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Case Report

Case Report: Hypoinsulinaemic Hypoketotic Hypoglycaemia Due to an Activating Variant in AKT2

Sayol-Torres et al. AKT2 Activating Variant and Hypoketotic Hypoinsulinaemic Hypoglycaemia

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What is already known on this topic?
AKT2 gene activating variants are a very rare genetic disorder that causes hypoinsulinaemic hypoketotic hypoglycaemia. The same genetic change presented in this case report has only been previously described in 9 patients in the literature, all presenting a similar phenotype: severe persistent hypoketotic, hypofattyacidemic, hypoinsulinemic related with fasting hypoglycaemia, hemihypertrophy and obesity; associated to postnatal overgrowth and in some cases, with prenatal overgrowth.

What this study adds?
Most of the patients on the literature were diagnosed of hypoglycaemia and started consequent treatment and follow-up in the early infancy (<1 year old). Herein we present a patient diagnosed during adolescence.
As part of the initial study and diagnosis, this patient underwent continuous glucose monitoring, and the results are reported.

Abstract
AKT2 is a serine/threonine kinase that plays a key role in regulating insulin signalling. The gain-of-function alteration in the AKT2 gene (c.49G>A, p.Glu17Lys) has been described in 9 patients with clinical findings consisting in severe persistent hypoketotic, hypofattyacidaemic, hypoinsulinaemic fasting hypoglycaemia, hemihypertrophy and obesity.
A new patient with the same activating AKT2 alteration leading to autonomous activation of the insulin signalling pathway and dysmorphic features is reported. Moreover, to our knowledge, this is the first report using continuous glucose monitoring (CGM) for diagnoses and follow-up in this condition. 12-year-old boy who started follow-up by neuropaediatric clinic for long-term history of seizures started at 8 months old, having been diagnosed with epilepsy in his country of origin. Physical examination revealed proptosis and abnormal fat distribution with lipomastia. Intellectual disability was confirmed. Due to the phenotype and the intellectual impairment, a whole-exome sequencing was done identifying a heterozygous missense variant in AKT2 (NM 001626:c.49G>A:p.(Glu17Lys). With this finding, CGM was started revealing severe hypoglycaemia below 40 mg/dl (2.2 mmol/L) with dawn predominance, coinciding with nocturnal focal seizures. To achieve euglycaemia, a high carbohydrate intake (milk with cereals and cocoa powder) with short fasting periods (maximum 3-4 hours) was indicated, with an improvement of hypoglycaemia episodes and resolution of symptomatic seizures. This report reinforces the phenotypic variability of gain-of-function change in AKT2 as our patient exhibits symmetric overgrowth. The reported patient was diagnosed later than those previously reported, already displaying abnormal fat distribution suggesting a dependence on genetic alteration rather than caloric excess. Responding favourably to reduced fasting time, our patient's management has been aided by continuous glucose monitoring (CGM), proving useful for both diagnosis and follow-up.
Keywords: AKT2, Hypoinsulinaemic Hypoglycaemia, hypoketot, p.Glu17Lys

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Introduction
Hyperinsulinaemic hypoglycaemia (HH) is an important cause of persistent and severe hypoglycaemia (1), characteristically hypoketotic and hypofattyacidaemic with normally normal or elevated serum insulin levels (2). A rare condition with similar clinical and biochemical presentation, except for undetectable serum insulin/C-peptide levels, has been described associated with autonomous activation of the downstream insulin signalling pathway, occurring independently of the insulin ligand. The underlying cause is attributed to a specific activating variant in the *AKT2* gene (3, 4).
The *AKT2* gene is located in 19q13.2. It encodes Akt2 protein that belongs to a subfamily of serine/threonine kinases containing Src Homology 2 (SH2)-like domains (5, 6). Akt2 plays a critical role in transducing insulin stimulation into metabolic responses and its activation normally depends on the stimulation of the insulin receptor requiring phosphatidylinositol-3,4,5-trisphosphate (PIP3) for its recruitment to the plasma membrane. The overexpression of p.Glu17Lys activating variants relaxes this requirement, permitting the binding to phospholipid phosphatidylinositol-4,5- bisphosphate (PIP2) and riding to a non-insulin-dependent membrane localization of the GLUT4 glucose transporter (5, 7) (shown in Fig.1). Additionally, an activating *AKT2* mutation may enhance mTOR signaling, leading to neuronal hyperexcitability and synaptic plasticity impairments, which are mechanistically linked to epileptogenesis through dysregulated mTORC1/2 activity and downstream effects on cortical/hippocampal circuit function (8, 9).
To date, only nine patients (3, 4, 7, 10, 11, 12) with hypoinsulinaemic hypoketotic hypoglycaemia associated with the activating p.Glu17Lys change in *AKT2* have been described. All of them additionally presented the characteristic facial phenotype, abnormal fat distribution and overgrowth. Herein, we present another case with the same phenotype and the same activating *AKT2* variant (c.49G>A; p.Glu17Lys), providing additional insight into the phenotypic spectrum. Moreover, to our knowledge, this is the first report to use Continuous Glucose Monitoring (CGM) to confirm diagnosis and monitor treatment efficacy.
Case Report

