Association of Tuberous sclerosis complex (TSC) and Insulinoma in a pediatric patient

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INTRODUCTION Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by a loss-of-function mutation in tumor suppressor genes:TSC1/TSC2 which encode hamartin and tuberin. The complex of hamartin-tuberin is a negative regulator in the mammalian target of rapamycin complex 1 (mTOR) signal transduction pathway which is implicated in cell proliferation. A constitutive activation of mTORC1 pathway in TSC lead to unregulated cellular growth and proliferation. Major clinical features includes cardiac rhabdomyomas, epilepsy, cortical tubers, subependymal nodules and cerebral dysplasia. Others manifestation include hypomelanotic macules, facial angiofibromas, renal cysts and angiomyolipoma.

Neuroendocrine tumors (NETs) are not considered a feature of TSC. Current guidelines do not recommend routinely screening for this tumors. However there are case reports of different NETs in patients with TSC such us pituitary adenomas, parathyroid tumors, gastrinoma, phaeochromocytoma, pancreatic islet cell neoplasm and insulinoma, the latter only six cases reported in adult population on our knowledge.

A pathogenic relationship between TSC1/TSC2 mutations and insulinoma had been proposed based on the observation of development of insulinoma a lower age in TSC compared to sporadic cases, the finding of hypoglycemia and hyperinsulinemia and pancreatic β-cell hypertrophy in mice with deletion of the TSC2 gene, and in the observation of higher levels of activated mTOR and its downsteam products in insulinoma cells.

The mTORC1 inhibitors such as everolimus had demonstrated prolonged tumor control in pancreatic tumors, and sirolimus has enabled better control in congenital hyperinsulinism.

Childhood insulinoma is rare, occurring either in isolation or in association with MEN1. Diagnosis of insulinoma is based on detectable plasma insulin level during hypoglycemia and located by MRI scan or (18-F-DOPA)PET-CT.

OBJECTIVE: To present a patient with diagnosis of TSC who developed an insulinoma

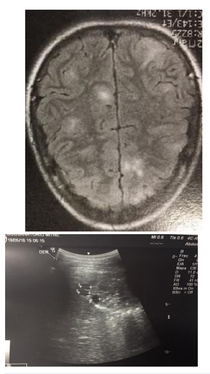
CASE REPORT

An adolescent girl is with a personal history of TSC was admitted for study of hypoglycemia detected in the frame of studies performed because of multiple episodes of confusion with slurred speech upon awakening after prolonged sleeps in weekend during the 7 months prior to the evaluation

She was born at term, with normal weight/length after a pregnancy with an incidental finding of cardiac rhabdomyomas, without other complication. At birth cardiac tumors were confirmed by ultrasound and cardiac MRI. Multiple renal cysts were detected during US evaluation. At one-year-old presented absence epilepsy, cerebral MRI showed abnormalities consistent with cerebral tubers. Learning was normal.

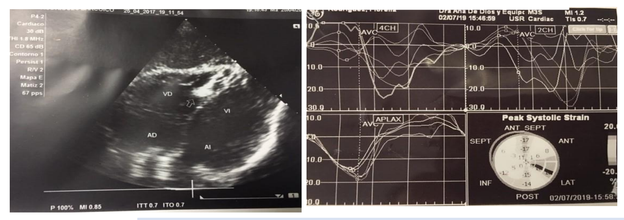
Although the electroencephalograph was normal, changes in anti-epilepsy pharmacotherapy were made in an attempt to resolve these episodes.

Cerebral tubers

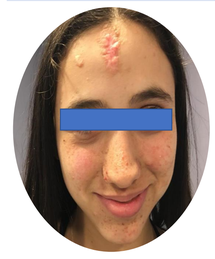


Renal cysts (US)

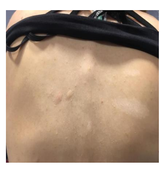
Rhabdomyomas 3 cm right ventricule



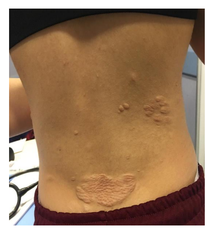
Heart Strain: ultrasound technique related to speckle tracking bidimensional (2DSTD) showing right ventricular dysfunction



Fibrous cephalic plaque
Nose:Facial angiofibromas



Hipopigmented macules



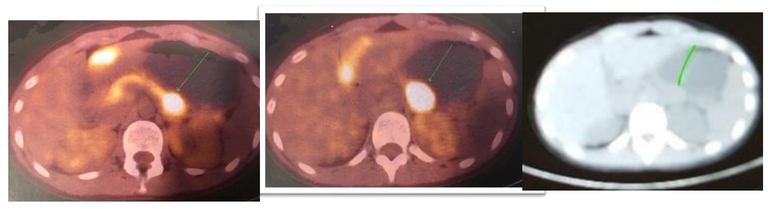
Connective tissue nevi
Lumbar Shagreen plaque

Physical examination: normal stature and BMI, angiofibromas, fibrous cephalic plaque and Shagreen patch were found. A fasting tolerance test allowed to detect after 10 hours:

Glucose 41mg/dl(55-110), insulin28,7mUI/l (<1) C-peptide 4,6 ng/ml(0,8-5,2)

Cortisol 109 nmol/l(101-536), GH 4,76ng/ml (>5). Diagnosis of hyperinsulinism was performed. To locate the lesion abdominal MRI with contrast scan showed a low-signal-density on T1-weighted-images and a high-signal-density on T2-weighted-images that enhanced with contrast of 27x23x20 mm in the pancreas body.

18-F-DOPA-PET-CT scanning: Showed increased focal uptake in an oval lesion of 33x27 mm in the pancreas body and tail Diagnosis of insulinoma was made



18-F-DOPA-PET-CT increased focal uptake (SUV max 23.3)
Normal uptake in adrenal glands and thorax.

She underwent to partial pancreatectomy with perioperative frozen section.

Histology: Benign tumor surrounded by a fibrous capsule with no infiltration consistent NET grade I

Inmunohistochemistry positive for: Chromogranin, sinaptofisin, INSM1, cytokeratine AE1-AE3 and negative for CD56. Proliferation index (MIB-1): 2%.

Postoperatively euglycemia, elevated β-OHbutyrate:0,39(< 0,35mmol/l) and elevated NEFA:0,64 mmol/l(0,09-0,60)

with normal plasmatic glucose level after prolonged fasting suggested absence of recurrence of insulinoma during

6 months of follow-up

No post prandial hyperglycaemia or steatorrhea were detected

GH 2.56 ng/ml (0-5)
IGF1 369 ng/ml (49-520)
PRL:7,7 ng/ml (0-14),
Ca:9.3 mg% (8,4-10.2)
P:2,5mg% (2,5-5.0)
PTH:18.04 pg/ml (10-55).
Cortisol 409 nmol/L (101-536)
ACTH 13.5 pg/ml (0-46)
FUC 22.03 nmol/24 hs (11.8-485.6)
FSH 7,5 mUI/ml (1.3-10.8)
LH 5,3 mUI/ml (0.4-12)
Estradiol 21,3 pg/ml (21-200)
Normal gastrina
Normal cathecholamines

Laboratory performed to ruled out MEN 1 and other possible associated neuroendocrine tumors

Conclusions: Insulinoma should be consider in patients with TSC especially in patients with changes in pattern of seizures without response to pharmacotherapy or worsening of neurobehavioral manifestations.