Growth hormone treatment for childhood short stature and risk of stroke in early adulthood

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ABSTRACT

Objectives: We investigated the incidence of stroke and stroke subtypes in a population-based cohort of patients in France treated with growth hormone (GH) for short stature in childhood.

Methods: Adult morbidity data were obtained in 2008–2010 for 6,874 children with idiopathic isolated GH deficiency or short stature who started GH treatment between 1985 and 1996. Cerebrovascular events were validated using medical reports and imaging data and classified according to standard definitions of subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke. Case ascertainment completeness was estimated with capture-recapture methods. The incidence of stroke and of stroke subtypes was calculated and compared with population values extracted from registries in Dijon and Oxford, between 2000 and 2012.

Results: Using both Dijon and Oxford population-based registries as references, there was a significantly higher risk of stroke among patients treated with GH in childhood. The excess risk of stroke was mainly attributable to a very substantially and significantly higher risk of hemorrhagic stroke (standardized incidence ratio from 3.5 to 7.0 according to the registry rates considered, and accounting or not accounting for missed cases), and particularly subarachnoid hemorrhage (standardized incidence ratio from 5.7 to 9.3).

Conclusions: We report a strong relationship between hemorrhagic stroke and GH treatment in childhood for isolated growth hormone deficiency or childhood short stature. Patients treated with GH worldwide should be advised about this association and further studies should evaluate the potentially causal role of GH treatment in these findings. ***Neurology*® 2014;83:780–786**

GLOSSARY

CI = confidence interval; **GH** = growth hormone; ***ICD-10*** = *International Classification of Diseases, tenth revision*; **ICH** = intracerebral hemorrhage; **IS** = ischemic stroke; **SAGhE** = Safety and Appropriateness of Growth hormone treatments in Europe; **SAH** = subarachnoid hemorrhage; **SIR** = standardized incidence ratio.

Little information is available about the long-term outcome after growth hormone (GH) treatment, particularly in individuals who received treatment in childhood.[1] Because of the mitogenic and proliferative properties of GH, most attention has focused on the risk of cancer after GH treatment.[2,3] The Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) project is a multinational European study that aims to evaluate long-term mortality and cancer morbidity in subjects who were treated with GH in childhood. A preliminary report describing the French cohort of the SAGhE study showed increased cardiac and cerebrovascular mortality, raising the issue of cerebrovascular morbidity after GH treatment.[4] Several studies have shown that patients with acromegaly have higher than normal mortality rates associated with cardiovascular and cerebrovascular diseases, independently of other risk factors.[5,6] There is also an increased prevalence of intracranial aneurysm in patients with acromegaly and this is associated with excess GH in serum at the onset of the disease.[7] These observations and the

