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Clinical Research Article

Cerebrovascular Abnormalities in Adults Born SGA at 12 Years After Growth Hormone Cessation Compared to Controls

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Abstract

Context: 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. However, previous studies did not have an appropriate control group, which is a major limitation.

Objective: To study cerebrovascular abnormalities (aneurysms, previous intracerebral hemorrhages and microbleeds) using magnetic resonance imaging (MRI) in adults born SGA at 12 years after cessation of childhood GH treatment (SGA-GH) compared to appropriate controls.

Methods: In this single-center, prospective study, brain MRIs were performed between May 2016 and December 2020 on a 3T MRI system. MRI images were scored by 2 neuroradiologists who were blinded to patient groupings. Participants included adults born SGA previously treated with GH and 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). The intervention was long-term GH treatment during childhood and the main outcome measure was cerebrovascular abnormalities.

Results: A total of 301 adults were investigated. Aneurysms were found in 6 adults: 3 (3.6%) SGA-GH, 1 (2.9%) SGA-S and 2 (2.2%) AGA adults, without differences between SGA-GH adults and the controls. Previous intracerebral hemorrhages were only found in 2 SGA-S adults (4.8%). Microbleeds were found in 17 adults: 4 (4.3%) SGA-GH, 4 (9.5%) SGA-S, 3 (4.3%) SGA-CU and 6 (6.3%) AGA adults, without differences between SGA-GH adults and the controls.

Conclusion: Our findings suggest that SGA-GH adults at 12 years after GH cessation have no increased prevalence of cerebrovascular abnormalities compared to appropriate controls. Further research is needed to confirm our findings.

Key Words: small for gestational age, growth hormone treatment, cerebral vascular abnormalities, cerebral aneurysms, previous intracerebral hemorrhage, cerebral microbleeds

Abbreviations: AGA, appropriate for gestational age; AH, adult height; CVD, cerebrovascular disease; FLAIR, fluid-attenuated inversion recovery; GH, growth hormone; MRI, magnetic resonance imaging; SGA, small for gestational age; SGA-CU, SGA with spontaneous catch-up growth to a normal height; SGA-S, SGA with persistent short stature; SS, short stature; SWAN, susceptibility-weighted angiography; TOF-MRA, time of flight magnetic resonance angiography.

Of all infants worldwide, 2.3% are born small for gestational age (SGA). The majority of these children has sufficient catch-up growth in the first years of life, but 8% to 10% show persistent short stature (SS) with a height <−2 standard deviation score (SDS) (1, 2). In these children, growth hormone (GH) treatment effectively induces catch-up growth and improves adult height (AH) (3-7).

Our previous studies on the long-term metabolic and cardiovascular safety of GH treatment, showed that adults born SGA who were treated with GH during childhood (SGA-GH) had similar metabolic and cardiovascular health profiles at age 21 and 30 years compared with untreated short adults born SGA (SGA-S) and adults born appropriate for gestational age with a normal height (AGA), while adults born SGA with spontaneous catch-up growth to a normal height (SGA-CU) had less favorable profiles (8-11). The French population-based cohort of the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study reported increased cerebrovascular morbidity due to hemorrhagic stroke (standardized incidence ratio from 3.5 to 7.0) in GH-treated subjects, including those born SGA, compared with the general population (12). 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 whether the increased cerebrovascular morbidity was caused by GH treatment itself or by the underlying condition of being born SGA.

Cerebrovascular disease (CVD) is a multifactorial process negatively affecting the structure and function of the cerebral

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vasculature and a major cause of morbidity and mortality (13). CVD can display acute symptoms due to bleeding or ischemia. Various cerebrovascular abnormalities like aneurysms, cavernous hemangiomas, and arteriovenous malformations give an increased risk for acute intracranial bleeding. However, CVD also includes a wide spectrum of disease processes that are clinically asymptomatic or only become symptomatic over time. These disease processes, like cerebral microbleeds, can serve as markers of CVD and can be assessed using magnetic resonance imaging (MRI).

