Cerebral white matter hyperintensities in adults born small for gestational age at 12 years after cessation of childhood growth hormone treatment: a prospective cohort study including untreated controls

Demi J. Dorrepaal,[a,*] Wesley J. Goedegebuure,[a] Manouk van der Steen,[a] Daniel Bos,[b,c] and Anita C. S. Hokken – Koelega[a]

[a]Department of Pediatrics, Erasmus MC - University Medical Center-Sophia Children's Hospital, 3015 CN, Rotterdam, the Netherlands
[b]Department of Radiology & Nuclear Medicine, Erasmus MC - University Medical Center, 3015 CN, Rotterdam, the Netherlands
[c]Department of Epidemiology, Erasmus MC - University Medical Center, 3015 CN, Rotterdam, the Netherlands

eClinicalMedicine 2024;72: 102637
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102637

Summary

Background Increased cerebrovascular morbidity was reported in adults born small for gestational age (SGA) who were treated with growth hormone (GH) during childhood compared to the general population. Yet, previous studies lacked an appropriate control group which is a major limitation. We prospectively studied cerebral white matter hyperintensities (WMHs) in adults born SGA at 12 years after cessation of childhood GH-treatment (SGA-GH), compared to appropriate controls.

Methods In this prospective cohort study, performed between May 2016 and December 2020, total WMHs, periventricular WMHs (PVWMHs) and deep WMHs (DWMHs) were the primary outcomes of the study, they were qualitatively assessed using 3 Tesla (T) Magnetic Resonance Imaging (MRI) and scored using the Fazekas scale in SGA-GH adults and in 3 untreated control groups: adults born SGA with persistent short stature (SGA-S), adults born SGA with spontaneous catch-up growth to a normal height (SGA-CU) and adults born appropriate for gestational age with a normal height (AGA). Regression analyses were performed in the total cohort to evaluate the associations of GH-treatment and birth characteristics with WMHs.

Findings 297 adults were investigated (91 SGA-GH, 206 controls). Prevalence of total WMHs was 53.8% (95% CI 43.1–64.3) in SGA-GH, 40.5% (95% CI 25.6–56.7) in SGA-S, 73.9% (95% CI 61.9–83.7) in SGA-CU and 41.1% (95% CI 31.1–51.6) in AGA adults. No statistically significant differences in total WMHs, PVWMHs and DWMHs were found between SGA-GH compared to SGA-S and AGA adults. Highest prevalence of all type of WMHs was found in SGA-CU adults compared to all groups. Higher prevalence of total WMHs was associated with lower birth weight standard deviation score (SDS), but not with GH-treatment.

Interpretation Our findings suggest that GH-treatment in children born SGA has no negative impact on the prevalence of all type of WMHs at 12 years after GH cessation compared to appropriate controls. SGA-CU adults had the highest prevalence of all type of WMHs around age 30 years.

Funding Novo Nordisk.

Keywords: Small for gestational age; Growth hormone treatment; Cerebral white matter hyperintensities; Cerebrovascular health

Introduction

The majority of children born small for gestation age (SGA) show catch-up growth to a normal height in the first years of life.[1] In approximately 10% of children born SGA, short stature persists (height <–2 standard deviation score (SDS)).[2] In these children, growth hormone (GH) treatment effectively induces catch-up growth and improves adult height.[3–7]

As low birth weight has been associated with a higher risk for adult diseases,[8] recent research has

*Corresponding author. Erasmus University Medical Center, Department of Pediatrics, P.O. 2060, 3000 CB, Rotterdam, the Netherlands.
E-mail address: d.dorrepaal@erasmusmc.nl (D.J. Dorrepaal).

Research in context

Evidence before this study

We searched PubMed with the terms "small for gestational age" and "growth hormone treatment" to identify publications in English relating to primary outcomes after cessation of growth hormone (GH) treatment published between January 1, 2000 and September 1, 2023. Data of the French cohort of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study raised concerns about the long-term effects of GH-treatment on the cerebrovascular system, because an increased cerebrovascular morbidity was found in GH-treated subjects, including those born SGA. However, the main limitations of the SAGhE project was that data of GH-treated subjects were retrospectively compared with the general population and not with an age-matched group of untreated SGA patients. To adequately study the effects of GH-treatment on the cerebrovascular system, it is important to prospectively compare data of adults born SGA treated with GH during childhood with those of untreated adults born SGA.

Added value of this study

This is the first study that prospectively explored white matter hyperintensities (WMHs), markers for subclinical cerebrovascular disease, in adults born SGA who were treated with GH during childhood (SGA-GH), results were compared with appropriate control groups, including a group of untreated adults born SGA with persistent short stature (SGA-S). Because we included untreated SGA-S adults, we were able to distinguish if the increased cerebrovascular morbidity in GH-treated subjects found in the SAGhE study was related to GH-treatment itself or to the underlying condition of being born SGA. Long-term data at 12 years after GH cessation were assessed using a 3 Tesla (T) Magnetic Resonance Imaging (MRI) system, a high-quality research tool. Such detailed brain MRI measurements are not feasible in population studies.

Implications of all the available evidence

No statistically significant difference in prevalence of WMHs between adults born SGA treated with GH during childhood and untreated control groups around the age of 30 years was found. Our results suggest that long-term GH-treatment in children born SGA has no adverse effects on the prevalence of WMHs up to 12 years after GH cessation. Further research is needed to confirm our findings. It is important to investigate the long-term effects of GH-treatment on health-related quality of life and psychosocial functioning as well.

focused on the long-term consequences of being born SGA and whether GH-treatment might have a negative impact, particularly with regard to the risk of cardio- and cerebrovascular diseases. The French population-based cohort of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study reported an increased cerebrovascular morbidity due to strokes, including ischemic stroke (standardized incidence ratio 5.3 (95% confidence interval (CI), 2.1–11.2) in GH-treated subjects, including those born SGA, compared to the general population of the Oxford cohort.[9,10] These data raised concerns about long-term effects of GH-treatment on the cerebrovascular system. However, the main limitation of the SAGhE study was absence of an appropriate control group of untreated SGA subjects to distinguish if the increased cerebrovascular morbidity was related to GH-treatment itself or by the underlying condition of being born SGA.

