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X-linked acrogigantism syndrome

Akrogigantyzm sprzężony z chromosomem X

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Summary

X-linked acrogigantism (X-LAG) is a recently identified clinical syndrome of GH excess with early-onset of gigantism, typically in the first few months of life. X-LAG is more often diagnosed in females. This disorder results from the germline or somatic duplication of the *GPR101* gene located on chromosome Xq26.3 which encodes a G-protein coupled receptor. Clinical features include early onset and marked overgrowth. Besides the excess of GH and IGF-1, most patients present concomitant increased prolactin levels without galactorrhoea. Interestingly, around half of the patients demonstrate fasting hyperinsulinemia and 20% present acanthosis nigricans, but no diabetes mellitus. Radiological (MRI) evaluation reveals pituitary tumor or general enlargement of pituitary. Histopathological studies showed pituitary hyperplasia or pituitary adenoma with or without associated hyperplasia. Patients with X-LAG syndrome require multi-modal treatment. Data from literature concerning X-LAG syndrome suggests the highest effectiveness of combined treatment that includes neurosurgery and pharmacotherapy with somatostatin analogues, dopamine agonists (cabergoline) and pegvisomant.

Streszczenie

Akrogigantyzm sprzężony z chromosomem X jest niedawno opisaną formą gigantyzmu przysadkowego wynikającego z nadmiernego wydzielaniem GH i IGF-1. Klinicznie charakteryzuje się nie tylko wczesnym początkiem wystąpienia objawów – zwykle już w pierwszych miesiącach życia, ale także znacznym nadmiarem wzrostu. Ta forma gigantyzmu występuje częściej u płci żeńskiej i jest spowodowana mutacją zarodkową lub somatyczną polegającą na duplikacji genu *GPR101* zlokalizowanego na chromosomie Xq26.3, kodującego receptor związany z białkiem G. Poza podwyższonymi stężeniami GH i IGF-1 u większości pacjentów występują hiperprolaktynemia, ale bez obecności mlekotoku. U połowy pacjentów stwierdza się hiperinsulinemię na czczo, a u około 20% cechy acanthosis nigricans. Nie obserwowano dotychczas występowania cukrzycy. Badanie MR najczęściej pozwala uwidocznić gruczolak przysadki lub też uogólnione powiększenie gruczołu bez separującej się zmiany ogniskowej. Badanie histopatologiczne ujawnia izolowany rozrost komórek przysadki lub też gruczolak przysadki powstały na podłożu rozrostu. Pacjenci z akrogigantyzmem sprzężonym z chromosomem X wymagają zwykle wieloetapowego i skomplikowanego postępowania terapeutycznego. Dane z piśmiennictwa wskazują na najwyższą skuteczność leczenia obejmującego operację neurochirurgiczną i farmakoterapię z zastosowaniem analogów somatostatyny, agonistów dopaminy (kabergoliny) oraz pegvisomantu.

Conflict of interest
Konflikt interesów
None
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INTRODUCTION

Gigantism and acromegaly are rare diseases caused by growth hormone (GH) excess. In the majority of cases the overproduction of growth hormone is related to pituitary lesion. Increased amount of GH induces enhanced synthesis of IGF-1 in the liver. Persistent exposition to elevated GH and IGF-1 concentration has serious consequences including changes in external appearance, disfigurement of the internal organs and disability. Moreover, if an excess of GH occurs in childhood before the complete fusion of cartilages, growth velocity is progressively accelerated leading to pathological tall stature. Undiagnosed and untreated GH excess results in shortening of life expectancy, increased risk of developing neoplasm of different kind and reduced quality of life.

The patient with excessively rapid growth velocity as referred to age standards or tall stature exceeding

normal range must be diagnosed with maximum accuracy to avoid misleading diagnosis. It should be put into account that growth velocity and stature result from complex processes involving genetic and environmental factors. Although tall stature may be a normal feature of individual, all pathological causes should be excluded.

Amongst genetic abnormalities found in patients with tall stature there are chromosomal causes (Klinefelter syndrome), gene mutations not connected with GH excess (e.g. Marfan syndrome) and those mutations resulting in increased GH secretion due to pituitary tumour or pituitary hyperplasia (1).

