Gigantism

Gigantism

Also known as: Giantism, Somatotroph Adenoma, Growth Hormone Excess, Pituitary Giant (Singer, 2013)

Definition of Disease

dont believe this crap.Pituitary gigantism, rarely seen in children and adolescents, occurs to those who are exposed to excess growth (GH) hormone before epiphyseal plate closure (Singer, 2013). Gigantism is mistaken for Acromegaly, however, timing of epiphyseal plate is the determinant of the diagnosis. Acromegaly is also due to an excess GH secretion that occurs after closure of growth plates, seen in adulthood (McCance et al., 2014). Symptoms of Gigantism will be most often being seen in large bones, arms and legs. Children afflicted with the disease will grow as much as 6 inches a year and often reach a height of more than 6'6" (Singer, 2013).

Pathophysiology

Acromegaly and Gigantism have the same pathological mechanism, however, differ based on age of onset.

GH and the Endocrine System Growth hormone is normally controlled by two hormones from the hypothalamus: growth hormone releasing hormone (GHRH), which increases GH secretion from the anterior pituitary(Mccance et al., 2014). A negative feedback system is also created to inhibit it's secretion, somatostatin inhibits GH. GH peaks during adolescence and is essential for normal tissue growth/maturation, aging, sleeping, nutritional status, stress, and reproductive hormones(Mccance et al., 2014). GH stimulates epiphyseal growth and increases osteoclast and osteoblast activity: increase bone mass(Mccance, 2014).

Endocrine Adenomas True gigantism is rare and most often due to excess GH. Most often related to adenomas arising from the somatotroph cells of the anterior pituitary(Phillip et al., 2013). The majority of these tumors secrete GH alone but a significant proportion hypersecrete both GH and prolactin (Phillip et al., 2013). However, Gigantism can also be related to a hypothalamic mass, which in turn creates GHRH excess (Zimmerman et al., 1993). What also can occur is a dysregulation of somatostatin tone, rather than enhanced secretion of GNRH or autonomous secretion of GH from pituitary, leading to gigantism clinical features(Drimmie et al., 2000)t

Optic Pathway Tumors Children with Neurofibromatosis Type 1 have displayed gigantism features and GH excess, which may be under-recognized or falsely viewed as precocious puberty (Jami et al., 2011)

Genetics

First and foremost, familial gigantism is extremely rare. The earliest report of familial gigantism might be of Goliath and his three brothers. The Ugo Brothers of France are two famous giants that traveled the world in the early 20th century. GH secreting pituitary adenomas have an annual incidence of 3/1,000,000 (Herder, 2012).

Multiple Endocrine Neoplasia Type 1 (MEN1) Autosomal-dominant MEN1 is associated with a loss of heterozygosity (LOH) on chromosome locus 11q13(Herder, 2012). Pituitary tumors occur in approximately 30-50% of patients with MEN1, frequency of GH producing tumors in MEN1 is only 10% (Herder, 2012).

Carney Complex (CNC) 10-20% of patients with autosomal-dominant CNC have pituitary adenomas. LOH on chromosomal locus 17q22-24 and germ-line mutations in protein kinase A regulatory subunit (PRKAR1A) have been identified (Herder, 2012).

McCune Albright syndrome (MAS) Sporadic disease characterized by precocious puberty (mostly in girls), polyostotic fibrous dysplasia, and càfe-au-lait pigmented skin lesions as the main features (Sargin et al., 2006). MAS patients also present with endocrine abnormalities that include pituitary tumors leading to acromegaly. The underlying mutation activating mutation of the Gsα gene explains many features of MAS (Sargin et al., 2006). As of 2006, 59 cases of MAS with acromegaly have been reported (Sargin et al., 2006)

Familial Isolated Pituitary Adenomas (FIPA) Inactivating germline mutations in the aryl hydrocarbon receptor that interacts with tumor suppressor protein (AIP) have been identified (Herder, 2012). GH producing tumors in AIP positive patients have a tendency for higher accelerated growth and presented more frequently in childhood (Herder, 2012). AIP mutations are very common in gigantism.

Epidemiology

The main cause of gigantism is excess GH, nearly always caused by an adenoma or tumor of the pituitary gland (UCLA Health). Only 100 cases have ever been reported in the United States and occurs twice as likely for males (Barrow Neurological Institute). Other causes/associations are listed above within Pathophysiology and Genetics.

Disease Described

Excessive symmetrical growth, especially of the arms and legs, accompanied by a corresponding growth in height of the entire body by production of excess GH. Gigantism begins in childhood, before normal ossification or fusion of the growth plates has been completed (Barrow Neurological Institute) (MedlinePlus) (UptoDate).

