

Long-term risk of stroke in children treated with growth hormone for short stature

Looking at the big picture

David Spencer, MD

WHAT IS GROWTH HORMONE AND WHY IS IT USED? Growth hormone (GH) is one of several substances produced in a gland near the base of the brain called the pituitary gland. The pituitary gland is sometimes called the “master gland” because the substances that it produces have effects on many body systems. For example, it sends signals to the thyroid, ovaries, and adrenal glands to regulate their output. It also regulates growth by producing GH.

The action of GH is complicated. It has direct effects on many different cells in the body. It also triggers release of another hormone called insulin-like growth factor 1 (IGF-1), which does some of the work. As the name suggests, GH helps to regulate the complex process of growth. It also plays an important role in directing how fat, protein, and sugars are processed in the body. If a child produces too little GH, he or she will not grow normally and will be short compared to others. If too much GH is produced in a child (very rare), he or she will grow too large and will have other health problems. If too much GH is produced in a fully grown adult, a condition called acromegaly results. Adults with acromegaly don't grow much taller, but certain body parts are affected. These include the skull and jaw, the tongue, and the skin.

GH can now be produced in the laboratory, and it can be given to children who don't make enough GH. This is called hormone replacement. It is similar to the process of replacing other hormones that many people are familiar with, such as thyroid hormone. For children with GH deficiency, hormone replacement can allow them to grow normally. There are also inappropriate uses of GH. Some athletes may use GH in an attempt to improve their performance. Bodybuilders may abuse GH for its muscle-building effects. Others have used it with the belief that it has anti-aging properties. Use of GH in children who are small but who don't have GH deficiency is controversial. Our society often views tall people as more successful. But inappropriate (and even appropriate) use of GH may carry risks.

In this study, the researchers looked at the long-term risk of stroke in children who had been treated with GH for short stature.¹

WHY DID THE RESEARCHERS STUDY STROKE RISK? GH has been used for many years, and the current form of GH produced in the lab generally

has a good safety record. Nonetheless, researchers have been concerned about the long-term safety of GH use. Because GH promotes growth, many of the previous safety studies were focused on the risk of developing cancers. Cancer results from uncontrolled growth of groups of cells in the body. Some studies suggest that cancer risk might be elevated in children who were given GH, while others do not. This is very difficult to study because cancers may take many years to develop. The amount of possible cancer risk remains uncertain.

GH and its partner IGF-1 also have effects on blood vessels. Researchers had observed that some adults who were treated with GH as children had strokes as young adults. Was there a connection? The answer would be very important regardless of whether it was yes or no. Dr. Poidvin and colleagues¹ set out to answer this question using the best available information.

HOW WAS THE STUDY DONE? The researchers relied on a large registry (list) of patients who had been treated with GH as children. For many years, every child in France treated with GH had to be tracked in a national registry. The researchers identified children who were treated with GH and who did not have a lot of other health problems. Usually their only health problem was low GH levels. Some of these children actually had normal GH levels but they were very small, so they were treated with GH to help them grow to a more average size. Altogether, 6,874 children could be tracked through this system. These children did not have other conditions to make the researchers think they would be at higher risk for stroke than other children.

The researchers then reviewed many years of medical records to determine what happened to the GH-treated children as adults. Specifically, they counted how many developed strokes as adults. It is hard to track every person over many years, so they also estimated how many strokes might have been missed by this method and adjusted the results. They then compared the stroke rate in this group to the expected stroke rate in the overall population. To do this, they used 2 existing databases of stroke risk in the overall population—one from France and one from England.

WHAT DID THE RESEARCHERS FIND, AND WHAT DOES THIS MEAN FOR PEOPLE WHO TAKE GH? Stroke was not very common in the young adults who were studied. But when those treated with GH as children were compared to the general population, there was a definite increase in stroke risk in those who had been exposed to GH.