White matter hyperintensities (WMHs), markers for subclinical cerebrovascular disease, originate from chronic ischemia/hypoperfusion in the brain and can be assessed using Magnetic Resonance Imaging (MRI). We, therefore, prospectively studied WMHs using MRI in adults born SGA at 12 years after childhood GH cessation (SGA-GH) around the age of 30 years in comparison with three untreated age-matched control groups: adults born SGA with persistent short stature (SGA-S), adults born SGA with spontaneous catch-up growth to a normal height (SGA-CU) and adults born appropriate for gestational age with a normal height (AGA). We hypothesized that the prevalence of WMHs would be similar in SGA-GH adults compared to SGA-S and AGA adults. In addition, we investigated if GH-induced catch-up growth has a different long-term effect on WMHs than spontaneous catch-up growth, by comparing the results of SGA-GH and SGA-CU adults. We hypothesized a higher prevalence of WMHs would be found after spontaneous catch-up growth during early childhood, as SGA-CU adults are known to have a less healthy cardiometabolic profile at age 30 years.[11,12] Finally, we performed regression analyses to evaluate the associations of GH-treatment and birth characteristics with WMHs.

Methods

Study design and participants

This prospective cohort study, performed between May 2016 and December 2020, comprised 297 adults, of whom 91 born SGA (birthweight or birth length SDS <–2) had participated in Dutch GH trials during their childhood (SGA-GH).[11,13] As a child, these adults were included in the Dutch GH trials from age 4 years (the minimum eligible age) if they fulfilled the following criteria: a birth length or birthweight SDS <–2 for gestational age; a height SDS for age <–2 according to Dutch standards; a height velocity SDS <0; a Tanner breast stage 1 for girls and a testicular volume of less than 4 mL for boys; an uncomplicated neonatal period, with no signs of severe asphyxia (defined as an Apgar

score <3 after 5 min), sepsis, or long-term complications of respiratory ventilation, such as chronic lung disease; and no growth hormone deficiency (defined as a growth hormone peak >10 μg/L during two growth hormone stimulation tests). Children with endocrine or metabolic disorders, chromosomal defects, or syndromes and growth failure caused by other conditions (eg, emotional deprivation, severe chronic illness, or chondrodysplasia) were excluded. GH-treatment was continued until adult height attainment, defined as the height reached when growth velocity had decreased to less than 0.5 cm during the past 6 months. SGA-GH adults were invited to participate in the current study when they had stopped GH-treatment for at least 10 years. The SGA-GH group was compared with three GH untreated control groups of similar age from the PROgramming factors for GRowth And Metabolism (PROGRAM32) study,[12] all subjects were included between May 2016 and December 2020. Two of the control groups (SGA-S and SGA-CU) were recruited after reviewing hospital records from several Dutch hospitals (Erasmus University Medical Center, Rotterdam, Netherlands; University Medical Center, Groningen, Netherlands; University Medical Center, Leiden, Netherlands; University Medical Center, Amsterdam, Netherlands; Wilhelmina Children's Hospital, Utrecht, Netherlands; Catharina Hospital, Eindhoven, Netherlands; and Radboud University Hospital, Nijmegen, Netherlands) where these individuals had been registered because of being born SGA, followed by either persistent short stature (adult height SDS <–2) (SGA-S) or spontaneous catch-up growth during early childhood to a typical adult height (SDS >–1) (SGA-CU).[12] Additionally, healthy adults with normal stature who were born appropriate for gestational age (AGA) with different educational levels were randomly selected as controls.[12–14] All AGA adults had visited schools in Rotterdam. SGA-S adults had not participated in the GH trials as children, as pediatricians in the eastern part of the Netherlands were not involved in the Dutch SGA-GH trials. Therefore, these individuals made the most appropriate control group of untreated adults with persistent short stature. Individuals included in this control group fulfilled all eligibility criteria of the SGA-GH group but were never treated with GH. SGA-CU adults had not participated in the GH trials as children, because of their spontaneous catch-up growth they did not fulfill all eligibility criteria.

Ethics

The Medical Ethics Committee of Erasmus University Medical Center (Rotterdam, The Netherlands) approved the study and all participants gave written informed consent.

Outcomes

The main outcome parameters of the study were the prevalence of total WMHs, periventricular WMHs (PVWMHs) and deep WMHs (DWMHs) in the four groups. Total WMHs prevalence included the prevalence of PVWMHs or DWMHs, or both. PVWMHs are located near the ventricular system, while DWMHs are located in the subcortical white matter.

Procedures

All brain MRIs were performed on the same 3 Tesla (T) MRI system (GE Healthcare, Milwaukee, WI, USA). The scan protocol included a fluid-attenuated inversion recovery (FLAIR) sequence, which was used to evaluate the WMHs.[15] The Fazekas scale was used to evaluate the presence and severity of PVWMHs and DWMHs.[16] MRI images of the different grades of the Fazekas scale are shown in Fig. 1, the description of the Fazekas scale is displayed in Table 1. PVWMHs and DWMHs were scored by DD and DB, an inter-rater reliability analysis was performed on 50 scans, weighted Cohen's kappa coefficient was 0.716 for PVWMHs and 0.833 for DWMHs, which was similar as reported in literature.[17,18] The few disagreements of scale were resolved by discussion until consensus.