We prospectively studied cerebrovascular abnormalities like aneurysms, previous intracerebral hemorrhages, and microbleeds using MRI in SGA-GH adults at 12 years after GH cessation around the age of 30 years in comparison with 3 untreated age-matched control groups: SGA-S, SGA-CU, and AGA adults. Firstly, we hypothesized that the prevalence of cerebrovascular abnormalities would be similar in SGA-GH adults compared with SGA-S and AGA adults. Secondly, to evaluate whether GH-induced catch-up growth has a different long-term effect on cerebrovascular abnormalities than spontaneous catch-up growth, we compared results of SGA-GH and SGA-CU adults. We hypothesized a higher prevalence of cerebrovascular abnormalities after spontaneous postnatal catch-up growth would be found, as we previously found that SGA-CU adults have a less healthy cardiometabolic profile at age 30 years. In addition, we performed regression analyses to determine whether GH treatment and birth characteristics associate with cerebrovascular abnormalities.

Materials and Methods

Study Design and Participants

The study population comprised 301 adults, of whom 94 (SGA-GH) had participated in Dutch GH trials during their childhood because of being born SGA (birthweight or birth length SDS < −2) with persistent SS (height SDS < −2) (11). They were treated with GH until AH attainment and were invited to participate in the current study when they had stopped GH treatment for at least 10 years. More details on inclusion and exclusion criteria of the Dutch GH trials have been previously reported (8). Two of the control groups (SGA-S and SGA-CU) were recruited after reviewing hospital records from several Dutch hospitals where these individuals had been registered because of being born SGA, followed by either persistent SS (AH SDS < −2) (SGA-S) or spontaneous catch-up growth to a normal AH (SDS > −1) (SGA-CU) (9). Additionally, healthy adults with normal stature who were born AGA were randomly selected as controls. Participants of the control groups were asked to participate in the present study at around age 30 years as appropriate controls of the SGA-GH group. The Medical Ethics Committee of Erasmus University Medical Center (Rotterdam, The Netherlands) approved the study and participants gave written informed consent.

MRI Examinations

All brain MRIs were performed between May 2016 and December 2020 on the same 3T MRI system (GE Healthcare, Milwaukee, WI, USA). The scan protocol consisted of 4 sequences: (1) T1-weighted 3D spoiled gradient recalled echo, (2) T2*-weighted susceptibility-weighted angiography (SWAN), (3) T2-weighed fluid-attenuated inversion recovery (FLAIR), and (4) time of flight magnetic resonance angiography (TOF-MRA). MRI images were scored by 2 neuroradiologists (A.v.d.L. and L.S.) who were blinded to patient groupings. We assessed presence, location, and size of aneurysms in intracranial arteries on TOF-MRA. Presence and location of previous intracerebral hemorrhages was assessed using SWAN sequence and defined as areas of low signal intensity not compatible with bone, iron accumulation, calcifications, or vessels and accompanied by brain atrophy on T1-weighted spoiled gradient recalled echo and SWAN images. Microbleeds were assessed using SWAN sequence and defined as small (<5 mm), round, or ovoid areas of low signal in the brain parenchyma not compatible with bone, iron accumulation, calcifications, or vessels (14). The location of microbleeds was subdivided into lobar, deep, or infratentorial, and number of microbleeds was subdivided into 1, 2 to 5, or >5. Figure 1 shows examples of MRI scans with such cerebrovascular abnormalities. Other cerebrovascular abnormalities found using these sequences were also included in our results.

Assessment of Demographic and Clinical Characteristics

Clinical characteristics at birth were obtained via birth records of hospitals. At around age 30 years, we assessed participants' height and weight, 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 AH and adult weight as SDS, adjusted for sex; based on references for Dutch adults, using Growth Analyser Research Calculation Tools https://growthanalyser.org/(15). After 10 minutes of rest, systolic blood pressure and diastolic blood pressure were measured repeatedly (7 times every 5 minutes) using an automated device for 30 minutes with participants in a supine position on the nondominant arm (Accutorr Plus; Datascope; Montvale, NJ, USA). The mean of 7 measurements was used for analyses of resting blood pressure. Total cholesterol was measured by an automated enzymatic method with the CHOD-PAP reagent kit (Roche Diagnostics; Mannheim, Germany). 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 nontertiary 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/day or week), illicit drug use (frequency, amount, and type of drugs), and exercise level (hours/week or month) was provided to assess lifestyle factors. In total, 12 of the 301 participants did not complete the questionnaire (3 SGA-GH, 2 SGA-S, 2 SGA-CU, and 5 AGA).

