Severe obesity caused by GNAS mutations and clinical heterogeneity associated with impairment of various molecular pathways *(N Engl J Med 2021;385:1581-92)*

GNAS regulates G-protein coupled receptor (GPCR) signalling, and its mutations are known to be associated with obesity and hormone resistance in pseudohypopara-thyroidism. The present study was conducted on 2548 children (aged <10 year) with early onset severe obesity. Exome sequencing was performed and *GNAS* mutations were identified in 22 of them. Investigators aimed to study the molecular pathways explaining obesity and clinical variability associated with these mutations. They revealed that all GNAS mutations caused impairment of melanocortin (MC4R) pathway, explaining the obesity. Six out of 22 patients, having poor growth, had disruption of growth hormone–releasing hormone receptor signaling caused by GNAS mutations, but growth remained unaffected when this pathway was not impaired. Mutations disrupting thyrotropin receptor signaling, led to developmental subnormality and high thyrotropin levels. GNAS mutations can differentially affect GPCR pathway leading to the clinical variability. Since presentation as isolated obesity and clinical heterogeneity is evident for these mutations, authors advocate the screening of children with severe obesity for GNAS mutations. Unbiased genetic analysis may aid in early detection and better clinical outcome of such patients.

Vosoritide improves bone growth in children with achondroplasia (*Genet Med. 2021;23:2443-47*)

Vosoritide, a C-type natriuretic peptide analog, has been in development for the treatment of achondroplasia. A phase III study was conducted to determine the efficacy and safety of vosoritide in children (121 children, 5 to <18 years) with achondroplasia. Participants completed six months of a baseline growth study, followed by 52 weeks of a placebo- controlled study. Then they were eligible to participate in the phase 3 extension study, to receive vosoritide at a dose of 15.0 µg/kg/day (daily injections). Vosoritide group had annualized growth velocity 1.57 cm/year (mean difference) more than that of the placebo group suggesting vosoritide to be a promising and persistent growth-promoting agent in children with achondroplasia. Vosoritide has now been approved by FDA for treatment of achondroplasia.

Improved detection of focal congenital hyperinsulinism with 68Ga-NODAGA-exendin-4 PET *(J Nucl Med. July 2021. Epub ahead of print)*

Focal congenital hyperinsulinism (CHI) can be treated successfully, provided an accurate pre-surgical localization of the lesion is made. The present study compared 18F-DOPA positron emission tomography (DOPA PET) (the current standard imaging method for CHI) with 68Ga-NODAGA-exendin-4 (Exendin PET) for pre-surgical detection of focal CHI in 19 patients with CHI. Both the scans were done in all patients. The images were evaluated by an expert in hyperinsulinism along with a nuclear medicine physician. Surgery was performed in 14/19 patients having focal lesions. Based on expert readings, clinical sensitivity of exendin PET (100%) was higher than DOPA PET (71%). Inter-observer correlation was higher for exendin than for DOPA PET. Pediatric surgeons rated exendin PET superior to DOPA PET on a five point scale. Thus, exendin proves to be a superior technique with its better image quality and leads to precise intra-operative localization during surgeries.

Potential marker for accurate prediction of pubertal onset in delayed puberty *(J Clin Endocrinol Metab. 2021;106:e3495-3505)*

A cutoff level of gonadotropins, whether basal or GnRH stimulated, which can differentiate constitutional delay of puberty from hypogonadotropic hypogonadism, has hitherto eluded investigators. This study was conducted to explore the potential role of FSH stimulated inhibin B (FSH-iB) for prediction of pubertal onset. FSH and GnRH analogue stimulation test were performed on exploratory cohorts (*n*=42, group 1-spontaneous puberty, group 2-hypogonadotropic hypogonadism [HH]) and a validation cohort (*n*=19, delayed puberty). Statistically significant increase in FSH-iB occurred in group 1 in both males and females, while the increment was not significant in group 2. Cutoffs of FSH-iB (males- 116.14 pg/mL and females- 116.50 pg/mL) had 100% sensitivity and specificity for marking pubertal onset. These cutoffs showed 100% positive predictive value, negative predictive value and diagnostic accuracy when applied to the validation cohort. Thus, FSH-iB can be considered as a novel and promising marker for prediction of pubertal onset, but requires further studies before labeling it as the gold standard.

Systematic cranial MRI in girls with central precocious puberty *(J Clin Endocrinol Metab. 2021;106:e2557-66)*

The necessity of performing magnetic resonance imaging (MRI) in girls with central precocious puberty (CPP), aged 6-

8 years has always been considered debatable. This study was done on 770 Turkish girls with CPP to investigate the frequency of central nervous system (CNS) lesions and their potential predictors. In 654 out of 770 girls, pubertal onset occurred between 6 to 8 years; 104 (13.5%) girls had an abnormality on brain MRI. Out of these, only 2 (0.25%) girls had neoplastic lesions (1 low grade glioma and 1 meningioma), but they did not require any intervention on follow up. Pubertal onset age <6 years and leutinizing hormone/follicle-stimulating hormone (LH/FSH) ratio >0.6 were associated significantly with CNS lesions. However, both girls with neoplastic lesions were >6 years old, thus making the predictive power of age and LH/FSH ratio weak. The authors concluded that systematic MRI is an efficient approach to diagnose an occult CNS lesion in girls with CPP, but that the likelihood of finding a lesion requiring intervention remains low.

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