Clinical characteristics at birth, including the sex of study participants, were obtained via birth records of hospitals. At around age 30 years, we assessed participants' height and weight, body composition, blood pressure and serum lipids. We measured standing height to the nearest 0·1 cm (Harpenden stadiometer; Holtain, Crymmyth, UK) and weight to the nearest 0.1 kg on a digital scale (Servo Balance KA-20-150S; Servo Berkel Prior, Katwijk, Netherlands). We expressed adult height and weight as SDS, adjusted for sex; based on references for Dutch adults, using Growth Analyser Research Calculation Tools Growth Analyser–Monitor growth with ease.[19] Furthermore, body composition, blood pressure and serum lipid levels measurements were performed, more details on performing these measurements are previously reported.[11] Adults provided information regarding socioeconomic status and lifestyle factors at around age 30 years through a structured questionnaire. Yearly income (low: <€10.000; middle: €10.000–50.000; high: >€50.000) and highest completed level of education (low: lower secondary education; middle: upper secondary education or post-secondary non-tertiary education; high: bachelor's degree or higher) were used to determine socioeconomic status. Information regarding smoking status (never, history or cigarettes/day), alcohol consumption (units/week or day), illicit drug use (frequency, amount and type of drugs) and exercise level (hours/week or month) was provided to assess lifestyle factors.

Statistics

Statistical analyses were performed using SPSS version 28.0 for Windows. Clinical characteristics are presented as mean and standard deviation (SD) or percentages. Analysis of variance (ANOVA) with post-hoc Dunnett's

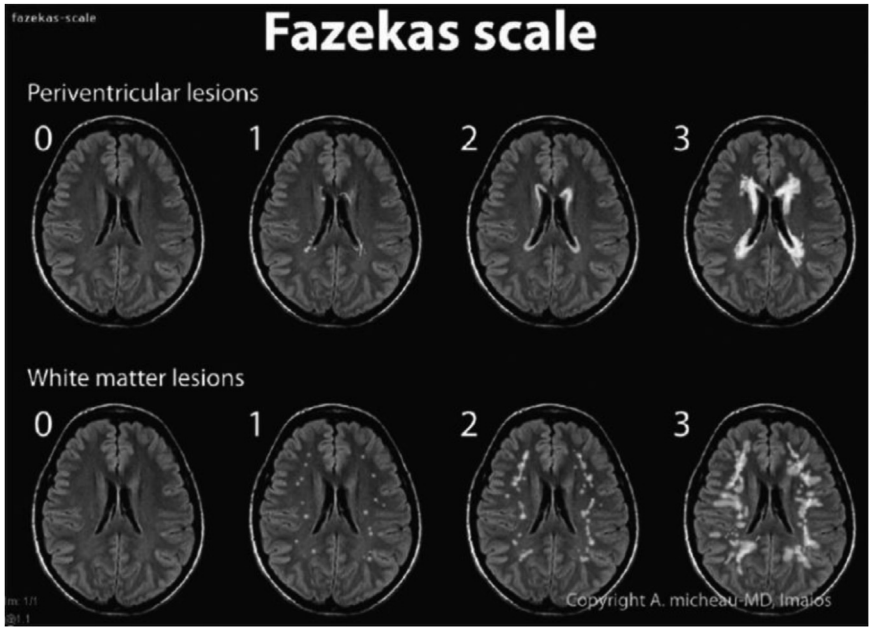

***Fig. 1:* Magnetic Resonance Imaging (MRI) images of the different grades of the Fazekas scale**. Visual information regarding the Fazekas scale. Examples of Magnetic Resonance Imaging (MRI) images of the different grades (0, 1, 2 and 3) of the Fazekas scale are displayed. More descriptive information is found in Table 1.

test or Chi-square test were used to compare the clinical characteristics between all groups and between the SGA-GH group and the control groups. First, we assessed the total prevalence of total WMHs (consisting of PVWMHs or DWMHs), PVWMHs and DWMHs and the prevalence per Fazekas score separately in the four groups, and compared the prevalence using the Chi-square test. Confidence intervals (95% CI) of the prevalence and the difference in prevalence between the groups are given. Second, we performed multivariable logistic regression analyses in the total cohort to investigate the association of GH-treatment and birth characteristics (birth weight SDS, birth length SDS) with total WMHs, PVWMHs and DWMHs (absent vs. present). Logistic regression analyses were also performed to determine the odds of total WMHs, PVWMHs and DWMHs in SGA-S adults compared to SGA-GH adults, after adjustment for potential confounders. Adult height SDS and the interaction term birth length SDS * adult height SDS was added to the models because the study groups had been selected on birth length SDS and adult height SDS, in order to ensure that the effect of these variables were modeled correctly. Furthermore, known risk factors that could increase the development of cardio- and cerebrovascular disease were added to the total WMH model as potential confounders. We included the following potential confounders: sex, age, mean arterial pressure, total cholesterol, fat mass index, alcohol consumption (yes vs. no), smoking (yes vs. no) and drug use (yes vs. no).[20–23] As the number of adults with PVWMH was low and no major changes occurred regarding odd ratio and significance when we added the potential confounders to the unadjusted total WMH model, we only included sex and age as potential confounders in the models regarding PVWMHs and DWMHs. Before performing the regression analyses, 10-fold multiple imputation was performed, using the fully conditional specification method, to impute missing data. The variable with the highest percentage of missing data was birth length SDS (9.1%), the percentage of missing data of the other variables varied between 0.7 and 4.4% (legend Table 2). Data missing at random (MAR) was

Grade	0	1	2	3
Periventriculair WMHs (PVWMHs)	Absent	"Caps" or pencil-thin lining	Smooth "halo"	Irregular periventricular signal extending into the deep white matter
Deep WMHs (DWMHs)	Absent	Punctate foci	Beginning confluence	Large confluent areas

Description of the different grades of the Fazekas scale.