Statistical Analyses

Statistical analyses were performed using SPSS version 28.0 for Windows. Clinical characteristics are presented as mean and SD or percentages. Analysis of variance, the unpaired t-test, and the chi-square test were used to compare the clinical characteristics between the groups. The chi-square test and Fisher's exact test were used to compare the prevalence

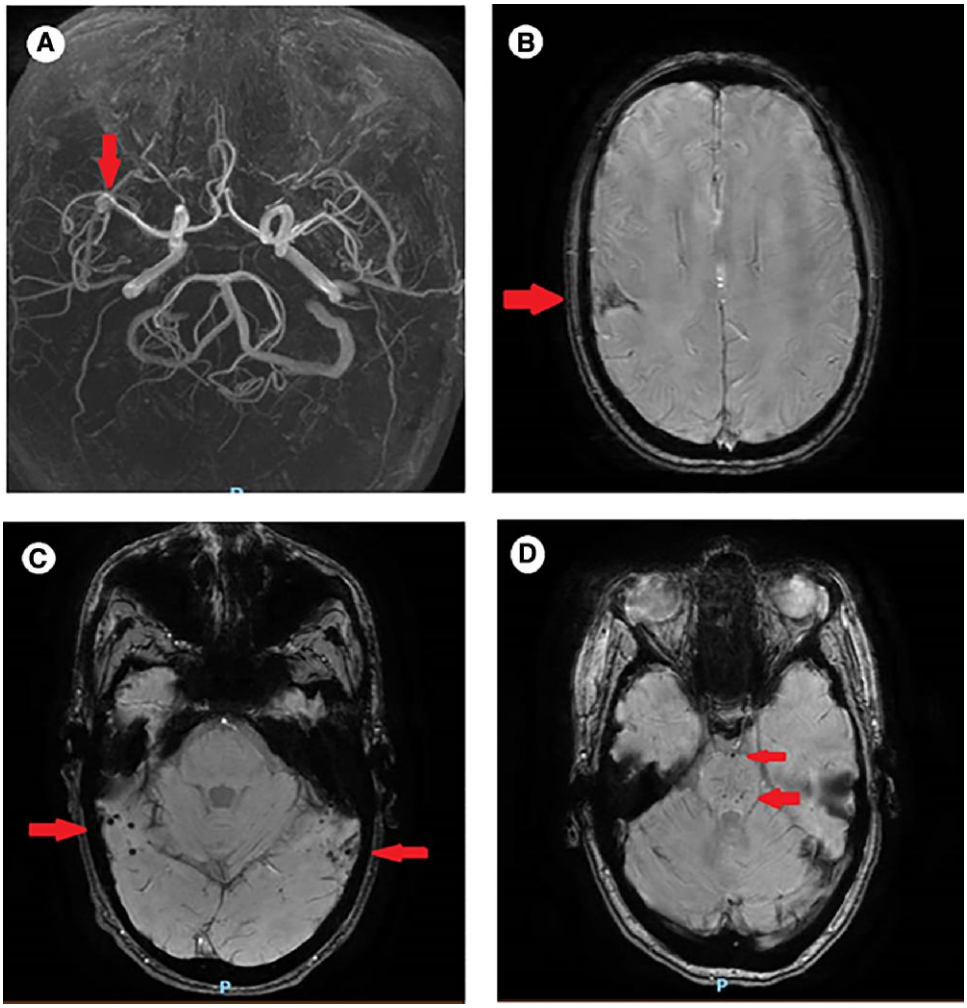

Figure 1. Examples of intracerebral aneurysm (A), previous intracerebral hemorrhage (B), lobar microbleeds (C), and deep microbleeds (D).

of cerebrovascular abnormalities between the groups. CIs of the prevalence and the difference in prevalence between the groups are given. Multivariable logistic regression analyses were performed to determine whether GH treatment and birth characteristics (birth weight SDS, birth length SDS, gestational age) were associated with cerebral microbleeds. The unadjusted analyses are shown in model A, the adjusted analyses are shown in model B. We adjusted for sex, age, body mass index, mean arterial pressure, serum total cholesterol, and smoking (ever vs never) (16-19). *P* values less than .05 were regarded as statistically significant.