Stroke can be caused by a blockage in blood vessels to the brain or by bleeding in the brain (see “About types of stroke”). Most of the increased stroke risk in people treated with GH came from an increase in the bleeding type of stroke. The risk of a type of bleeding stroke called a subarachnoid hemorrhage (SAH) was especially increased. SAH has several causes. The most common cause is rupture of an aneurysm. An aneurysm results from a weak spot in the wall of a blood vessel. The weak spot can stretch like a balloon (become an aneurysm) and then pop, causing very serious bleeding in the brain.

Some previous studies have suggested that treatment with GH may have effects on blood vessels. Some animals given GH have had bleeding problems. Adults with acromegaly (too much GH) are more likely to have aneurysms. Could exposure to GH in childhood over a period of several years

weaken blood vessels, leading to aneurysms and strokes?

We still don't know the answer. But this is an important focus for future research. For now, many children will still require treatment for GH deficiency. In general, GH treatment has an excellent safety record. Until we have more information, there are no new recommended tests or procedures to assess stroke risk in people who were treated with GH in childhood. Overall, the risk of stroke is still fairly small.

Studies like this one do send an important message to those who might consider taking GH for less clear reasons. There are already reasons to think that GH should not be given to otherwise healthy children simply because their parents don't want them to be short. There are strong arguments against an adult taking GH to look stronger or younger. This and other research points out that there are real risks to taking GH. We must continue to ensure that there are sound reasons for treatment with GH and that the benefits outweigh the risks.

REFERENCE

1. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology* 2014;83:780–786.

Section Editors

David C. Spencer, MD

Steven Karceski, MD

About stroke: Types of stroke

Ischemic stroke^{1,2} occurs when blood vessels full of oxygen-supplying blood to the brain are blocked or become more narrow because there is a buildup of plaque. Plaque is made up of fatty materials and cholesterol. Because the pathway is reduced, the blood flow to brain cells is prevented. There are 2 types of ischemic stroke. An embolic stroke is a blood clot that forms somewhere in the body and then travels to the brain, and a thrombotic stroke is the result of a clot in an artery that supplies blood to your brain called thrombosis. Thrombosis can be large vessel or small vessel depending on the size of the artery. High blood pressure is the most important risk factor for ischemic stroke.

Hemorrhagic stroke^{1,2} occurs when a blood vessel becomes weak and breaks or begins to leak. Aneurysms and arteriovenous malformations can cause hemorrhagic stroke. As a result of hemorrhagic stroke, blood collects in the brain and this can cause brain cells to die. This happens because blood is toxic to brain tissue. The 2 types of hemorrhagic stroke are intracerebral and subarachnoid. In an intracerebral hemorrhage, a blood vessel inside the brain leaks blood or ruptures. A subarachnoid hemorrhage occurs when a blood vessel on the surface of the brain

leaks blood or ruptures and then there is bleeding within the layers of the membranes that cover the brain.

Transient ischemic attack (TIA)^{1,2} is caused by a temporary clot in the blood vessel. This type of stroke is also called mini-stroke or minor stroke. The symptoms of a TIA are like those of a stroke, but they last only a few minutes.

FOR MORE INFORMATION

Neurology Now[®]

<http://journals.lww.com/neurologynow/Pages/Resource-Central.aspx>

National Stroke Association

<http://www.stroke.org>

American Stroke Association

<http://www.strokeassociation.org>

REFERENCES

1. Types of stroke. Available at: <http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke>. Accessed July 3, 2014.
2. Types of stroke. Available at: <http://www.nhlbi.nih.gov/health/health-topics/topics/stroke/types.html>. Accessed July 3, 2014.

Neurology®

Long-term risk of stroke in children treated with growth hormone for short stature:

Looking at the big picture

David Spencer

Neurology 2014;83:e103-e105

DOI 10.1212/WNL.0000000000000808

This information is current as of August 25, 2014

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/83/9/e103.full
References	This article cites 1 articles, 0 of which you can access for free at: http://n.neurology.org/content/83/9/e103.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Cerebrovascular disease/Stroke http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke All Pediatric http://n.neurology.org/cgi/collection/all_pediatric Pediatric stroke; see Cerebrovascular Disease/ Childhood stroke http://n.neurology.org/cgi/collection/pediatric_stroke_see_cerebrovascular_disease-childhood_stroke
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2014 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