***Table 1:* Fazekas scale.**

	Study group	Comparison groups			p-value
	SGA-GH	SGA-S	SGA-CU	AGA	
Subjects (female)	91 (51)	42 (25)	69 (36)	95 (53)	0.90
At birth					
Gestational age (weeks)	36.5 (3.7)[b]	37.7 (3.1)	36.5 (3.1)	38.8 (2.5)	**<0.001**
Birth length SDS	−3.36 (1.50)[b,c]	−2.95 (1.31)	−2.51 (1.09)	0.13 (0.95)	**<0.001**
Birth weight SDS	−2.48 (0.95)[b]	−2.19 (0.93)	−2.29 (1.00)	0.29 (0.97)	**<0.001**
At start GH treatment					
Age, years	7.7 (2.4)	NA	NA	NA	
At GH cessation					
Age, years	16.1 (1.4)	NA	NA	NA	
GH treatment duration, years	8.3 (2.3)	NA	NA	NA	
At 12 years after GH cessation or at around age 30 years					
Age at MRI	29.1 (3.5)[a,b,c]	31.9 (3.6)	33.0 (2.6)	32.9 (2.7)	**<0.001**
Adult height SDS	−1.61 (1.03)[a,b,c]	−2.33 (0.57)	−0.17 (0.69)	0.36 (0.85)	**<0.001**
Fat mass index (kg/m^2)	7.16 (3.1)	7.81 (3.2)	7.81 (3.3)	7.61 (3.5)	0.57
Mean arterial pressure (mm Hg)	85.9 (7.5)	86.1 (8.5)	86.3 (7.8)	86.1 (7.9)	0.99
Total cholesterol	4.47 (0.9)[a]	4.88 (0.8)	4.77 (0.9)	4.41 (0.7)	**0.003**
SES (income) (%)					**<0.001**
Low	14.3[b,c]	10.3	5.1	3.4	
Medium	81.8	79.4	71.2	67.8	
High	3.9	10.3	23.7	28.8	
SES (education) (%)					**<0.001**
Low	20.9[b,c]	10.0	10.6	4.4	
Medium	44.2	52.5	28.8	21.1	
High	34.9	37.5	60.6	74.4	
Smoking (%)					0.30
Never	64.4	72.5	65.7	72.2	
<10 cigarettes/day	12.6	12.5	19.4	8.9	
≥10 cigarettes/day	10.3	7.5	10.4	4.4	
History	12.7	7.5	4.5	14.4	
Alcohol consumption (%)					0.17
Never	18.2	17.5	7.5	12.2	
<1 unit/week	27.3	25.0	37.3	27.8	
1–3 units/week	31.8	40.0	19.4	31.1	
4–6 units/week	15.9	15.0	26.9	16.7	
>1 units/day	6.8	2.5	9.0	12.2	
Illicit drug use (%)					0.37
Total	16.1	12.5	20.9	11.1	
Cannabis	11.0	9.5	10.1	3.2	
Ecstasy	4.4	0	11.6	7.4	
Cocaine	5.5	0	5.8	4.2	
Exercise (%)					0.55
Never	37.9	35.0	26.9	20.0	
<1 h/week	3.4	2.5	3.0	5.6	
1–2 h/week	32.2	35.0	31.3	40.0	
3–5 h/week	16.1	17.5	28.4	23.3	
>5 h/week	10.3	10.0	10.4	11.1	

Values are presented as mean (SD) or percentages. Abbreviations: SGA-GH, adults born small for gestational age treated with growth hormone during childhood; SGA-S, adults born small for gestational age with persistent short stature; SGA-CU, adults born small for gestational age with spontaneous catch-up to a normal height; AGA, adults born appropriate for gestational age with a normal height; SDS, standard deviation score. NA, not applicable. Bold p-values in the last column are considered significant differences among all groups. The different symbols indicate a significant difference among two groups, they are as follows defined. [a]$p < 0.05$ SGA-GH compared with SGA-S. [b]$p < 0.05$ SGA-GH compared with AGA. [c]$p < 0.05$ SGA-GH compared with SGA-CU. Missing values were present for birth weight SDS (1.0%), birth length SDS (9.1%), gestational age (1.0%), fat mass index (2.0%), mean arterial pressure (0.7%), total cholesterol (0.7%), smoking (4.4%), alcohol consumption (4.0%) and drug use (4.0%).

Table 2: **Clinical characteristics of 297 subjects.**

considered plausible. p-values of less than 0.05 were regarded as statistically significant.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Clinical characteristics

Table 2 shows the clinical characteristics of all 297 adults at birth, at start and cessation of GH-treatment in SGA-GH adults, and at the time of cerebral imaging around the age of 30 years. In the 91 SGA-GH adults, mean (SD) age at start of GH-treatment was 7.7 years (2.4), mean GH-treatment duration was 8.3 years (2.3) and mean age at cessation of GH-treatment was 16.1 years (1.4). Mean age at MRI was 29.1 years (3.5) in SGA-GH adults, 31.9 years (3.6) in SGA-S adults, 33.0 years (2.6) in SGA-CU adults and 32.9 years (2.7) in AGA adults ($p < 0.001$). Birth length and birth weight were different between the SGA groups and the AGA group, as this was part of the inclusion criteria. Mean adult height SDS in SGA-GH was −1.61, which was higher than in SGA-S (−2.33, $p < 0.001$) but lower than in SGA-CU (−0.17, $p < 0.001$) and AGA (0.36, $p < 0.001$). There were differences in income and educational level between the groups ($p < 0.001$). Twelve of the 297 participants did not complete the questionnaire regarding socioeconomic status and lifestyle factors (3 SGA-GH, 2 SGA-S, 2 SGA-CU and 5 AGA).

Total white matter hyperintensities (total WMHs)

Table 3 shows the prevalence of total WMHs, consisting of PVWMHs or DWMHs (or both), of all 297 adults in the 4 groups. The prevalence of total WMHs was 53.8% (95% CI 43.1–64.3) in SGA-GH, 40.5% (95% CI 25.6–56.7) in SGA-S, 73.9% (95% CI 61.9–83.7) in SGA-CU and 41.1% (95% CI 31.1–51.6) in AGA adults. The difference in prevalence between SGA-GH and SGA-S adults was 13.3% (95% CI −4.6 to 31.1) and between SGA-GH and AGA adults 12.7% (95% CI −3.3 to 28.7). No statistically significant differences in total WMHs were found between SGA-GH compared to SGA-S and AGA adults.