Results

Clinical Characteristics

Table 1 shows the clinical characteristics of all 301 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 94 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 GH cessation was 16.1 years (1.4). Mean age at MRI was 29.1 years (3.5) in SGA-GH, 31.9 years (3.6) in SGA-S, 33.0 years (2.6) in SGA-CU, and 32.9 years (2.7) in AGA adults ($P < .001$). Birth length and birth weight were different between the SGA groups and the AGA group, as this was part of the inclusion criteria. Mean AH SDS in SGA-GH was −1.61 SDS, which was higher than in SGA-S (−2.33 SDS, $P < .001$) but lower than in SGA-CU (−0.17 SDS, $P < .001$) and AGA (0.37 SDS, $P < .001$). There were significant differences in income and educational level between the groups ($P < .001$).

MRI Findings

Aneurysms

The number of aneurysms in the total cohort was 6 (2.2%): 3 (3.6%, 95% CI 0.8-10.2%) in SGA-GH, 1 (2.9%, 95% CI 0.1-15.3%) in SGA-S, and 2 (2.2%, 95% CI 0.3-7.6%) in AGA adults (Tables 2 and 3). As the number of aneurysms was very small in all groups, we could not statistically test the difference between the SGA-GH group and the controls, but the prevalence was quite similar between the groups. The difference in prevalence between SGA-GH and SGA-S adults was 0.7% (95% CI −11.5-8.0%), between SGA-GH and AGA adults 1.4% (95% CI −4.9-8.7%), and between SGA-GH and SGA-CU adults 3.6% (95% CI −2.5-11.3%). Aneurysms were found in 5 different locations and varied in size between 2 and 6 mm. Adults with aneurysms had no other vascular abnormalities. Table 3 shows demographic characteristics and mean blood pressure of adults with aneurysms.

Table 1. Clinical characteristics of 301 subjects

	Study group	Comparison groups			*P* value
	SGA-GH	SGA-S	SGA-CU	AGA	
Subjects (female)	94 (51)	42 (25)	69 (36)	96 (53)	.90
At birth					
Gestational age (weeks)	36.4 (3.8)[a]	37.7 (3.1)	36.5 (3.1)	38.8 (2.5)	**<.001**
Birth length SDS	−3.44 (1.5)[a,b]	−2.95 (1.3)	−2.51 (1.1)	0.12 (0.9)	**<.001**
Birth weight SDS	−2.58 (1.0)[a,c]	−2.20 (0.9)	−2.29 (1.0)	0.28 (1.0)	**<.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)	**<.001**
Adult height SDS	−1.61 (1.0)[a,b,c]	−2.33 (0.6)	−0.17 (0.69)	0.37 (0.8)	**<.001**
Lifestyle factors					
SES (education) (%)					**<.001**
Low	22.7[a,b]	10.0	10.6	4.4	
Medium	43.2	52.5	28.8	22.0	
High	34.1	37.5	60.6	73.6	
SES (income) (%)					**<.001**
Low	13.9[a,b]	10.3	5.1	3.4	
Medium	82.3	79.4	71.2	67.0	
High	3.8	10.3	23.7	29.6	
Smoking (%)					.27
Never	63.4	72.5	65.7	72.3	
<10 cigarettes/day	13.3	12.5	19.4	8.9	
≥10 cigarettes/day	11.1	7.5	10.4	4.4	
History	12.2	7.5	4.5	14.4	
Alcohol use (%)					.20
Never	17.5	17.5	7.4	12.0	
<1 unit/week	27.5	25.0	37.3	28.6	
1-3 units/week	31.9	40.0	19.4	30.8	
4-6 units/week	16.5	15.0	26.9	16.5	
>1 units/day	6.6	2.5	9.0	12.1	
Illicit drug use (%)					.35
Total	16.7	12.5	20.9	11.1	
Cannabis	11.7	9.5	10.1	3.1	
Ecstasy	4.3	0.0	11.6	7.3	
Cocaine	5.3	0.0	5.8	4.2	
Other	2.0	2.2	2.8	0.0	
Exercise (%)					.52
Never	37.8	35.0	26.9	20.2	
<1 hour/week	4.4	2.5	3.0	5.6	
1-2 hours/week	32.2	35.0	31.3	39.3	
3-5 hours/week	15.6	17.5	28.4	23.6	
>5 hours/week	10.0	10.0	10.4	11.2	

Values are presented as mean (SD) or percentages. Bold *P* values are considered statistically significant differences between groups. The letters *a*, *b*, *c* indicate a significant difference of the SGA-GH group compared with another group.
Abbreviations: AGA, adults born appropriate for gestational age with a normal height; SDS, standard deviation score; NA, not applicable; SGA-CU, adults born small for gestational age with spontaneous catch-up to a normal height; 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.
[a]$P < .05$ compared with AGA.
[b]$P < .05$ compared with SGA-CU.
[c]$P < .05$ compared with SGA-S.