The proband is a 12-year-old boy who starts follow-up by neuropaediatrics for an early onset epilepsy and intellectual disability, previously assessed in his country of origin.

He was born at 34 weeks after an uneventful pregnancy from nonconsanguineous Colombian parents. Delivery was induced due to maternal preeclampsia. Prenatal overgrowth was observed (weight 3.4 kg (+4.01 SDS), length 50 cm (+2.86 SDS)).

Past medical history was consistent with mild global developmental delay and epilepsy under treatment with valproic acid. His parents reported frequent events of uncertain nature since infancy, including episodes of arrested activity and cyanosis, bilateral tonic clonic seizures (BTCS) and nocturnal apnoeas. Previous CT scan and EEGs were reported as normal. On first examination at the Paediatric Neurology clinic at the age of 12 years, he showed remarkable dysmorphic features including hypertelorism, prominent bilateral exophthalmos with puffy eyelids, gynecomastia and an abnormal fat distribution consistent with symmetric lipodystrophy. EEG showed bitemporal epileptiform activity. Brain MRI showed fatty infiltration of ocular muscles but was otherwise normal. Whole Exome Sequencing (WES) revealed a *de novo* c.49G>A; p.Glu17Lys variant in the *AKT2* gene.

Following the genetic findings, he was remitted to the Paediatric Endocrinology outpatient clinic at the age of 12. At our evaluation he weighed 67.5 kg (+2.27 SDS, *Millennials' Growth, 1995-2017*), with a height of 166.9 cm (+1.1 SDS, *Millennials' Growth, 1995-2017*) and BMI of 24.2 kg/m^2 (+1.91 SDS, *Millennials' Growth, 1995-2017*), with normal corporal sections and with Tanner Stage 2 and testicular volume of 5/6 cc. He presented important bilateral lipomastia (no glandular tissue identified by echography) with an alteration of the body fat distribution with facial and thoracoabdominal predominance (Fig.2). A blood test with lipidic, thyroidal and pituitary hormonal axis was assessed with normal results. Despite the family denying any history of hypoglycaemia during his development, after reviewing the battery of tests conducted upon his arrival in our country a fasting glucose of 57 mg/dL (3.1 mmol/L) with undetectable insulin levels (<0.5 mU/L) was reported. According to the genetic findings and suspecting that the patient might be experiencing hypoglycaemia, it was decided to monitor glucose levels through continuous glucose monitoring sensor (*FreeStyle2 Abbott* and *DexcomG6*). Its analyses revealed severe hypoglycaemia episodes below 40 mg/dL (2.2 mmol/L) with dawn predominance and coinciding with nocturnal seizures, systematically confirmed through fingerstick tests. High carbohydrate intake (milk with cereals and cocoa powder) with short fasting periods (maximum 3-4 hours) was then indicated, with an improvement of hypoglycaemia episodes and resolution of symptomatic seizures (shown in Fig.3).

The patient is currently 13 years and 5 months old and has gained abdominal fat since first evaluation (weight 75 kg (+3.18 SDS), with a height of 175 cm (+2.12 SDS) and BMI of 24.5 kg/m^2 (+1.82 SDS). He still presents some seizures with normal sensor and capillary glucose; therefore, he remains under treatment with antiepileptic drugs (eslicarbazepine acetate and lacosamide). Brain magnetic resonance imaging did not reveal lesions consistent with previous episodes of severe hypoglycaemia. Dawn hypoglycaemia is well-controlled on his current nutritional regime (nocturnal milkshakes with cereal, sugar and cocoa). However, he still presents low blood glucose levels if not following a regular meal schedule.