In recent years an extensive research was conducted to identify genetic factors associated with pituitary dysfunction with abnormal activity of GH axis. According to the current knowledge, predisposition to somatotroph adenomas or hyperplasia leading to acromegaly or gigantism may be connected with mutations in genes such as *GNAS* (Guanine Nucleotide Binding Protein Alpha Subunit), *PRKAR1A* (Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha) and *AIP* (aryl hydrocarbon receptor-interacting protein) (1). Also gigantism or acromegaly may occur in multiple endocrine neoplasia type 1 and 4, as well as in syndromes characterized by defects in succinate dehydrogenase genes (*SDHx*) (2, 3). In 2014, a novel mutation was described by Trivellin et al. In details, these authors found Xq26.3 genomic duplication in a group of patients with early-onset gigantism resulting from an excess of growth hormone. They also reported that only one of the genes in this particular genomic region, *GPR101*, which encodes a G-protein–coupled receptor, was overexpressed in patients' pituitary lesions. This research team identified also a recurrent *GPR101* mutation in patients with acromegaly, with the mutation found mostly in tumors. The new syndrome was termed X-linked acrogigantism (X-LAG) (4).

This review focuses on the genetic aspects of X-LAG syndrome, as well as on the clinical features of this disease, therapeutic options and treatment outcome.

Genetic features of X-linked acrogigantism

Genetic studies revealed that X-LAG is caused by microduplication at chromosome Xq26.3. This mutation was described for the first time by the group of Trivellin and confirmed in further reports (1-6). Microduplication at Xq26.3 affects an area of 500 Kb containing 4 genes. Although 4 genes are involved, only one, *GPR101*, is thought to be associated with X-LAG. *GPR101* gene encodes an orphan G protein-coupled receptor (GPCR). *GPR101* in humans is expressed in equivalent amount in the hypothalamus and the pituitary gland. The endogenous ligand for *GPR101* is not known. Furthermore, studies performed *in silico* indicate that *GPR101* is likely coupled to Gs (5). However, the exact function of *GPR101* is still unknown. Interestingly, pituitary samples from patients carrying the microduplication of *GPR101* gene were characterized by increased GHRH receptor expression as compared to both sporadic somatotropinomas and normal pituitaries (1). Besides, a microduplication of *GPR101* gene, a missense mutation has been revealed in some acromegaly cases. This mutation was found mostly in tumours (5).

Previous analyses of X-LAG cases revealed that duplication of *GPR101* gene may result from germline or somatic mutation. Very recently, a somatic mosaicism was described (6, 7). Thus, it should be highlighted that a negative genetic test for Xq26.3 microduplication or *GPR101* duplication on peripheral blood DNA does not exclude the diagnosis of XLAG (6, 7). Interestingly, females were found to have germline mutations and the sporadic male patients reported so far were somatic mosaics with variable levels of mosaicism (8). However, no differences in the clinical phenotype were observed between patients with germline or somatic duplication (8).

Clinical and biochemical characteristics

X-LAG syndrome, which is characterized by a particularly early age at onset, can present sporadically or as FIPA (familial isolated pituitary adenoma). Although most patients affected by pituitary gigantism are males (78%), the X-LAG patients are predominantly females (1, 4, 5, 9). Patients are usually born at full-term from uncomplicated pregnancies with the birth weight, length and head circumference within normal range (4, 9). In the international cohort of 18 X-LAG patients the overall median age at the onset of rapid growth was 12 months ranging from 2 to 48 months. The median age of diagnosis was 41 months ranging from 14 to 264 months (9). The onset of symptoms in X-LAG patients is significantly earlier comparing to giant patients with *AIP* positive mutation or with negative genetic tests. Among patients with pituitary gigantism who did not carry a Xq26.3 microduplication, none presented symptoms before the age of 5 years (4). At diagnosis not only median height SDS score is increased (+ 3.9) but also median weight score is similarly increased (4, 5, 9). The most frequent complaints at diagnosis, apart from abnormally increased growth in all patients, include typically acromegalic features such as acral enlargement, coarsened facial features and enlarged head circumference (1, 4). An unique feature that is not typical of other forms of gigantism is a preceding history of increased appetite or food seeking behaviors in some patients (9). Neurological symptoms such as headache, visual field defects or seizure have not been reported. Around half of the patients demonstrated fasting hyperinsulinemia and 20% presented acanthosis nigricans, but no patient had diabetes mellitus at the time of diagnosis or during follow-up (9). Basal GH levels at diagnosis were increased in all patients. Oral glucose tolerance test showed unsuppressed GH concentration in all patients and paradoxical increase of GH levels after glucose load in some of the patients (5, 9). IGF-1 levels are also markedly elevated at diagnosis with the median fold increase above the ULN 3.4 in one study (9) and 2.9 in another international study (5). X-LAG is also

