

**Endocrine Society Statement on Possible Association Between GH Therapy in Childhood and  
Later Stroke  
August 25, 2014**

A just published study in Neurology described a possible association between growth hormone (GH) therapy during childhood among “low risk patients” (isolated GH deficiency, idiopathic short stature and small for gestational age) and increased risk for stroke (both hemorrhagic and ischemic stroke) in young adulthood in France<sup>1</sup>. The study found that 11 out of the 6,874 GH recipients had a fatal or non-fatal stroke. While this raises some concerns, there are several significant limitations to this study identified by experts from the Society, Pediatric Endocrine Society, and Growth Hormone Research Society that necessitate caution in interpreting the conclusions.

Data for cause of death in those individuals (4 out of 11) who had fatal stroke were obtained from the French Death Certificates. Death certificates in France may not reflect the underlying (proximate) cause of death because they document only the immediate symptom prior to death. A review of medical records, a much more accurate way to determine the cause of death, is the preferred method of ascertaining cause and would give more credence to the conclusions.

There may have been significant ascertainment bias of the cases since the data were obtained from mailed questionnaires which had a low (45%) response rate. There is lack of adjustment for the other major risk factors for stroke such as hypertension, diabetes, obesity, smoking/alcohol, and family history of stroke; and the lack of sufficient detail about GH therapy (e.g., dose and duration of therapy, interval between treatment and event, and age at the time of the event) in 4 of the 11 patients. Given the low numbers for incidence of stroke in this cohort, any small change in the observed rates could potentially significantly alter the analyses and results.

Perhaps most importantly, the two control groups that were used to compare estimated stroke rates in the cohort were from a general population and one of the two control groups was from a different country (United Kingdom). A suitable cohort for comparison might have been untreated French adults of the same age and size with the same diagnoses since untreated adult GH deficiency itself is a risk factor for cardiovascular disease and short stature itself has been associated with adverse cardiovascular outcomes. The elevated mortality rate observed in the shortest subjects (at initiation of treatment)



seems to reinforce the contention that some element of the underlying condition which imparted this increased risk, rather than the treatment, *per se* was the culprit.

Of note is that the same group concluded that there was an association between childhood GH therapy for low risk indications and mortality risk in adulthood in 2012<sup>3</sup>. This was contradicted by a concurrent publication in which co-investigators in that study reported a very low mortality rate due to diseases of the circulatory system with no deaths due to diseases of the circulatory system in “low risk” individuals in Belgium, the Netherlands and Sweden. In addition, the U.S. Food and Drug Administration “identified a number of study design weaknesses that limit the interpretability of the study results” making “the evidence regarding recombinant hGH and increased risk of death is inconclusive”<sup>5</sup>.

The Endocrine Society believes that until rigorously performed studies are done which confirm the Poidvin et al’s observations, GH therapy can continue to be safely administered to children who would benefit from it. In addition, there is no current evidence of a need for cardiovascular surveillance or preventive strategies in adults who received growth hormone therapy in childhood. In addition, the Endocrine Society discourages patients from stopping their GH therapy without discussing the risks and benefits with their physician.

1. Poidvin A, Touzé E, Ecosse E, Landier F, Béjot Y, Giroud M, Rothwell PM, Carel JC, Coste J. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology*. 2014 Aug 13
2. Ichord, RN. Adult stroke risk after growth hormone treatment in childhood. First do no harm. *Neurology* 2014;83:776–777
3. Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *J Clin Endocrinol Metab* 2012;97:416-425
4. Säwendahl L, Maes M, Albertsson-Wikland K, Borgström B, Carel JC, Henrard S, Speybroeck N, Thomas M, Zandwijken G, Hokken-Koelega A. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *J Clin Endocrinol Metab* 2012;97:E213-217
5. FDA Drug Safety Communication: Safety review update of Recombinant Human Growth Hormone (somatropin) and possible increased risk of death: <http://www.fda.gov/Drugs/DrugSafety/ucm265865.htm>.