Title: Clinical features of acromegaly/pituitary gigantism (A/G) due to ectopic GHRH-producing tumor (eGHRH) and its epidemiology in East Asia 2019 Update.

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[Background] eGHRH is a rare cause of A/G. Unlike normal pituitary adenoma, A/GHRH is ectopically overproduced from extracranial neuroendocrine tumors (etc., NET), and proliferation of pituitary GH producing cells (hyperplasia-rarely adenoma) and GH excess. It leads to A/G as a clinical picture. An accurate diagnosis is essential because the treatment is different from pituitary A/G, but it is sometimes difficult because it is a rare disease.

[Purpose] To clarify the latest (2019) clinical picture and epidemiology, we investigated cases of eGHRHa and its regional differences in onset of A/G by eGHRH (eGHRHa) reported in both Japan and East Asia (China, Taiwan, Korea).

[Subjects / Methods] Reports of extracranial eGHRHa in Japan and East Asia in the past 30 years (1989-2018). Japanese A/G registry was 1604 cases of Japanese brain tumor statistics during1984-1996. eGHRHa were reported by the Japanese Endocrine Society or the Japan Pituitary Tumor Society from 1989 to 2018, and by the Pituitary Expert Meeting in Asia (PEMA, 2012-2018). Diagnosis was based on the previously reported a human GHRH ultrasensitive assay (Katakami et al, Endocrine J 45:S67-S70, 1998), GHRH immunohistochemistry (Katakami et al, JCI 77:1704-1711, 1986) or qPCR.

[Results] There were 14 cases of eGHRHa reported in Japan by 2018. The prevalence of eGHRHa in A/G was 3/1604 cases (0.2%) during 1984-1996. They were 8 males and 6 females, age 31-70 y-o. Basal levels of GH, IGF-1, and GHRH were 1.0~183ng/mL (CNT: 0.05~2.0ng/mL), 290~1400ng/mL (>+2SD vs. age- & sex-matched CNT), and 300~8,969pg/mL (CNT: 4.0~14.0pg/mL), respectively. One case in China (a 41 y-o white male living in Hong Kong, Cheung et al). The etiology of most cases in Japan was neuroendocrine tumor/carcinoma of the gastroenteropancreas (GEP-NET/NEC: 10 cases, plus. NEC of cholangiocarcinoma: 1): 11 cases (79%, MEN 1: 5 cases), lung NET (bronchial carcinoma): 1, thymoma (MEN 1): 1 and pheochromocytoma: 1. Cases of MEN 1 were 6 in total (43%). One case from China, Hong-Kong, was due to lung NET. Clinical signs, symptoms and endocrinological data of patients with eGHRHa were indistinguishable from those of patients with pituitary GH-producing adenomas. After successful removal of eGHRH-producing tumors, swollen pituitaries became normalized in size within a few weeks.

[Discussion] The prevalence of eGHRHa in East Asia is low as compared to that in Japan probably due to deficiency of GHRH measurement and low awareness of eGHRHa among endocrinologists. In addition to this society, it is necessary to raise awareness of the disease not only at the endocrine society of each Asian county but also at the gastroenterological Society.

[Conclusion] 1. In every patient with A/G who is complicated with extra-pituitary tumors (NET/NEC in MEN 1), eGHRHa must be suspected. 2. For atypical A/G, we ask for measurement of blood GHRH concentration. 3. Regional differences in eGHRHa prevalence could be related to eGHRHa awareness.