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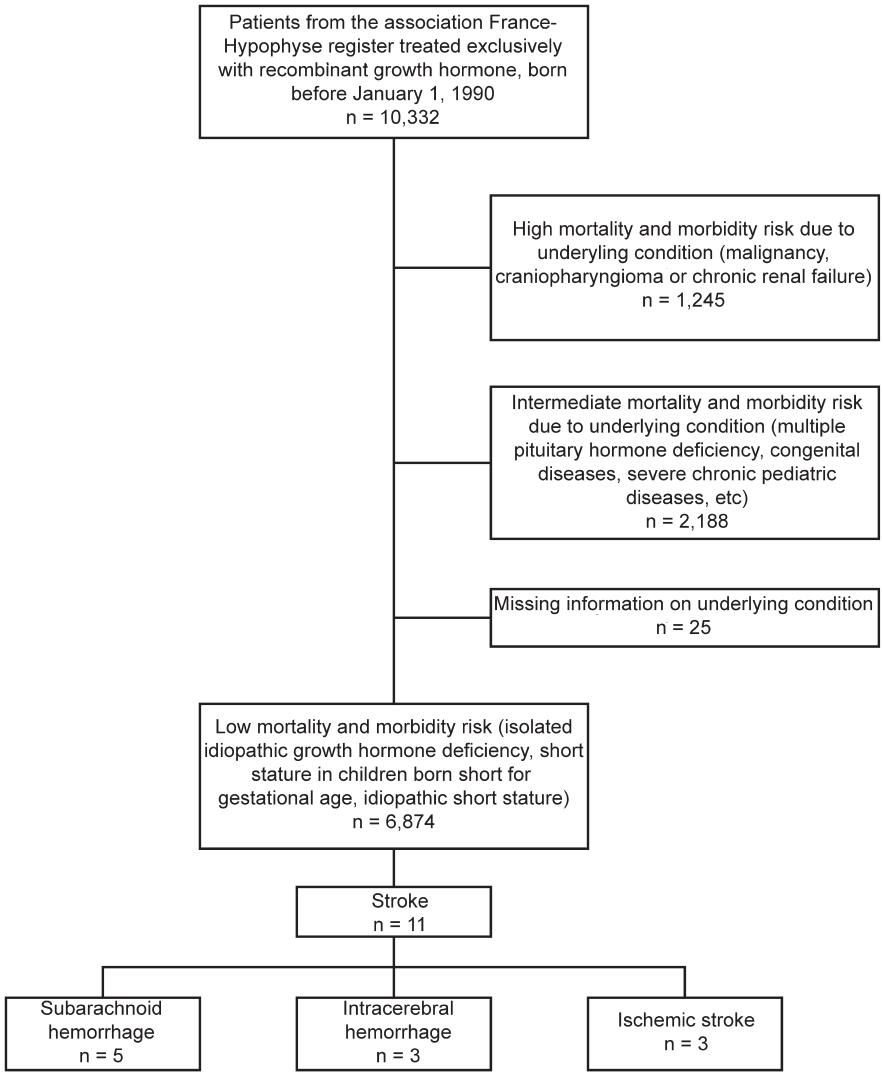
clearly demonstrated effects of GH–insulinlike growth factor-I axis on blood vessels[8,9] prompted us to examine the relationship between exposure to GH treatment during childhood and the risk of stroke in early adulthood.

We used the French SAGhE study, which has collected extensive morbidity data, to examine cerebrovascular morbidity in a population-based cohort of patients treated with GH for short stature in childhood. We specifically studied the incidence of stroke and of various stroke subtypes (subarachnoid hemorrhage [SAH], intracerebral hemorrhage [ICH], and ischemic stroke [IS]).

METHODS **Patients.** As described previously,[4] we used the mandatory register of all patients treated with GH in France until 1996 (Association France-Hypophyse) and selected those who had been treated exclusively with recombinant GH, and not with pituitary-derived GH, and who were born before January 1, 1990. Patients were assigned to 3 risk categories for long-term morbidity and mortality, based on the clinical condition leading to the initiation of GH treatment (figure). Patients were classified in the high-risk group if they had been treated for severe conditions such as cancer or chronic renal failure, and in the intermediate-risk group if they had been treated for multiple pituitary hormone deficiency or pediatric syndromes such as the Turner, Prader-Willi, or Fanconi syndrome. The low-risk group included those treated for idiopathic isolated GH deficiency, idiopathic short stature, short stature in children born short for gestational age, or isolated GH deficiency associated with a minor craniofacial malformation, such as cleft lip; low-risk patients were included in this study because their baseline risk of stroke is believed to be similar to that of the general population. After collection of further data relevant to background conditions leading to GH treatment in childhood, we reclassified 102 patients (1.5%) as compared with our previous report[4]: 62 patients were moved from the low to higher risk groups and 44 added to the low-risk group such that there were 6,874 patients included in the analysis.

Figure **Flowchart of the study, with mortality and morbidity risk groups, showing the total and subtype stroke groups**



Data collected. ***Childhood data.*** Data on patient characteristics, treatment, and growth progression were routinely collected at baseline and at regular follow-up visits, and were obtained from pediatric endocrinologists until 1996 when the national compulsory France-Hypophyse register was disbanded. Additional follow-up data on GH treatment were collected from clinical centers in 2008–2010. Birth weight and birth length are expressed as SD according to the Usher and McLean charts,[10] and height and weight as SD scores. Mean doses of GH treatment were calculated in microgram/kg/day.

Follow-up data. Information on vital status was collected from the Répertoire National d'Identification des Personnes Physiques (http://www.insee.fr/fr/methodes) and the Répertoire National Inter-régimes de l'Assurance Maladie. The cause of death, as indicated on death certificates, was obtained from the French Center for Epidemiology on Medical Causes of Death (CépiDC, Institut National de la Santé et de la Recherche Médicale) and coded according to *ICD-10*.