Table 2. Overview of cerebral vascular abnormalities

		Study group	Comparison groups			*P* value
	Total cohort	SGA-GH	SGA-S	SGA-CU	AGA	
n	274	83	34	65	92	
Aneurysms n (%)	6 (2.2%)	3 (3.6%, 0.8-10.2%)	1 (2.9%, 0.1-15.3%)	0	2 (2.2%,0.3-7.6%)	[a]
n	301	94	42	69	96	
Previous intracerebral hemorrhages n (%)	2 (0.7%)	0	2 (4.8%, 0.6-16.2%)	0	0	[a]
n	301	94	42	69	96	
Microbleeds n (%)	17 (5.6%)	4 (4.3%, 1.2-10.5%)	4 (9.5%, 2.7-22.6%)	3 (4.3%, 0.9-12.2%)	6 (6.3%, 2.3 13.1%)	.60
n	301	94	42	69	96	
Other vascular abnormalities n (%)						
Cerebral arteriovenous malformation	1 (0.3%)	0	1 (2.4%)	0	0	
Cerebral cavernous angioma	1 (0.3%)	0	1 (2.4%)	0	0	

Values are presented as absolute numbers and as percentages with the 95% CI.
[a]As the numbers of aneurysms and previous intracerebral hemorrhages were very small in all groups, we could not statistically test the difference between the SGA-GH and the 3 untreated control groups.
Abbreviations: AGA, adults born appropriate for gestational age with a normal height; SGA-CU, adults born small for gestational age with spontaneous catch-up to a normal height; 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.

Table 3. Overview of aneurysms

		Study group	Comparison groups		
	Total group	SGA-GH	SGA-S	SGA-CU	AGA
N	274	83	34	65	92
Aneurysms n (%)	6 (2.2%)	3 (3.6%, 0.8-10.2%)	1 (2.9%, 0.1-15.3%)	0	2 (2.2%, 0.3-7.6%)
Location and size aneurysms					
A. cerebri media 6 mm	1 (0.4%)	1 (1.2%)	0	0	0
A. communicans posterior 2 mm	1 (0.4%)	0	0	0	1 (1.1%)
A. communicans anterior 2 mm	1 (0.4%)	1 (1.2%)	0	0	0
A. ophthalmica 3 mm	1 (0.4%)	1 (1.2%)	0	0	0
A. carotis interna (cavernous part) 2 mm and 4 mm	2 (0.7%)	0	1 (2.9%)	0	1 (1.1%)
Demographic characteristics of adults with aneurysms					
Male: female	1:5	1:2	0:1	0	0:2
Term birth: preterm birth	3:2	1:1	0:1	0	2:0
Alcohol consumption 1-3 units/week	4	2	1	0	1
Current smoking <10/day)	1	1	0	0	0
Current smoking (≥10/day)	1	0	1	0	0
Cannabis use	1 (daily)	1 (daily)	0	0	0
Blood pressure of adults with aneurysms					
Mean systolic BP (mm Hg)	117	117	126	—	111
Mean diastolic BP (mm Hg)	70	72	79	—	63

Information about aneurysms is presented as absolute numbers and percentages with the 95% confidence interval. As the number of cerebral aneurysms was very small in all groups, we could not statistically test the difference between the SGA-GH and the 3 untreated control groups. Demographic characteristics are presented as absolute numbers. Blood pressure is presented as mean.
Abbreviations: AGA, adults born appropriate for gestational age with a normal height; SGA-CU, adults born small for gestational age with spontaneous catch-up to a normal height; 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.

Previous intracerebral hemorrhages

The number of previous intracerebral hemorrhages in the total cohort was 2 (0.7%), both in SGA-S adults (4.8%, 95% CI 0.6-16.2%) (Table 2). One adult had a previous infarct with hemorrhagic transformation located right paracentral without aneurysms or microbleeds. The origin was unknown. This 35-year-old female was born term, did not consume alcohol, was a current smoker (<10 cigarettes/day), and used cannabis daily but no other drugs. The other adult, a 36-year-old male, had signs of a previous intracerebral hemorrhage in the right frontotemporal lobe. The origin was thought to be traumatic because of multiple adjacent microbleeds. He reported a serious car accident in his past. No aneurysms were found. He was born term, consumed ≥4 units of alcohol/week, was a current smoker (≥10 cigarettes/day), and used no drugs.