Discussion

Hypoinsulinaemic hypoketotic hypoglycemia is a very rare condition characterized by an increased glucose consumption without hyperinsulinism. This disorder has mainly been reported in literature in cases with *AKT2* activating variant and rarely in cases with *PTEN* activating variant (13). It is known that PTEN–PI3K–AKT–mTOR pathway has a central role in the regulation of glucose metabolism, with downstream effects on the insulin receptor (14).

Hypoinsulinaemic hypoketotic hypoglycaemia due to genetic activation of Akt2 (*AKT2* c.49G>A variant) has only been reported in 9 patients to date (3, 4, 7, 10, 11, 12). Dysmorphic features, abnormal fat distribution and variable neurological manifestations are inconsistently mentioned but precise clinical descriptions are lacking. Almost all patients shared the following clinical features: severe persistent hypoketotic, hypofattyacidaemic, hypoinsulinaemic related with fasting hypoglycaemia, hemihypertrophy and obesity. Some of the patients also presented postnatal overgrowth with inconsistent prenatal overgrowth. Hemihypertrophy has been described among several of the reported patients; some literature has linked it to the presence of mosaicism (11). Our patient presented an abnormal fat distribution consistent with symmetrical lipodystrophy, without hemihypertrophy. His body sections were normal and symmetrical, with facial and thoracoabdominal fat leading to lipomastia, fatty liver and bilateral ptosis with proptosis due to ocular muscles fat infiltration; in keeping with the dysmorphic features previously described in some patients with the *AKT2* c.49G>A variant. These findings are summarised and compared to previous reports in Table 1.

The report of obesity in patients with the *AKT2* c.49G>A variant has been proposed to support an important role of Akt2 in adipocyte development (15). In addition, murine studies have suggested that Akt2 plays a critical role in the expansion of visceral adipose tissue upon exposure to a high-fat diet. However, the evidence that Akt2 activation is necessary for adipose tissue expansion does not necessarily explain the abnormal fat distribution in these patients because, as a major confounder, the need to avoid prolonged fasting leads these patients to a chronic caloric excess (5). Nevertheless, our patient already had central obesity and abnormal fat distribution, despite not avoiding prolonged fasting, as he had not yet been diagnosed with recurrent hypoglycaemia.

MORFAN syndrome (16) is an acronym for Mental retardation, pre- and post-natal Overgrowth, Remarkable Face, and Acanthosis Nigricans). It was first described as a syndrome of unknown etiology (17), but some years later was also included within the phenotypic spectrum of the *AKT2* activating variants (7). Our patient could only partially fit under the label of MORFAN because of the absence of acanthosis nigricans, although he does meet the rest of the clinical features. It seems likely that *AKT2* disease causes a broad and variable phenotype with hypoinsulinaemic hypoglycaemia, dysmorphic features, lipodystrophy, and some degree of neurodevelopmental disorder as cardinal symptoms in addition to other variable features.

Neurological features are also scantly reported. When mentioned, almost all patients have some degree of developmental delay (ranging from mild to moderate) and/or intellectual disability. Symptomatic seizures secondary to hypoglycaemia are a frequent initial presentation, although further epilepsy is not reported. Our patient is still suffering temporal lobe seizures despite being normoglycaemic and no evidence of structural brain lesions was observed on the MRI. Akt is one of the most important downstream effectors of phosphatidylinositol 3-kinase/mTOR pathway. Hyperactivation and expression of this pathway are seen in a variety of neurological disorders including human temporal lobe epilepsy with hippocampal sclerosis (TLE-HS) (18). Whether the neurological dysfunction is attributable to recurrent hypoglycaemia and/or mTOR pathway dysfunction itself is a question that remains to be answered.