Morbidity data were collected through a health questionnaire sent to all live patients (despite several repeats, the response rate was 45.5%). Data were also extracted using patient identifiers from the French national health insurance information system (Système National d'Information Inter-régimes de l'Assurance Maladie), which includes the French hospital discharge database, also called *Programme de Médicalisation des Systèmes d'Information*, from January 1, 2008 to December 31, 2010, and long-lasting affection statements, which identify conditions with 100% reimbursement coverage. We set a census date of December 31, 2010.

Validation of events. Cerebrovascular events were validated by a stroke neurologist (E.T.) using all medical reports and imaging data obtained from patients and physicians. They were then classified according to standard definitions of IS, ICH, and SAH.[11]

Statistical analyses. The risk of stroke was evaluated by calculating standardized incidence ratios (SIRs), with adjustment for age and sex, using reference rates of the overall incidence of stroke, including separate subtypes (IS, ICH, SAH), from 2 population-based registries: the stroke registry of Dijon, France, between 2000 and 2010,[12] and the stroke registry of Oxford, UK, between 2002 and 2012 (OXVASC Study).[13] The number of person-years at risk was calculated for GH-treated subjects, for each 5-year age class and separately for men and women, from the date of first administration of GH to the date of stroke, death, loss to follow-up, or December 31, 2010.

The expected number of events was then calculated for GH-treated subjects by multiplying the age- and sex-specific incidence rates by the number of person-years at risk. SIRs were estimated by dividing the number of observed events by the number of expected events. Significance tests and 95% confidence intervals (CIs) for the SIR were calculated with Byar approximation to the exact Poisson test and the exact Poisson limits.

The various sources used to identify fatal and nonfatal events were not exhaustive. We therefore used capture-recapture methods[14,15] and log-linear modeling to estimate the number of cases missed. Source dependence was modeled by including the corresponding interaction term into the model. The significance of the interaction was assessed using likelihood ratio statistics. A CI for the estimated number of cases missed was computed by the profile likelihood method. The Akaike information criterion was used for selection of the model.

Two analyses were performed for the risk of stroke: one with observed events, giving the crude SIR, the other including estimated events using the capture-recapture method, giving the corrected SIR.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé and the Commission Nationale de l'Informatique et des Libertés (the national data protection agency). The use of the Registre National Inter-Régimes de l'Assurance Maladie was approved by a specific statute.

RESULTS The low-risk mortality and morbidity group (n = 6,874) was mainly composed of patients treated for the indication of isolated GH deficiency, as determined by GH stimulation tests (peak <10 ng/mL; n = 4,600, 67%) (table 1). Subjects who had a peak GH >10 μg/L and who were not diagnosed as having neurosecretory dysfunction based on nocturnal GH profiles were classified as idiopathic short stature (n = 868, 13%), although this is not an approved indication in France. In this group, there were more than 111,000 person-years at risk and the mean follow-up between the beginning of GH treatment and the date of last follow-up, event, or death was 17.4 years. The mean (±SD) treatment duration was 3.9 (±2.6) years, with mean doses slightly below the recommendations for isolated GH deficiency.

Eighteen events were identified in this group through the different sources, of which 11 were finally validated as incident cases of stroke (table 2): there were 5 SAH, 3 ICH, and 3 IS. Three of the subjects had been small for gestational age, and none had had severe GH deficiency.[16] The mean (±SD) age at the time of the stroke was 24.2 (±7) years. Four patients died, including 3 of SAH.

The results of the capture-recapture analysis are presented in table e-1 on the *Neurology*® Web site at Neurology.org. The smallest Akaike criterion was obtained for the model taking the interaction between the long-lasting affection statements and the French hospital discharge database into account, and the estimated number of missed cases was 5.3 (95% CI 0.6–50.4). Consequently, the estimated total number of incident strokes was 16.3 (11 cases detected and an estimated 5.3 cases missed). Similarly, the estimated number of missed hemorrhagic strokes was 4.9, giving an estimated total of 12.9 incident hemorrhagic strokes (table e-2). Because of the small number of events for each subtype of hemorrhagic stroke, the ratio of estimated/observed events for the whole hemorrhagic stroke group (4.9/4) was used to estimate the number of cases for each subtype.