Microbleeds

The number of microbleeds in the total cohort was 17 (5.6%): 4 (4.3%, 95% CI 1.2-10.5%) in SGA-GH, 4 (9.5%, 95% CI 2.7-22.6%) in SGA-S, 3 (4.3%, 95% CI 0.9-12.2%) in SGA-CU, and 6 (6.3%, 95% CI 2.3-13.1%) in AGA adults (Tables 2 and 4). No difference in prevalence of microbleeds was found between SGA-GH and the control groups. The difference in prevalence between SGA-GH and SGA-S adults was −5.3% (95% CI −18.2-4.3%), between SGA-GH and AGA adults −2.0% (95% CI −9.7-5.8%), and between SGA-GH and SGA-CU adults −0.1% (95% CI −8.7-7.6%). Most microbleeds had a lobar location in the brain (n = 12, 4.0%), followed by deep (n = 3, 1.0%) and infratentorial (n = 2, 0.7%). Most adults with microbleeds had only 1 microbleed (n = 12, 4.0%), followed by 2 to 5 microbleeds (n = 3, 1.0%) and 5+ microbleeds (n = 2, 0.7%). Most adults with microbleeds had no other cerebrovascular abnormalities (n = 15), 1 had an intracerebral hemorrhage, and 1 an arteriovenous malformation. Table 4 shows the demographic characteristics, mean blood pressure, and total cholesterol of adults with microbleeds.

Other cerebrovascular abnormalities

In the total cohort, 2 adults had other cerebrovascular abnormalities, namely 1 arteriovenous malformation (SGA-S) and 1 cavernous angioma (SGA-S) (Table 2).

Multivariable Logistic Regression Analyses

We performed multivariable logistic regression analyses to determine whether GH treatment and birth characteristics (birth weight SDS, birth length SDS, gestational age) were associated with the prevalence of microbleeds (Table 5). GH treatment was not associated with microbleeds in the unadjusted model nor in the adjusted model. Birth characteristics were also not associated with microbleeds in both models.

Discussion

This is the first study that prospectively studies cerebrovascular abnormalities like aneurysms, previous intracerebral hemorrhages, and microbleeds by obtaining brain MRI in SGA-GH adults at 12 years after GH cessation at around age 30 years compared with appropriate untreated control groups: SGA-S and AGA adults. No differences in cerebrovascular abnormalities were found between SGA-GH adults compared with the control groups, but due to the low number of events in the groups, the statistical power was limited despite the relatively large group of subjects. Additionally, we found no difference in prevalence of cerebrovascular abnormalities in adults with GH-induced catch-up growth compared with adults with spontaneous catch-up growth during childhood. GH treatment and birth characteristics were not associated with microbleeds in our multivariable regression analyses in the total cohort.

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 microbleeds in SGA-GH compared with SGA-S. There was also no different prevalence of microbleeds between SGA-GH and AGA adults. In addition, the prevalence of aneurysms and previous intracerebral hemorrhages was not different between SGA-GH and SGA-S and AGA adults, although we could not statistically test this due to the very low prevalence in all groups. Poidvin et al reported an increased cerebrovascular morbidity, with a standardized incident ratio ranging from 3.5 to 7.0 for hemorrhagic stroke in GH-treated subjects, including those born SGA, compared with the general population (12). Based on these results the prevalence could have been 3.5 to 7 times higher in our group of SGA-GH adults of the same age than in our control groups. However, the SGA-GH adults showed a low number of cerebrovascular abnormalities similar to the control groups. Altogether, our findings suggest that long-term GH treatment does not lead to an increased prevalence of cerebrovascular abnormalities at around age 30 years.

We previously investigated cardiometabolic changes after GH cessation and showed that fat mass, insulin sensitivity, and blood pressure of SGA-GH adults were similar to SGA-S and AGA adults at around the ages of 21 and 30 years, respectively (8, 10, 11). GH treatment has well-documented anabolic, lipolytic, and insulin-antagonistic effects during childhood, resulting in an increased lean body mass and decreased fat mass, lipid levels, insulin sensitivity, and blood pressure (20-26), while cessation of GH treatment leads to pronounced opposite changes (27, 28). Our data on cerebrovascular abnormalities are in line with the cardiometabolic results and suggest additional support that GH treatment during childhood has no long-term negative health effects.