Highest prevalence of total WMHs was found in SGA-CU adults, being significantly higher compared to SGA-GH ($p = 0.01$) and AGA adults ($p < 0.001$), with a difference in prevalence of 20.1% (95% CI 3.6–36.9) and 32.8% (95% CI 18.2–46.9) respectively.

Periventricular white matter hyperintensities (PVWMHs)

Prevalence of PVWMHs was 25.3% (95% CI 16.8–35.5) in SGA-GH, 14.3% (95% CI 5.4–28.5) in SGA-S, 33.3% (95% CI 19.6–49.6) in SGA-CU and 15.8% (95% CI 9.1–24.7) in AGA adults. The difference in prevalence between SGA-GH and SGA-S adults was 11.0% (95% CI −7.4 to 28.2) and between SGA-GH and AGA adults 9.5% (95% CI −4.4 to 21.0). Fazekas grade 1 was most common and Fazekas grade 3 was not found. No statistically significant differences in total, grade 1 and grade 2 PVWMHs prevalence were found between SGA-GH compared to SGA-S and AGA adults.

Highest prevalence of total and grade 1 PVWMHs was found in SGA-CU adults, being not significantly different compared to SGA-GH adults but significantly higher compared to AGA adults ($p = 0.009$ and $p = 0.003$ respectively), with a difference in prevalence of 17.5% (95% CI 3.5–31.4) and 19.3% (95% CI 5.5–33.3), respectively.

	Total group	SGA-GH	SGA-S	SGA-CU	AGA	p-value
N	297	91	42	69	95	
% total WMHs	52.5	53.8 (43.1–64.3)	40.5 (25.6–56.7)	73.9 (61.9–83.7)[a,d]	41.1 (31.1–51.6)	**<0.001**
% PVWMHs						
Presence	22.6	25.3 (16.8–35.5)	14.3 (5.4–28.5)	33.3 (22.4–45.7)[b]	15.8 (9.1–24.7)	**0.03**
Grade 1	19.9	22.0 (14.0–31.9)	11.9 (4.0–25.6)	31.9 (21.2–44.2)[b]	12.6 (6.7–21.0)	**0.01**
Grade 2	2.7	3.3 (0.7–9.3)	2.4 (0.1–12.6)	1.4 (0.0–7.8)	3.2 (0.7–9.0)	0.89
Grade 3	0	0	0	0	0	
% DWMHs						
Presence	45.8	47.3 (36.7–58.0)	33.3 (19.6–49.6)	63.8 (51.3–75.0)[a,d]	36.8 (27.2–47.4)	**0.002**
Grade 1	43.1	40.7 (30.5–51.5)	33.3 (19.6–49.6)	63.8 (51.3–75.0)[a,c]	34.7 (25.3–45.2)	**<0.001**
Grade 2	2.7	6.6 (2.5–13.8)[d]	0	0	2.1 (0.3–7.4)	**0.04**
Grade 3	0	0	0	0	0	

Results of Chi-square analysis, presented as percentages with 95% confidence intervals. Abbreviations: SGA-GH, adults born small for gestational age treated with growth hormone during childhood; SGA-S, adults born small for gestational age with persistent short stature; SGA-CU, adults born small for gestational age with spontaneous catch-up to a normal height; AGA, adults born appropriate for gestational age with a normal height; Bold p-values in the last column are considered significant differences among all groups. The different symbols indicate a significant difference among two groups, they are as follows defined. [a]$p < 0.001$ SGA-CU compared with AGA. [b]$p < 0.01$ SGA-CU compared with AGA. [c]$p < 0.01$ SGA-CU compared with SGA-GH. [d]$p < 0.05$ SGA-CU compared with SGA-GH.

Table 3: **Percentage of total, deep and periventricular WMHs.**

Dependent variables	Total WMHs			PVWMHs			DWMH		
Independent variables	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
GH-treatment (vs. no treatment)	1.56	0.74–3.32	0.25	1.84	0.83–4.08	0.35	1.28	0.63–2.59	0.50
Birth weight SDS	0.66	0.49–0.89	**0.007**	0.66	0.47–0.93	**0.02**	0.73	0.55–0.97	**0.03**
Birth length SDS	1.11	0.85–1.45	0.46	1.09	0.81–1.46	0.57	0.99	0.77–1.28	0.95
Adult height SDS	0.87	0.62–1.24	0.44	1.06	0.70–1.61	0.78	0.92	0.65–1.29	0.62
BL[a] AH SDS	0.88	0.78–0.99	**0.04**	0.94	0.72–1.64	0.41	0.90	0.80–1.02	0.10

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. [a]BL AH SDS = interaction term between birth length SDS and adult height SDS. Significant p-values are in bold. Potential confounders added in the total WMHs model were: sex, age at MRI, mean arterial pressure, total cholesterol, fat mass index, alcohol consumption, smoking, drug use. Potential confounders added in the PVWMHs and DWMHs models were sex and age at MRI.

Table 4: **Multivariable logistic regression for total WMHs, PVWMHs and DWMHs in adults around age 30 years.**

Deep white matter hyperintensities (DWMHs)

Prevalence of DWMHs was 47.3% (95% CI 36.7–58.0) in SGA-GH, 33.3% (95% CI 19.6–49.6) in SGA-S, 63.8% (95% CI 51.3–75.0) in SGA-CU and 36.8% (95% CI 27.2–47.4) in AGA adults. The difference in prevalence between SGA-GH and SGA-S adults was 14.0% (95% CI –5.8 to 32.3) and between SGA-GH and AGA adults 10.5% (95% CI –4.4 to 25.4). Fazekas grade 1 was most common and Fazekas grade 3 was not found. No statistically significant differences in total, grade 1 and grade 2 DWMHs prevalence were found between SGA-GH compared to SGA-S and AGA adults.