Hypoglycaemia due to *AKT2* variant does not respond to diazoxide nor to somatostatin analogues; it can only be managed with a regular carbohydrate diet. *M.F Ochoa Molina et al* (10) showed no advantages between regular uncooked cornstarch (UCCS) versus waxy maize heat-modified starch (WMHMS; Glycosade). On the other hand, *Minic et al* (5) described a 17-years old proband with p.Glu17Lys variant that remained euglycaemic with a physiologically appropriate increase in free fatty acids during a fasting overnight test. Although this could suggest that hypoglycaemia driven by the *AKT2* p.Glu17Lys change may not be lifelong, it may be life-threatening. Therefore, new lines of treatment should be investigated. Some groups (12, 13) have started assessing the treatment with Sirolimus (mTOR inhibitor) in patients with hypoinsulinaemic hypoglycaemia, with apparent good results. Sirolimus may be a life-saving therapeutic option for some of these rare diseases caused by increased activation of insulin signalling with scant response to frequent feeding or difficulties on its implementation, although severe adverse events related to mTOR inhibitors should be considered (19, 20).

For now, our patient presented a good response to nutritional treatment with high carbohydrate intake at 3-4 am (milk with cereals and cocoa powder) and with short fasting periods (maximum 3-4 hours), showing an improvement of hypoglycaemia episodes and resolution of seizures associated to them. However, he is still suffering focal refractory epilepsy of unknown etiology.
CGM is not yet a validated tool for managing hypoglycaemia of metabolic origin, such as that caused by inborn errors of metabolism or enzymatic deficiencies, where glucose patterns and clinical interventions differ significantly (21). However, in the more recent years, the accuracy and precision of CGM devices particularly in the low blood glucose ranges have been gradually improved. Consequently, CGM devices have been used for diagnosis and follow-up in other disorders of glucose homeostasis that are associated with hypoglycaemias (22). One limitation of this report is that CGM values pre and post nutritional intervention were not obtained with the same type of device. *FreeStyle2 Abbott* may have overdiagnosed nocturnal hypoglycaemia, although fasting glucose levels were confirmed by capillary blood measurement.

Conclusion

The tenth individual presenting with hypoketotic hypoglycaemia secondary to an *AKT2* activating variant that causes autonomous activation of the downstream insulin signalling cascade is reported. This patient's dysmorphic features and developmental delay meet those of the previously described patients, and although hemihypertrophy is not present in our subject he presents remarkable lipodystrophy, providing additional evidence of a broad phenotypic spectrum.
Due to the life-threatening condition, safe and tolerable options of monitoring are needed. The use of CGM sensors was not previously reported in the literature and has been shown to be effective in supporting the diagnosis and describing the pattern of hypoglycaemia, as well as monitoring the response to treatment.

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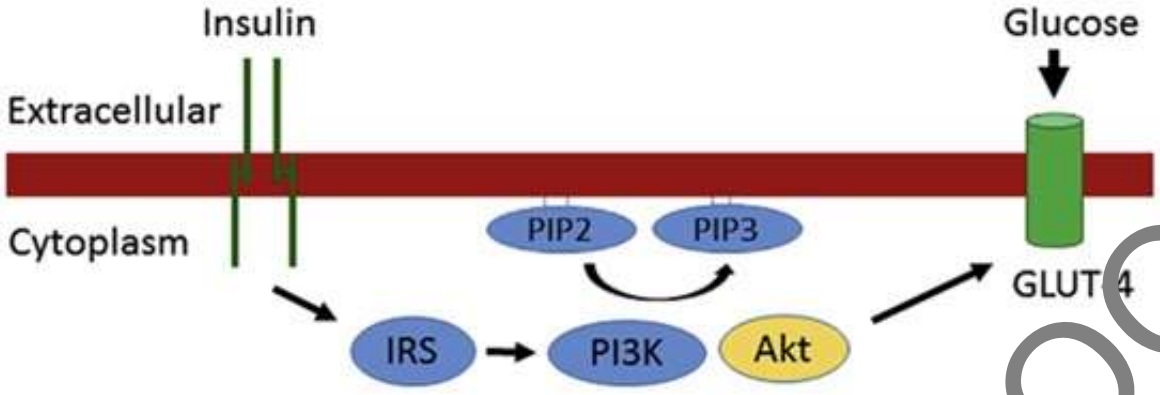