We found a prevalence of microbleeds in SGA-GH similar to SGA-CU adults. Prevalence of aneurysms and previous intracerebral hemorrhages was also similar between the groups, although we could not test statistically due to very low prevalence in all groups. In addition, our findings suggest that spontaneous postnatal catch-up growth does not lead to increased cerebrovascular abnormalities at around age 30 years compared with GH-induced catch-up growth. In our cardiometabolic study, we found SGA-CU adults had less favorable metabolic health than SGA-S and AGA adults at around age 21 and 30 years (9), but our current findings suggest this is not accompanied with higher prevalence of cerebrovascular abnormalities around the age of 30 years.

Prevalence of aneurysms and microbleeds in our cohort was respectively 2.2% and 5.4% in SGA adults and 2.2% and 6.3% in AGA adults at around age 30 years. Comparison with current literature is difficult because no other studies investigated the prevalence of aneurysms and microbleeds in

Table 4. Overview of microbleeds

		Study group	Comparison groups			*P* value
	Total group	SGA-GH	SGA-S	SGA-CU	AGA	
n	301	94	42	69	96	
Microbleeds n (%)	17 (5.6%)	4 (4.3%, 1.2-10.5%)	4 (9.5%, 2.7-22.6%)	3 (4.3%, 0.9-12.2%)	6 (6.3%, 2.3-13.1%)	0.60
Location of microbleeds n (%)						.13
Lobair	12 (4.0%)	4 (4.3%)	4 (9.5%)	2 (2.9%)	2 (2.1%)	
Deep	3 (1.0%)	0	0	0	3 (3.1%)	
Infratentorial	2 (0.7%)	0	0	1 (1.4%)	1 (1.0%)	
Number of microbleeds n (%)						.45
1	12 (4.0%)	2 (2.1%)	3 (7.1%)	3 (4.3%)	4 (4.2%)	
2-5	3 (1.0%)	2 (2.1%)	0	0	1 (1.0%)	
5+	2 (0.7%)	0	1 (2.4%)	0	1 (1.0%)	
Demographic characteristics of adults with microbleeds						
Male: female	9:8	3:1	3:1	1:2	2:4	
Term birth: preterm birth	11:5	2:1	3:1	1:2	5:1	
Alcohol consumption 1-3 units/week	5	1	2	1	1	
Alcohol consumption 4-6 units/week	6	1	2	1	2	
Alcohol consumption ≥1 units/day	2	1	0	0	1	
Current smoking (≥10/day)	3	2	0	1	0	
Cannabis use	1 (monthly)	1 (monthly)	0	0	0	
Blood pressure and TC of adults with microbleeds						
Mean systolic BP (mmHg)	116	111	114	122	119	
Mean diastolic BP (mmHg)	70	69	69	70	72	
Mean serum total cholesterol (mmol/L)	4.65	4.68	5.08	4.83	4.27	

Information about microbleeds is presented as absolute numbers and percentages with the 95% confidence interval. Demographic characteristics are presented as absolute numbers. Blood pressure and TC are presented as mean.
Abbreviations: AGA, appropriate for gestational age; SGA-CU, small for gestational age with spontaneous catch-up to a normal adult height; SGA-GH, small for gestational age treated with growth hormone; SGA-S, small for gestational age with persistent short stature; TC, total cholesterol.

Table 5. Multiple logistic regression for microbleeds in adults around age 30 years

Microbleeds	Model A			Model B		
	OR	95% CI	*P* value	OR	95% CI	*P* value
GH treatment(no vs yes)	0.75	0.18-3.14	0.69	0.65	0.14-2.96	.58
Birth weight SDS	1.04	0.61-1.77	.90	1.16	0.66-2.03	.61
Birth length SDS	1.01	0.63-1.61	.98	0.97	0.61-1.55	.89
Gestational age, weeks	1.01	0.85-1.19	.93	1.0	0.84-1.19	.99

Model A: unadjusted model. Model B: adjusted for sex, age, body mass index, mean arterial pressure, serum total cholesterol, and smoking.