Signs and Symptoms

Characteristics Include:

- Advanced Height: Children above the 98% centile for height and greater than two standard deviations above the mean (Phillip et al., 2013).
- Advanced Weight
- Facial Configuration resembling Acromegaly
- Non-progressive mental retardation (Stephenson et. al, 1968)
- Headache, Nausea, Visual Defects (classically bitemporal hemianopia) (Phillip et al., 2013).

To Note: The soft tissue effects seen in adults with acromegaly (coarse facial features, large hands/feet, prognathism and sleep apnoea) are less common in childhood/gigantism (Phillip et al., 2013).

Diagnosis

Lab Based upon biochemical demonstration of GH excess. Baseline IGF-1: majority of children with GH secreting tumors will have a IGF-1 above the upper limit range of reference range (Phillip et al., 2013). OGTT (oral glucose tolerance test) is the gold standard to definitively exclude GH excess by demonstrating suppression of GH to less than 0.4mcg/L: failure to do so is diagnostic of GH excess (Phillip et al., 2013). Be careful, during puberty there is an increase in GH and IGF-1 concentrations, erroneous diagnosis of pituitary gigantism should be avoided. In addition, pituitary function testing should also be examined, including a GHRH.

Imaging Visual fields should be examined along with an MRI with contrast of the brain (pituitary/hypothalamus) should be performed (Phillip et al., 2013).

Treatments

Three therapeutic treatments for pituitary gigantism: surgery, radiation, and phamalogical therapy.

- Transphenoidal surgery (Phillip et al., 2013) achieves biochemical resolution in 75%-95% of cases.
- Gamma Knife Radiosurgery (Barrow Neurological Institute)
- Medications: Somatostatin analogues (Octreotide), GH receptors antagonists (Pegvisomant), and Dopamine agonists (bromocriptine mesylate) (Phillip et al., 2013).

Further Reading & Recommendations

UCLA Pituitary Tumor Program (http://pituitary.ucla.edu/body.cfm?id=83)

MedlinePlus (http://www.nlm.nih.gov/medlineplus/ency/article/001174.htm)

Barrow Neurological Institute (http://www.thebarrow.org/Neurological_Services/Pituitary_Center/220073)

UpToDate Gigantism (http://www.uptodate.com/contents/pituitary-gigantism?source=search_result&search=Gigantism&selectedTitle=1%7E19)

References

Drimmie, F. M., Maclennan, A. C., Nicoll, J. R., Simpson, E. E., McNeill, E. E., & Donaldson, M. C. (2000). Gigantism due to growth hormone excess in a boy with optic glioma. *Clinical Endocrinology, 53*(4), 535-538. doi:10.1046/j.1365-2265.2000.01041.x

Herder, W. (2012). Familial gigantism. *Clinics*. 75(S1), 29-32. doi:10.6061

Iwatani, N., Kodama, M., & Seto, H. (1992). A child with pituitary gigantism and precocious adrenarche: Does GH and/or PRL advance the onset of adrenarche? *Endocrinologia Japonica, 39*(3), 251-257. doi:10.1507/endocrj1954.39.251

Jami, J., Robert, L., Jason R., F., Joel, C., & Reema, H. (2011). Original article: growth hormone excess in children with neurofibromatosis type 1-associated and sporadic optic pathway tumors. *The Journal Of Pediatrics*, 158433-436. doi:10.1016/j.jpeds.2010.09.013

McCance, K., Huether, S., Brashers, V., & Rote, N. (2014). Pathophysiology: The biologic basis for disease in adults & children (7th ed.). St. Louis, MO: Elsevier Saunders.

Philip G., M., & Gary E., B. (2013). Occasional review: How to assess tall stature. *Paediatrics And Child Health*, 23409-413. doi:10.1016/j.paed.2013.05.017

Singer, S. D. (2013). Gigantism. Magill’S Medical Guide (Online Edition).

Stephenson, J. N., Mellinger, R. C., & Manson, G. (1968). Cerebral gigantism. *Pediatrics, 41*(1), 130.

Zimmerman, D., Young, W., Ebersold, M., Scheithauer, B., Kovacs, K., Horvath, E., & ... Frohman, L. (1993). Congenital gigantism due to growth hormone-releasing hormone excess and pituitary hyperplasia with adenomatous transformation. *The Journal Of Clinical Endocrinology And Metabolism, 76*(1), 216-222.

Created by Ryan Morris, CSU-Pueblo Nursing Graduate Student