Crude and corrected SIRs are reported in table 3. With reference to both the Dijon and the Oxford population-based registries, the risk of stroke was significantly higher among patients treated with GH. Considering stroke subtypes, the excess risk of stroke was largely attributable to a significantly much higher risk of hemorrhagic stroke, and particularly SAH

Table 1 Main characteristics of patients and GH treatments for the sample studied (N = 6,874)

No. of male patients (%)	4,510 (66)
Indication for GH treatment, n (%)	
Isolated GH deficiency	
Maximum peak GH <3 μg/L	295 (4)
Maximum peak GH ≥3 and <7 μg/L	1,557 (23)
Maximum peak GH ≥7 and <10 μg/L	2,748 (40)
Missing value for maximum peak GH	516 (8)
Maximum peak GH ≥10 μg/L	
Neurosecretory dysfunction	547 (8)
Idiopathic short stature	868 (13)
Small for gestational age	343 (5)
Year of treatment start, n (%)	
1985–1987	506 (7.4)
1988–1990	2,470 (36)
1991–1993	2,362 (34)
1994–1996	1,536 (22.6)
Birth length (SDS for gestational age)	−1.2 ± 1.2 (n = 4,875)
Birth weight (SDS for gestational age)	−0.6 ± 1.2 (n = 5,130)
Children born small for gestational age (birth weight or length ≤ −2 SDS for gestational age), n (%)	
Yes	1,298 (19)
No	3,864 (56)
Missing data	1,712 (25)
Chronological age at start of treatment, y	11.0 ± 3.4 (n = 6,874)
Height at start of treatment, SDS	−2.7 ± 0.8 (n = 6,285)
Weight at start of treatment, SDS	−1.6 ± 0.9 (n = 6,242)
Mean dose, μg/kg/d	24.5 ± 12.3 (n = 6,212)
Treatment duration, y	3.9 ± 2.6 (n = 6,380)
Chronological age at end of treatment, y	15.1 ± 2.7 (n = 6,380)
Person-years of observation, n	111,875
Chronological age at the time of census, event, or death, y	28.4 ± 6.2
Duration of follow-up from start of GH treatment to time of census, event, or death, y	17.4 ± 5.3 (n = 6,616)

Abbreviations: GH = growth hormone; SDS = SD score.
Mean ± SD or n (%) is shown.

(crude SIR 5.7 and 6.3 with reference to the Dijon and Oxford data, respectively). All findings were highly consistent between the 2 reference populations.

The proportion of hemorrhagic stroke cases in our cohort was 73% (8/11), which is high compared with the 29.5% in the Dijon stroke registry, and the 30.1% in the Oxford stroke registry (exact significance test for comparing a proportion to a reference value, $p = 0.008$).

After exclusion of subjects born small for gestational age, for which an increase in metabolic risk is expected, the excess risk persisted and remained statistically significant for hemorrhagic stroke (crude SIR = 2.6, 95% CI 1.0–5.8) and for SAH (crude SIR = 4.6, 95% CI 1.2–11.8).

DISCUSSION Using the largest register available of patients treated with GH during childhood and also data from 2 population-based studies, we show that there is an increased long-term risk of stroke and more specifically of SAH among subjects treated with GH for idiopathic isolated GH deficiency, idiopathic short stature, or short stature in children born short for gestational age. The results obtained with the 2 population-based studies used for reference were consistent, and were strengthened when potentially missed cases were estimated using a capture-recapture approach and taken into account. Our previous analysis of the same French registry data suggested an increased risk of fatal hemorrhagic stroke, although the diagnoses were not independently validated.[4] Here, we extend our previous observations and reinforce the message of an abnormally high risk of hemorrhagic stroke in this patient population; in particular, the proportion of hemorrhagic strokes is much higher than expected. This raises the issues of the mechanisms involved, possible confounders, and causality of GH treatment.

It is conceivable that long-term GH treatment affects arterial structure and function.[8,9] Pigs treated with GH to promote increases in their protein mass display excess mortality due to gastric hemorrhage.[17,18] In acromegalic patients, increased abundance of GH and insulinlike growth factor-I affect the proliferation of smooth muscle cells and endothelial function, predisposing the patients to atherosclerotic changes, even in the absence of other risk factors such as hypertension or diabetes.[5,6] More importantly, several studies have suggested that patients with acromegaly are more likely to develop intracranial aneurysms[19–22]: one study reports a prevalence of 17% with most patients having multiple aneurysms and that there was a correlation between intracranial aneurysms and GH serum values at disease onset.[7] Thus, previous reports and our findings are consistent with chronic exposure to GH weakening vessel walls leading to intracranial aneurysm formation and vessel rupture.