Figure 1. *Garg et al* (7) illustration. Role of AKT2 in glucose homeostasis in muscle and adipose tissue. In the insulin-sensitive tissues, the binding of insulin to the receptor results in autophosphorylation and subsequent activation of the receptor's intrinsic tyrosine kinase activity. It then phosphorylates insulin-receptor substrate (IRS) proteins, which recruit phosphatidylinositol-3-kinase (PI3K). PI3K catalyzes the formation of phosphatidylinositol (3,4,5)P3 on the plasma membrane, which acts as a docking site for AKT2. AKT2 is phosphorylated by PDK-1 and mTORC2; thereby, activating AKT2's kinase activity on a number of downstream targets. This eventually leads to exocytosis of the GLUT4 storage vesicle and fusion with the plasma membrane

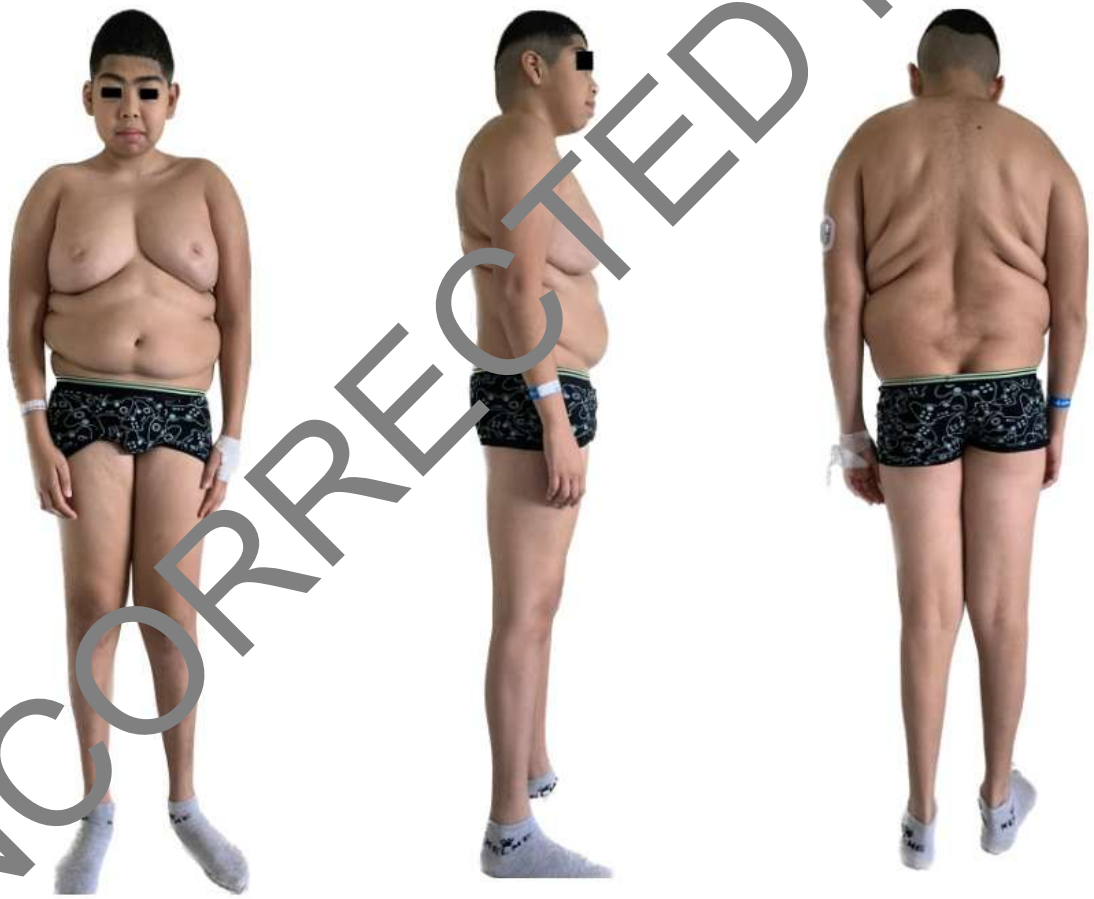

Figure 2. Clinical photographs of the proband showing abnormal fat distribution. Consent for publishing was obtained.