SGA and AGA adults at around age 30 years, as only studies in older AGA populations have been performed. Regarding aneurysms, a systematic review reported a prevalence of 2.8% (range 0-41.8%) at mean age of 50 years, range 30 to 80 years (29). Most of the aneurysms (66%) had a size <5 mm and the most common locations were the internal carotid artery and medial cerebral artery. A higher prevalence of aneurysms was found in women than in men, also after adjustment for age and comorbidity (prevalence ratio 1.61, 95% CI 1.02-2.54). Compared with our findings, similar prevalence, size, and location of aneurysms were found. Regarding microbleeds, Poels et al investigated the prevalence of microbleeds in different age categories in the population and found a prevalence of 6.5% in 45- to 50-year-old adults using a 3D T2*-weighted gradient-recalled echo sequence on a 1.5-Tesla scanner (16). Another study reported a microbleed prevalence of 7.0% in adults aged 40-69 years using susceptibility- weighted imaging on a 3-Tesla scanner (17). Most participants had only 1 microbleed. Lobar lesions were mostly present, followed by deep and infratentorial lesions. Comparing our microbleed prevalence with these 2 studies is difficult because the sensitivity for microbleeds detection depends on the MRI field strength (1.5, 3, or 7 Tesla scanner) and the sequence used. As studies investigating the prevalence of microbleeds in SGA and AGA adults around age 30 years using the same MRI sensitivity settings are lacking, we were not able to compare the prevalence of microbleeds in our study with reported data in the literature.

Our multivariable regression analyses suggested that GH treatment was not associated with microbleeds. Birth characteristics were also not associated with microbleeds. Although our analyses suggested no indications to adjust for birth characteristics when analyzing microbleeds, the study of Albertsson–Wikland suggested that adjustment for birth characteristics is essential to interpret results regarding long-term health. They developed an advanced mortality model that adjusted for birth characteristics and compared the mortality ratio in GH-treated subjects with the general Swedish population (30). The advanced model showed an equal mortality ratio of 0.96, while the conventional model found a mortality ratio of 1.43, suggesting that the 50% increased overall mortality was related to differences in birth characteristics between the GH-treated subjects and the general population rather than the GH treatment itself. The Barker theory, which suggested that low birth weight is associated with a higher risk for adult cardiovascular disease, supports these findings (31). The French SAGhE study, however, which reported increased cerebrovascular morbidity in GH-treated subjects born SGA compared with the general population, had 2 main limitations: the absence of an appropriate control group of untreated SGA adults and the absence of adjustment for potential confounders like birth characteristics or lifestyle factors (12, 32). Our study included appropriate controls of untreated SGA adults, which made it possible to explore whether prevalence of cerebrovascular abnormalities was influenced by GH treatment itself or by the underlying condition of being born SGA. Furthermore, we adjusted for birth characteristics and other potential confounders in our multivariable regression analyses.

This is the first study that prospectively explored cerebrovascular abnormalities in SGA-GH adults at 12 years after GH cessation compared with appropriate control groups, including untreated SGA adults. All brain MRI was performed with the same 3T MRI system, a high-quality research tool. Such detailed brain MRI measurements are not feasible in population studies. There are, however, limitations. Due to the low number of events in all groups, the statistical power was limited despite the relatively large group of adults. However, compared with the 3.5 to 7 times increased risk for hemorrhagic stroke reported in the French SAGhE study, our finding of a prevalence of cerebrovascular abnormalities in SGA-GH adults similar to the control groups supports that there is no increased prevalence of cerebrovascular morbidity in SGA-GH adults. The proportion of SGA-S adults was smaller than the other groups due to the low prevalence of persistent SS after SGA birth (±0.1% of all live-born children) (1). In addition, most Dutch children with persistent SS were treated with GH for adult height improvement during the last 25 years. We, therefore, also compared our results of SGA-GH adults with the larger group of AGA adults and also showed a prevalence of cerebrovascular abnormalities similar to AGA adults.

In conclusion, our results suggest that GH treatment in children born SGA does not lead to increased prevalence of aneurysms, intracerebral hemorrhages, and microbleeds at 12 years after GH cessation compared with appropriate controls. Additionally, we found no difference in prevalence of cerebrovascular abnormalities in adults with GH-induced catch-up growth compared with adults with spontaneous catch-up growth during childhood. The prevalence of microbleeds was neither associated with GH treatment nor with birth characteristics in the total group. Further research is needed to confirm our findings.

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Disclosures

We declare no competing interests.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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