The risk of stroke has been linked to short stature in the general population, possibly through increased metabolic risk in short individuals. Several studies[23–27] provide evidence that the incidence of and mortality from stroke increase with short stature with hazard ratios or relative risks consistently found to be between 0.8 and 0.9 per SD of height. If the relative risk is 0.85 per SD of height, our population with a mean height of −2.7 SD should have a risk of stroke of approximately 1.55 relative to that of the general population (mean height of 0 SD). However, these

Table 2 Clinical characteristics and GH treatment for the 11 cases of incident stroke

Case	Sources	Sex	Birth length, cm	Birth weight, g	Birth length, SDS	Birth weight, SDS	SGA	GH peak max, μg/L	Age at start of GH treatment, y	Age at end of GH treatment, y	Treatment duration, y	Mean dose, μg/kg/d	Age of occurrence of stroke, y	Type of stroke, topography, and mechanism
1[a]	CépiDC	M	52	3,730	1.2	1.5	No	10.0	5.7	17.0	11.3	23.5	19.9	SAH
2[a]	CépiDC	M	—	2,460	—	—	NA	3.7	15.7	16.4	0.8	18.1	29.7	SAH due to cerebral aneurysm rupture
3[a]	CépiDC	M	49	3,700	0.2	2.2	No	10.0	5.1	8.9	3.7	17.8	21.4	SAH due to cerebral aneurysm rupture
4	Questionnaire	F	—	2,480	—	—	NA	8.1	13.5	15.3	1.7	21.4	13.9	SAH due to arteriovenous malformation break
5	Questionnaire	M	44	—	−3.8	—	Yes	6.9	12.2	18.2	6.0	27.0	20.4	SAH due to cerebral aneurysm rupture
6[a]	CépiDC	M	—	2,850	—	−0.7	No	9.0	15.0	17.5	2.5	10.4	32.8	ICH: temporofrontal hematoma
7	LLA	F	45	3,040	−3.5	−1.1	Yes	3.9	5.3	10.8	5.4	19.6	16.1	ICH
8	Questionnaire	F	50	3,320	−0.4	−0.1	No	7.6	11.2	—	—	—	24.5	ICH: frontal intraparenchymal hematoma
9	LLA, FHDD, questionnaire	F	49	3,260	−1.2	−0.5	No	9.9	12.9	16.1	3.3	15.0	34.5	IS: carotid dissection
10	Questionnaire	F	47	2,300	−2.0	−2.5	Yes	8.2	10.0	14.6	4.5	18.0	28.9	IS
11	Questionnaire	F	50	—	−0.6	—	NA	5.8	13.4	15.9	2.5	15.9	—	IS

Abbreviations: CépiDC = French Center for Epidemiology on Medical Causes of Death; FHDD = French hospital discharge database; GH = growth hormone; ICH = intracerebral hemorrhage; IS = ischemic stroke; LLA = long-lasting affection; max = maximum; NA = not ascertained; SAH = subarachnoid hemorrhage; SDS = SD score; SGA = small for gestational age.
[a] Died.

studies addressed older populations, with mean ages over 50 years, and refer mainly to risk of ischemic stroke. The estimated risks obtained in our study were higher in every case, and often much higher, especially for hemorrhagic strokes, which have not previously been found to be associated with short stature in populations.

Another possible confounder is the inclusion of patients with diseases specifically associated with both short stature and increased risk of stroke. Indeed, several severe conditions such as Majewski osteodysplastic primordial dwarfism syndrome[28] and syndromic moyamoya[29] or MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, OMIM #540000) are associated with short stature and stroke or stroke-like episodes. However, most of these conditions would not commonly be misdiagnosed as idiopathic isolated GH deficiency. However, we cannot rule out that less severe forms of these or similar conditions have been overlooked or that the diagnosis of idiopathic isolated GH has been used to allow the patient to qualify for GH treatment.