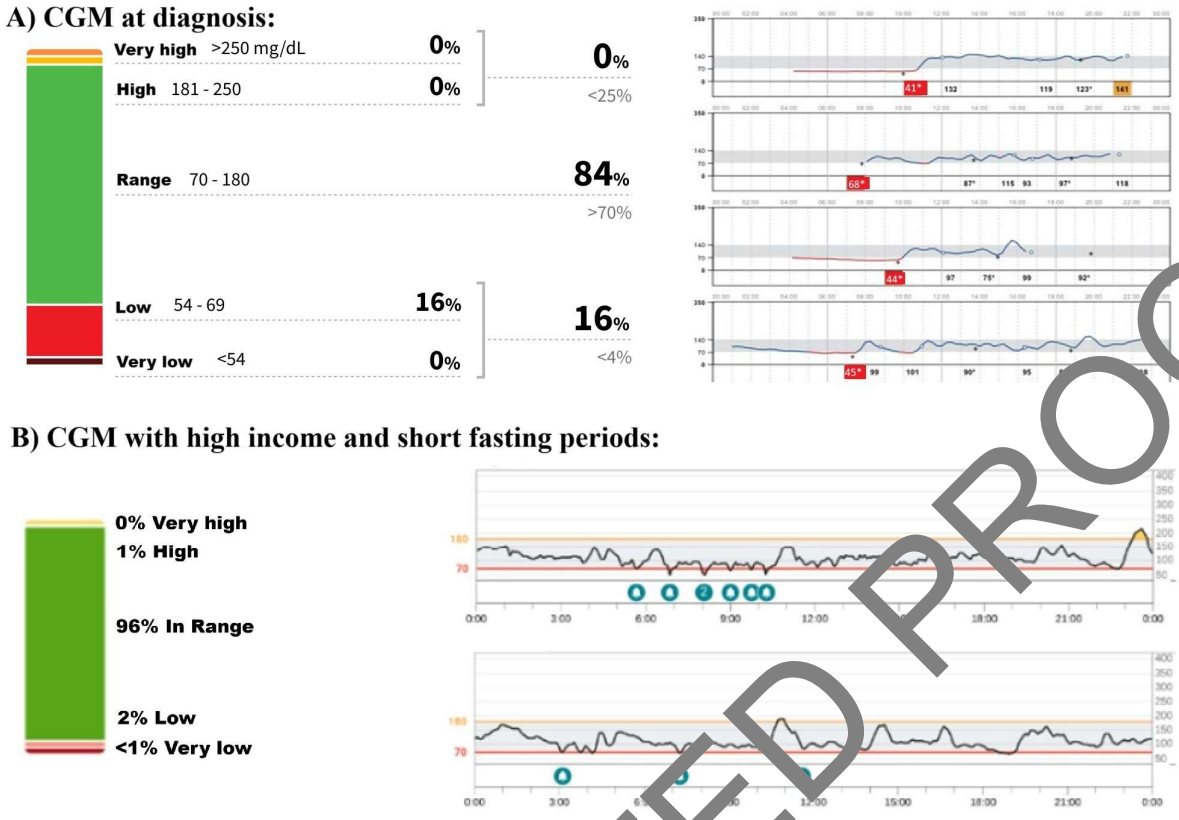

Figure 3. Continuous Glucose Monitoring before and after starting dietetic treatment.

Table 1. Summary of the clinical features of individuals described with hypoinsulinaemic hypoketotic hypoglycaemia due to c. 49G>A *AKT2* change.

Clinical features	***Our patient***	***Hussain et al.***			***Garg et al.***	***Arya et al.***	***Dushar et al.***		***Ochoa Molina et al.***	***Parker et al.***
Gender	M	M		F	F	F	M	M	M	F
Age at diagnoses (yo)	12	3	0.5	0.5	0.5	0.4	14	1.5	0.5	0.5
Ethnicity	Amerindian	Caucasian			Turkic	Caucasian	Caucasian			Caucasian
Hypoglycaemic seizures	X			X			X	X	X	X
Development delay/Intellectual impairment	X				X		X	X	X	X
Prenatal overgrowth	X	X	X	X	X	X	X	X		X
Postnatal Overgrowth	X	X			X	X			X	
Dysmorphic features	X Abnormal fat distribution Proptosis Puffy eyelid	X	X Left facial overgrowth	X Left facial overgrowth	X Proptosis		X	X	X Proptosis	X Proptosis Periorbital edema Left facial overgrowth
Acanthosis nigricans					X		X			
Hemihypertrophy		X		X		X	X	X		X
X: present, Blank: no present/not reported										