.8, -0.2)$ | $-0.4 (-0.7, -0.2)$ |
| Radiation (yes vs no)         | $3.1 (0.7-5.4)$   | $2.7 (0.7-4.6)$    |
| Age at investigation (yr)     | $0.13 (0.01-0.26)$ | $0.15 (0.05-0.25)$ |
| Adjusted $r^2$ for the multivariate model (%) |                    | 47                 |
CRT could be directly associated with increased WML volume or indirectly in a chain of event with reduced HT volume associated with more fat mass and higher cardiovascular risk.

Among patients with acromegaly and in patients in remission of Cushing’s syndrome an increased risk of neurovascular pathology with increased severity of WML has been shown.26 What the present study adds is data on WML volume using quantitative measurement of WML (mL) among patients with a pituitary tumour. There are scarce data on WML among CPs as only one CP patient was included in previous analyses of WML of 16 adult patients with pituitary tumours treated with CRT (mean dose 42 Gy).15 The mean age of this group was 40.5 years, but the average interval between completion of CRT and MRI was short (4.6 years) and no radiation-related WML was recorded in the group of radiated pituitary tumours in comparison to a large group of nonradiated other brain tumours.15 In contrast, in the latter group, a wide variety of WML were found.15 Miura et al27 retrospectively evaluated WML volume among 102 patients who had undergone radiation for a brain tumour, excluding pituitary tumours, and 12 patients with WML were identified after 19.8 years of follow up. Further, head and neck radiotherapy significantly increases the risk of transient ischaemic attack and ischaemic stroke28 and among radiated paediatric brain tumour survivors the stroke risk was increased.29 However, there is a difference in how CRT is provided among other brain tumour patients, in whom radiotherapy is both local to the specific tumour, and additionally to the whole brain. In contrast, radiation in CP is only provided locally, but with a somewhat higher radiation dose (50-60 Gy)30 compared to other pituitary tumours (40-50 Gy).31

An important question that needs to be considered is whether obstruction of cerebral small vessel disease with WML is more amenable to treatment than hypothalamic obesity. Previously we showed that CP patients have less physical activity and increased physical fatigue as compared to controls.9 This becomes relevant in the context of WML as greater physical activity is associated with larger brain volume or less atrophy.32,33 Interestingly, there are studies showing that increased physical activity is associated with lower WML volume34 and engaging in progressive resistance training may reduce WML progression.35

The present study population is small but against a rare disease and the background population of 2.5 million we managed to include an acceptable number (64%) of the eligible group of survivors of childhood-onset CP during 52 years in this area of Sweden. This study presents the longest follow up so far of childhood-onset CP and includes a control group matched for gender, age and smoking habits, lending us to control for several confounders. In addition, the study sample represents well both phenotypes (HT lesion vs non-HT lesion) illustrative for the whole spectrum of the disease. Patients not included were both patients with a more benign disease claiming not to have time for participation as well as to ill patients. However, it is important to stress that the size of the study means that we were not able to detect relatively small or moderate associations, which accordingly not can be excluded.

In conclusion, increased WML volume was recorded among the patients and particularly among patients undergone CRT. The presence of WML might be directly associated with CRT or indirectly via reduced HT volume related to high metabolic risk. Risk factors should be carefully monitored in these patients.

ACKNOWLEDGEMENTS
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CONFLICT OF INTEREST
Nothing to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon request.

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How to cite this article: Fjalldal S, Rylander L, van Westen D, et al. Brain white matter lesions are associated with reduced hypothalamic volume and cranial radiotherapy in childhood-onset craniopharyngioma. Clin Endocrinol (Oxf). 2021;94:48-57. https://doi.org/10.1111/cen.14307