Highest prevalence of total and grade 1 DWMHs was found in SGA-CU adults, being significantly higher in SGA-CU compared to SGA-GH ($p = 0.04$ and $p = 0.004$, respectively) and AGA adults ($p < 0.001$ and $p < 0.001$, respectively). The difference in prevalence being 16.5% (95% CI 3.8–31.1) and 23.1% (95% CI 4.5–37.3) compared to SGA-GH and 27.0% (95% CI 9.2–42.2) and 29.1% (95% CI 13.2–44.1) compared to AGA adults, respectively. SGA-GH adults had a significantly higher prevalence of grade 2 DWMHs compared to SGA-CU ($p = 0.03$), the difference in prevalence being 6.5% (95% CI 0.1–15.0).

Multivariable logistic regression analyses for total WMHs, PVWMHs and DWMHs

We performed multivariable regression analyses to determine the association of GH-treatment and birth characteristics with the prevalence of total WMHs, PVWMHs and DWMHs (Table 4). We found that GH-treatment was not associated with the prevalence of all types of WMHs, also not after adjustment for potential confounders. Birth length SDS was not associated with the prevalence of PVWMHs and DWMH. For total WMHs, the odds ratio (OR) of birth length SDS was not significant when adult height SDS is 0. Because of the significant OR for interaction birth length SDS * adult height SDS of 0.88, for adult height SDS decreasing below 0, the OR for birth length SDS will increase. Birth weight SDS was associated with total WMHs (OR 0.66, 95% CI 0.49–0.89), PVWMHs (OR 0.66, 95% CI 0.47–0.93) and DWMHs (OR 0.73, 95% CI 0.55–0.97), also after adjustment for all potential confounders in the total WMH model, showing that 1 SDS lower birth weight SDS increased the odds of having total WMHs at around age 30 years with 34%. Furthermore, we performed multivariable regression analyses to determine the odds of total WMHs, PVWMHs and DWMHs in SGA-S adults compared to SGA-GH adults after adjustment for potential confounders. We found no significant difference in the odds of total WMHs (OR 0.45, 95% CI 0.16–1.28, $p = 0.13$), PVWMHs (OR 0.39, 95% CI 0.12–1.30, $p = 0.13$) and DWMHs (OR 0.42, 95% CI 0.16–1.14, $p = 0.09$) in the SGA-S group compared to the SGA-GH reference group.

Discussion

This is the first study that prospectively explored total WMHs, periventricular WMHs (PVWMHs) and deep WMHs (DWMHs) by obtaining brain MRIs in SGA-GH adults at 12 years after GH cessation at around age 30 years in comparison with appropriate untreated control groups. No statistical significant differences in total WMHs, PVWMHs and DWMHs were found between SGA-GH adults compared to SGA-S and AGA adults. In addition, highest prevalence of all type of WMHs was found in SGA-CU adults compared to all groups. SGA-CU adults had a significantly higher prevalence of total WMHs and DWMHs compared to SGA-GH adults, suggesting a negative long-term effect of spontaneous catch-up growth compared to GH-induced catch-up growth. Multivariable regression in the total cohort showed that GH-treatment was not associated with all types of WMHs. Birth weight SDS was inversely associated with the presence of all types of WMHs, indicating that a lower birth weight SDS increased the risk of having WMHs at around the age 30 years.

White matter hyperintensities (WMHs), the most common markers for subclinical cerebrovascular disease, originate from chronic ischemia/hypoperfusion in the brain. The clinical relevance of WMHs is emphasized by the systematic review and meta-analysis of Debette et al., WMHs are associated with higher risk of death (hazard ratio (HR) 2.0, 95% confidence interval

1.6–2.7), stroke (HR 3.3, 95% CI 2.6–4.4) and dementia (HR 1.9, 95% CI 1.3–2.8), showing strong evidence that the presence of WMHs indicates an increased cerebrovascular risk in the elderly population (mean age 57.8–80.1 years and mean follow-up time 1.5–12 years).[24] Furthermore, progression of WMHs is positively associated with the incidence of stroke and dementia,[24] while age and cardiovascular risk factors positively associate with the prevalence and progression of WMHs.[22,25,26]

We explored the effect of previous GH-treatment itself, separately from the underlying condition of being born SGA, by including an appropriate control group of untreated SGA-S adults. Our findings suggest no increased prevalence of total WMHs, PVWMHs and DWMHs in SGA-GH compared to SGA-S and AGA adults, but the 95% CI of the differences were relatively large. Poidvin et al. reported an increased cerebrovascular morbidity due to ischemic stroke in the retrospective French SAGhE study, with a standardized incident ratio of 5.3 (95% CI 2.1–11.2) in GH-treated subjects at around age 30 years, including those born SGA, compared to the general population of the Oxford cohort.[9,10] Based on these results, the prevalence of WMHs could have been 5 times higher in our group of SGA-GH adults of the same age compared to the control groups, but we did not find this. After adjustment for birth weight SDS and potential confounders, our regression analyses showed that GH-treatment was not associated with all types of WMHs. Birth weight SDS was, however, significantly and inversely associated with all type of WMHs. These results are in line with those by Albertsson-Wikland et al., who showed that the increased overall mortality in GH-treated patients was related to differences in the birth characteristics between the GH-treated patients and the general population rather than the GH-treatment itself.[27] Current results are in line with our previous findings suggesting that SGA-GH adults at 12 years after GH cessation had no increased prevalence of cerebrovascular abnormalities (aneurysms, intracerebral hemorrhage and microbleeds) compared to appropriate controls.[28] Altogether, our findings suggest that long-term GH treatment does not result in a higher prevalence of WMHs at around age 30 years and that adjustment for birth weight SDS is essential when data of SGA-GH adults are compared with those of untreated SGA and AGA adults.