Our study has other potential limitations. First, noncompleteness of the sources of ascertainment of stroke was a limitation for the analysis of the incidence of stroke; we addressed this limitation by using the capture-recapture method, and our crude results were already highly significant despite the underestimation of the true risk of stroke. The construction of log-linear models fitting one or more sources of interaction allowed the number of patients not captured to be estimated by taking into account the independence of the sources. Moreover, our finding of a large relative excess of hemorrhagic vs ischemic stroke in the GH-treated population is unlikely to be explained by any ascertainment bias. The second limitation is that the small number of events (both in the study cohort and in the reference registries) led to wide CIs. Log-linear models could not be constructed for the analysis of hemorrhagic stroke subtypes because of the small numbers, so we applied the "patients estimated by the capture-recapture method/patients validated" ratio to the number of actual observed cases; it was thus possible to determine the order of magnitude of the SIR as if all cases had been identified. The number of events was too small to allow testing for a relationship between the dose of GH treatment and the incidence of stroke. A third limitation is that subjects born small for gestational age were included in the cohort; during adulthood, these subjects present an increased risk of various metabolic disorders, including metabolic syndrome, insulin resistance, and diabetes.[30] However, to date, no study has reported a higher than normal risk of cerebral hemorrhage in these individuals, and these

Table 3 Crude and corrected SIRs for all strokes and the different subtypes of stroke (without and with patients estimated by the capture-recapture method, respectively) with the Dijon and Oxford registries

	Crude			Corrected		
	Observed no.	Expected no.	SIR (95% CI)	Estimated no.	Expected no.	SIR (95% CI)
Dijon registry						
All strokes	11	7.4	1.5 (0.7–2.7)	16.3	7.4	2.2 (1.3–3.6)
Hemorrhagic stroke	8	2.3	3.5 (1.5–6.9)	12.9	2.3	5.7 (3–9.7)
Subarachnoid hemorrhage	5	0.9	5.7 (1.9–13.4)	7.5	0.9	8.6 (3.6–17.3)
Intracerebral hemorrhage	3	1.4	2.1 (0.4–6.3)	5.5	1.4	3.9 (1.3–8.8)
Ischemic stroke	3	5.2	0.6 (0.1–1.7)	6.7	5.2	1.3 (0.5–2.7)
Oxford registry						
All strokes	11	3.1	3.6 (1.8–6.4)	16.3	3.1	5.3 (3.0–8.5)
Hemorrhagic stroke	8	1.8	4.4 (1.9–8.6)	12.9	1.8	7.0 (3.7–12.0)
Subarachnoid hemorrhage	5	0.8	6.3 (2.0–14.6)	7.5	0.8	9.3 (3.9–18.8)
Intracerebral hemorrhage	3	1.0	2.9 (0.6–8.5)	5.5	1.0	5.3 (1.8–11.9)
Ischemic stroke	3	1.25	2.4 (0.5–7.0)	6.7	1.25	5.3 (2.1–11.2)

Abbreviations: CI = confidence interval; SIR = standardized incidence ratio.

metabolic disorders are more related to IS than to SAH or ICH. In addition, after exclusion from our analysis subjects who had been small for gestational age, the excess of risk of hemorrhagic stroke persisted and remained statistically significant. Finally, the methodology of the study did not allow an assessment of cardiovascular risk factors in adulthood, such as hypertension, diabetes, or dyslipidemia, which are risk factors for stroke. However, it seems very unlikely that these factors could have confounded the strong association we found between GH treatment in childhood and SAH.

This study therefore suggests a strong relationship between hemorrhagic stroke and GH treatment in childhood for isolated GH deficiency or childhood short stature. Although a causal relationship is biologically plausible, further work remains to be done before this is demonstrated. In addition, the natural history of cerebrovascular anomalies in this patient population needs to be studied in more detail to establish whether our findings can be explained by an increased risk of aneurysm and/or rupture. The lack of consensus on screening and management of unruptured aneurysm will complicate any such studies. However, given the strength of our results, with very high SIRs and their consistency across outcomes (increases of SIR and standardized mortality ratio associated with cerebrovascular diseases), we believe that the tens of thousands of patients treated with GH worldwide should be informed of the risk of hemorrhagic stroke. This information should also be made available to those who misuse GH for improving athletic performances, body building, and other questionable reasons.[31]

AUTHOR CONTRIBUTIONS

Joël Coste, Emmanuel Touzé, and Jean-Claude Carel designed the study. Fabienne Landier, Emmanuel Ecosse, Yannick Béjot, Maurice Giroud, and Peter M. Rothwell oversaw the data collection. Amélie Poidvin and Emmanuel Ecosse performed the statistical analysis. All authors contributed to data interpretation and to writing the article.

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DISCLOSURE

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