Adult stroke risk after growth hormone treatment in childhood

First do no harm

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Neurology® 2014;83:776–777

Childhood precursors of adult diseases are increasingly identified by studies that span the period from birth to senescence. This is particularly relevant for cerebrovascular disease, for which links have been discovered with childhood obesity and adolescent-onset hypertension.[1] In this issue of *Neurology*®, Poidvin et al.[2] report an increased risk of stroke in adults treated with growth hormone (GH) during childhood. This report has been much anticipated by the endocrinology community because it extends and clarifies findings in a 2012 study showing increased mortality in adults treated in childhood with GH from the prospective European cohort study—the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE).[3]

Increased availability of GH after US Food and Drug Administration approval in 1985 paved the way for its widespread use. Safety and late adverse effects have long been a concern, mainly related to the potential for malignancy. Clinical trials and postmarketing studies demonstrated a good safety profile for children while on therapy.[4,5] Nonetheless, there has been vigorous debate about the utility, ethics, and cost of GH treatment, especially for otherwise healthy children with idiopathic short stature (ISS).[6,7] This debate has resurfaced following the preliminary SAGhE report, and will likely intensify after the current report on increased stroke risk from the SAGhE investigators.

The SAGhE study involved data collection on long-term mortality and morbidity in a mandatory registry for patients treated with GH for all indications. The current study analyzed adult morbidity in the "low-risk" subgroup, comprising children with isolated GH deficiency, ISS, or short stature associated with intrauterine growth retardation. They measured incidence of all stroke subtypes among adults between 2008 and 2010 treated as children with GH for ISS or isolated GH deficiency between 1985 and 1996. Events were ascertained from questionnaires sent to patients, and by review of medical records and imaging data, and were classified centrally by a vascular neurologist using well-defined standardized World Health Organization criteria. Comparison data for stroke incidence were obtained from population-based registries in Dijon, France, and Oxford, UK, in a comparable time period.

The study population included 6,874 children with isolated GH deficiency (75%), and a minority with ISS (13%). Mean age at treatment onset was 11 years, mean treatment duration 3.9 years, giving a total of >111,000 person-years at risk. At a mean follow-up of 17.4 years, there were 11 incident strokes at a mean age of 24 years: 3 intracerebral hemorrhages, 3 ischemic strokes, and 5 cases of subarachnoid hemorrhage. Four of these patients died. The authors found an increased incidence of stroke relative to 2 population-based registries, with a standardized incidence ratio of 2.2 to 5.3 for all stroke subtypes, and 5.7 to 7.0 for hemorrhagic stroke.

This well-designed study shows a strong association between childhood treatment with GH and adult-onset cerebrovascular disease. Major strengths include the large sample size arising from a mandatory large national treatment registry, and the long duration of follow-up. The methods used to ascertain, verify, and classify stroke diagnoses are rigorous. The results are striking indeed, and have immediate clinical import, more so when considering the highly morbid nature of these events with a high rate of mortality in young adults.

The authors clearly articulated the limitations of their study, including uncertainty regarding a causal relationship and a small absolute number of events. An important limitation is that other stroke risk factors were not evaluated, such as hypertension, hyperlipidemia, and diabetes. A control group of GH-deficient patients not treated with GH and followed into adulthood and evaluated for stroke would have been a useful comparator group, but was not available for this study. The use of population-based registries for stroke incidence nonetheless serves as a strong basis for predicting expected rates from the general population. Despite the limitations, it is conceivable, indeed believable, that a cause-effect relationship exists between GH treatment and later hemorrhagic stroke. As the authors appropriately pointed out, this

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the editorial.

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idea is supported by preclinical studies showing GH modulates vasculogenesis and endothelial function,[8] and clinical studies showing an increased incidence of cerebral aneurysms in acromegalic patients.[9]

There are several implications for future research, echoing the recommendations of Rosenfeld et al.[5] articulating the need for ongoing rigorous research. In particular, studies are needed to more clearly define cause and effect relationships between childhood GH treatment and adult-onset cerebrovascular disease, with attention to dose, duration of treatment, age of exposure, positive family history of cerebrovascular disease, and other vascular predisposing factors.

The implications for clinical practice are potentially urgent and immediate. The first is whether and how adults exposed to treatment in childhood should undergo surveillance evaluation and primary preventive treatment strategies. Current published guidelines for treatment of children with GH provide little information about late posttreatment adult health outcomes.[10] It may be prudent now, based on the available data, for practitioners who prescribed GH to include this possible association in their counseling about risks, and to weigh it in their own recommendations when determining "net benefit" to the patient for this treatment. If the family and practitioner proceed with therapy, the family and patient should be counseled to be knowledgeable about signs and symptoms of, and the importance of seeking prompt treatment for, cerebrovascular disease. It may also be prudent to counsel these patients about the importance of primary prevention strategies for cerebrovascular risk factors throughout adult life, such as managing obesity, blood pressure, and smoking cessation. The concept of negligible risk is a standard by which treatments given to healthy children at very high cost should be judged.[11] Even a very small increase in risk of a condition with fatal or severely disabling consequences violates this standard.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

R. Ichord is on a data and safety monitoring board for the Berlin Heart EXCOR pediatric IDE trial; receives publishing royalties from UpToDate; and receives research support from NIH/National Institute of Neurological Disorders and Stroke. Go to Neurology.org for full disclosures.

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