Our study group previously investigated cardiometabolic changes after GH cessation and showed that fat mass, insulin sensitivity and blood pressure of SGA-GH adults were similar compared to SGA-S and AGA adults at around age of respectively 21 and 30 years,[11,13,29] indicating that childhood GH-treatment has no negative effects on cardiometabolic health. However, lean body mass was lower and adverse serum lipid levels were higher in SGA adults compared to AGA adults at around age 30 years, suggesting that this was due to the underlying condition of being born SGA.[11,12] This was supported by the inverse association of between birth weight SDS with the number of metabolic syndrome components.[12] These findings are in line with the inverse association between birth weight and adult diseases as reported by Barker in 1990 and later confirmed in large epidemiological studies.[8,30–32] Thus, adults who were born SGA have an increased risk to develop cardio- and cerebrovascular diseases, more research is required to investigate how this should best be monitored to prevent cardio- and cerebrovascular diseases.

SGA-CU adults had the highest prevalence of all type of WMHs compared to SGA-GH, SGA-S and AGA adults. The significantly higher prevalence of total WMHs and DWMHs compared to SGA-GH adults, suggests a negative long-term effect of spontaneous catch-up growth compared to GH-induced catch-up growth. SGA-GH adults had, however, significantly (6%) more grade 2 DWMHs than SGA-CU adults, but the number of adults with grade 2 DWMH was very low. The high prevalence of all types of WMHs in SGA-CU adults might be explained by the fact that this group had more catch-up in weight SDS than in length SDS during the first year of life, while 40% had an accelerated gain in weight-for-length (>0.67 SDS) in the first year of life, which is known for its adverse effects on body composition and cardiometabolic outcomes in adulthood.[12,14,33–35] In contrast, SGA-GH adults had GH-induced catch-up in height, which is not associated with adverse cardiometabolic effects.[11,13,29] So, while GH-induced catch-up growth in height showed no increased prevalence of all type of WMHs, spontaneous catch-up growth did show an increased prevalence of all type of WMHs.

Comparing the prevalence of WMHs in our study with the current literature is difficult because there are no studies that investigated the prevalence of WMHs in SGA adults or AGA adults around age 30 years. Large population studies investigating the prevalence of WMHs were only performed in the elderly population. Prevalence of PVWMHs and DWMHS was 68% and 87% in a Dutch population (n = 464, age range 60–70 years) and 76% and 92% in an European sample (including The Netherlands and 8 other countries, n = 1770, age range 65–75 years).[36,37] The study with the youngest sample, healthy adults in their forties, investigated the prevalence of total WMHs using the Fazekas scale and showed a prevalence of total WMHs of 50.9% (n = 428, age 44–48 years).[38] Comparing the prevalence of total WMHs in our study (52.5%, varying between 40.5 and 73.9% in the groups) with the sample of healthy adults in their forties, we found approximately similar prevalence despite the fact that our cohort is more than 10 years younger. This might additionally support the inverse association with birth weight SDS and WMHs prevalence, as our cohort mostly existed of adults born SGA.

This is the first study that prospectively explored total WMHs, PVWMHs and DWMHs in SGA-GH adults at 12 years after GH in comparison with appropriate control groups, including untreated SGA adults. All brain MRI's were performed with the same 3 T MRI system, a high-quality research tool. Such detailed brain MRI measurements are not feasible in population studies. Furthermore, we were able to adjust the prevalence of total WMHs for birth characteristics and potential confounders in our multivariable regression analyses. There are, however, limitations. Although our total study population was relatively large for an MRI study, the proportion of SGA-S adults was small due to the low prevalence of SGA-born subjects with persistent short stature (±0.1% of all live-born children).[1] This was complicated further, because most children with postnatal growth failure were treated with growth hormone for adult height improvement during the last 25 years. We, therefore, also compared the results of the SGA-GH adults with the larger group of age-matched AGA adults and this showed no difference in prevalence of WMHs either.

In conclusion, our results suggest that long-term GH-treatment in children born SGA has no negative impact on the prevalence of total WMHs, PVWMHs and DWMHs at 12 years after GH cessation around age 30 years compared to SGA-S and AGA adults. In fact, the highest prevalence of all type of WMHs was found in SGA-CU adults, with a significantly higher prevalence of total WMHs and DWMHs compared to SGA-GH adults, suggesting a negative long-term cerebrovascular effect of spontaneous catch-up growth compared to GH-induced catch-up growth. GH was not associated with all types of WMHs in the multiple regression models. Birth weight SDS was independently associated with all types of WMHs, with a lower birth weight SDS increasing the risk of all types of WMHs at around the age 30 years. Further research is needed to confirm our findings.

Contributors

ACSH-K was the principal investigator, conceived and designed the study, contributed to data collection and interpretation, and wrote the report. DJD collected, analyzed, and interpreted the data, wrote the report, and designed the figures. WJG and MvdS collected and interpreted data and critically reviewed the manuscript. DB scored and interpreted the MRI images and critically reviewed the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. DJD, WJG and MvdS have directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

Deidentified data, protocols, and all documentation around this analysis will be made available to academic researchers after authorization by authors of this manuscript after publication, with a signed data access agreement.

Declaration of interests

We declare no competing interests.

Acknowledgements

We would like to express our gratitude to all adults who participated in this study. We thank M de Ridder, statistician at the department of biostatistics, for her advice regarding the statistical analyses. We thank C Bruinings-Vroombout, N Khieroe, J Dunk, and E Lems, research nurses, for their contribution to the study; A van der Lugt and M Van den Ijssel for assisting with MRI scans. This investigator-initiated and –responsible study was financially supported by an independent research grant to ACSH-K from Novo Nordisk Health Care AG.