characterized by increased prolactin levels in majority of cases but no patient presented galactorrhoea so far (4, 5, 9). Overall, in X-LAG patients GH and IGF-1 levels at diagnosis are significantly higher comparing to *AIP* positive patients or with negative genetic studies. Similarly, the higher prevalence of hyperprolactinaemia occurs in these individuals. In recently published study, Daly and colleagues reported that female patient with sporadic X-LAG syndrome demonstrated consistently elevated circulating GHRH levels throughout preoperative testing, which was accompanied by marked GH and prolactin hypersecretion. In addition, GH showed a paradoxical increase following TRH administration. *In vitro* study, the pituitary cells dissected of this patient showed baseline GH and prolactin release that was further stimulated by GHRH administration (10). These findings may indicate hypothalamic dysregulation of GHRH secretion in X-LAG cases.

Tumor characteristics

All X-LAG patients had pituitary abnormality at diagnosis, of which the most prevalent was macroadenoma on MRI (75%), while the remaining had a diffuse pituitary enlargement without identifiable adenoma, suggesting pituitary hyperplasia. All adenomas showed suprasellar extension to the optic chiasm, whereas invasion of the cavernous sinus was not frequent. This feature is distinct from somatotropinomas found in patients with *AIP* positive mutation. The median maximum tumour diameter was 18 mm in two large studies (5, 9).

Pathological assessment revealed pituitary adenomas in majority of operated cases. Pituitary adenoma accompanied by generalized hyperplasia or global hyperplasia alone were less frequent findings (9). The features of the X-LAG-related adenomas were remarkably similar with predominantly sinusoidal, lobular and acinar rather than diffuse architecture (5). Immunohistochemistry of the resected tissues were usually positive for both GH and PRL and represented mixed GH-PRL secreting pituitary adenomas which contain both densely and sparsely granulated somatotroph cells (9). Proliferation rate was rather low with Ki-67 labelling index lower than 3% in all tumors (5).

Management and outcomes

Management of the X-LAG patients is challenging. In the majority of cases the applied treatment was multimodal and the median number of treatments per patients was 3.5 (5). In the largest cohort of X-LAG patients (n = 18) all but one underwent neurosurgery, in only 3 cases immediate GH/PRL control was achieved postoperatively. However, preoperatively pituitary deficiency was not present in any of the X-LAG cases. The control of excessive growth with neurosurgery or radiotherapy was usually accompanied by hypopituitarism (5, 9). In patients who received pharmacological therapy (somatostatin analogues and/or dopamine agonists) as the primary treatment none achieved control of either GH/IGF-1 or PRL secretion despite the use of doses normally used in adults. Postoperatively further use of somatostatin analogues and/or dopamine agonists did not lead to control of GH/IGF-1 excess. Only GH receptor antagonist-pegvisomant was effective in normalizing IGF-1 concentrations and excessive growth in previously operated patients without tumour expansion on therapy (5, 9). Somatostatin analogues use was associated with the median reduction in GH and IGF-1 levels of 37.5 and 15.2%, respectively, whether used as primary or secondary therapy but in no case was the reduction sufficient to bring patients under hormonal control (9).

Longer observation of patients with X-LAG syndrome suggests the highest effectiveness of combined treatment that includes neurosurgery and pharmacotherapy with somatostatin analogues, cabergoline and pegvisomant (7).

CONCLUSIONS

X-LAG results from genetic mutation that includes germline or somatic duplication of *GPR101*. The patients with XLAG syndrome present typical phenotype and tests results. Those individuals require multi-modal treatment.

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