References

1 Hokken-Koelega ACS, De Ridder MAJ, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama S, Drop SLS. Children born small for gestational age: do they catch up? *Pediatr Res*. 1995;38(2):267–271.
2 De Ridder MAJ, Engels MAMJ, Stijnen T, Hokken-Koelega ACS. Small for gestational age children without early catch-up growth: spontaneous growth and prediction of height at 8 years. *Horm Res*. 2008;70(4):203–208.
3 Sas T, De Waal W, Mulder P, et al. Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial. *J Clin Endocrinol Metab*. 1999;84(9):3064–3070.
4 Van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A. Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. *J Clin Endocrinol Metab*. 2003;88(8):3584–3590.
5 Dahlgren J, Wikland KA. Final height in short children born small for gestational age treated with growth hormone. *Pediatr Res*. 2005;57(2):216–222.
6 Renes JS, Willemsen RH, Mulder JC, et al. New insights into factors influencing adult height in short SGA children: results of a large multicentre growth hormone trial. *Clin Endocrinol*. 2015;82(6):854–861.
7 Carel J-C, Chatelain P, Rochiccioli P, Chaussain J-L. Improvement in adult height after growth hormone treatment in adolescents with short stature born small for gestational age: results of a randomized controlled study. *J Clin Endocrinol Metab*. 2003;88(4):1587–1593.
8 Barker DJ. The fetal and infant origins of adult disease. *BMJ*. 1990;301(6761):1111.
9 Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology*. 2014;83(9):780–786.
10 Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363(9425):1925–1933.
11 Goedegebuure WJ, van der Steen M, Smeets CCJ, Hokken-Koelega ACS. Childhood growth hormone treatment and metabolic and cardiovascular risk in adults born small for gestational age after growth hormone cessation in the Netherlands: a 12-year follow-up study. *Lancet Child Adolesc Health*. 2022;6(11):777–787.
12 Goedegebuure WJ, Van der Steen M, Smeets CCJ, Kerkhof GF, Hokken-Koelega ACS. SGA-born adults with postnatal catch-up have a persistently unfavourable metabolic health profile and increased adiposity at age 32 years. *Eur J Endocrinol*. 2022;187(1):15–26.
13 van der Steen M, Smeets CCJ, Kerkhof GF, Hokken-Koelega ACS. Metabolic health of young adults who were born small for gestational age and treated with growth hormone, after cessation of growth hormone treatment: a 5-year longitudinal study. *Lancet Diabetes Endocrinol*. 2017;5(2):106–116.
14 Leunissen RWJ, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA*. 2009;301(21):2234–2242.
15 Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–838.
16 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Neuroradiol*. 1987;8(3):421–426.

17 Sachdev P, Cathcart S, Shnier R, Wen W, Brodaty H. Reliability and validity of ratings of signal hyperintensities on MRI by visual inspection and computerised measurement. *Psychiatry Res*. 1999;92(2-3):103–115.
18 Haller S, Kövari E, Herrmann FR, et al. Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study. *Acta Neuropathol Commun*. 2013;1(1):1–7.
19 Fredriks AM, Van Buuren S, Burgmeijer RJF, et al. Continuing positive secular growth change in the Netherlands 1955–1997. *Pediatr Res*. 2000;47(3):316–323.
20 van Dijk EJ, Breteler MMB, Schmidt R, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension*. 2004;44(5):625–630.
21 De Leeuw FE, De Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. *Ann Neurol*. 1999;46(6):827–833.
22 Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77(5):461–468.
23 Anstey KJ, Jorm AF, Réglade-Meslin C, et al. Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosom Med*. 2006;68(5):778–785.
24 Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
25 Zhuang F-J, Chen Y, He W-B, Cai Z-Y. Prevalence of white matter hyperintensities increases with age. *Neural Regen Res*. 2018;13(12):2141.
26 Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: the framingham study. *Stroke*. 2004;35(8):1857–1861.
27 Albertsson-Wikland K, Mårtensson A, Sävendahl L, et al. Mortality is not increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics. *J Clin Endocrinol Metab*. 2016;101(5):2149–2159.
28 Dorrepaal DJ, Goedegebuure WJ, Smagge L, van der Steen M, van der Lugt A, Hokken-Koelega ACS. Cerebrovascular abnormalities in adults born SGA at 12 years after growth hormone cessation compared to controls. *J Clin Endocrinol Metab*. 2023;109:dgad622.
29 van der Steen M, Kerkhof GF, Smeets CCJ, Hokken-Koelega ACS. Cardiovascular risk factors and carotid intima media thickness in young adults born small for gestational age after cessation of growth hormone treatment: a 5-year longitudinal study. *Lancet Diabetes Endocrinol*. 2017;5(12):975–985.
30 Kajantie E, Osmond C, Barker DJP, Forsén T, Phillips DIW, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. *Int J Epidemiol*. 2005;34(3):655–663.
31 Risnes KR, Vatten LJ, Baker JL, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol*. 2011;40(3):647–661.
32 Baker JL, Olsen LW, Sørensen TIA. Weight at birth and all-cause mortality in adulthood. *Epidemiology*. 2008;19:197–203.
33 Ong KK, Loos RJF. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr*. 2006;95(8):904–908.
34 Ong KKL, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*. 2000;320(7240):967–971.
35 Kerkhof GF, Hokken-Koelega A. Rate of neonatal weight gain and effects on adult metabolic health. *Nat Rev Endocrinol*. 2012;8(11):689–692.
36 De Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The rotterdam scan study. *J Neurol Neurosurg Psychiatry*. 2001;70(1):9–14.
37 Launer LJ, Berger K, Breteler MMB, et al. Regional variability in the prevalence of cerebral white matter lesions: an MRI study in 9 European countries (CASCADE). *Neuroepidemiology*. 2005;26(1):23–29.
38 Wen W, Sachdev PS, Li JJ, Chen X, Anstey KJ. White matter hyperintensities in the forties: their prevalence and topography in an epidemiological sample aged 44–48. *Hum Brain Mapp*. 2009;30(4):1155–1167.