

# An unusual presentation of isolated ACTH-Deficiency secondary to TBX19 mutation revealed by late onset hypoglycemia seizure

C. Valentin<sup>1</sup>, A. Saveanu<sup>2</sup>, J. Beltrand<sup>3</sup>, I. Netchine<sup>1</sup>

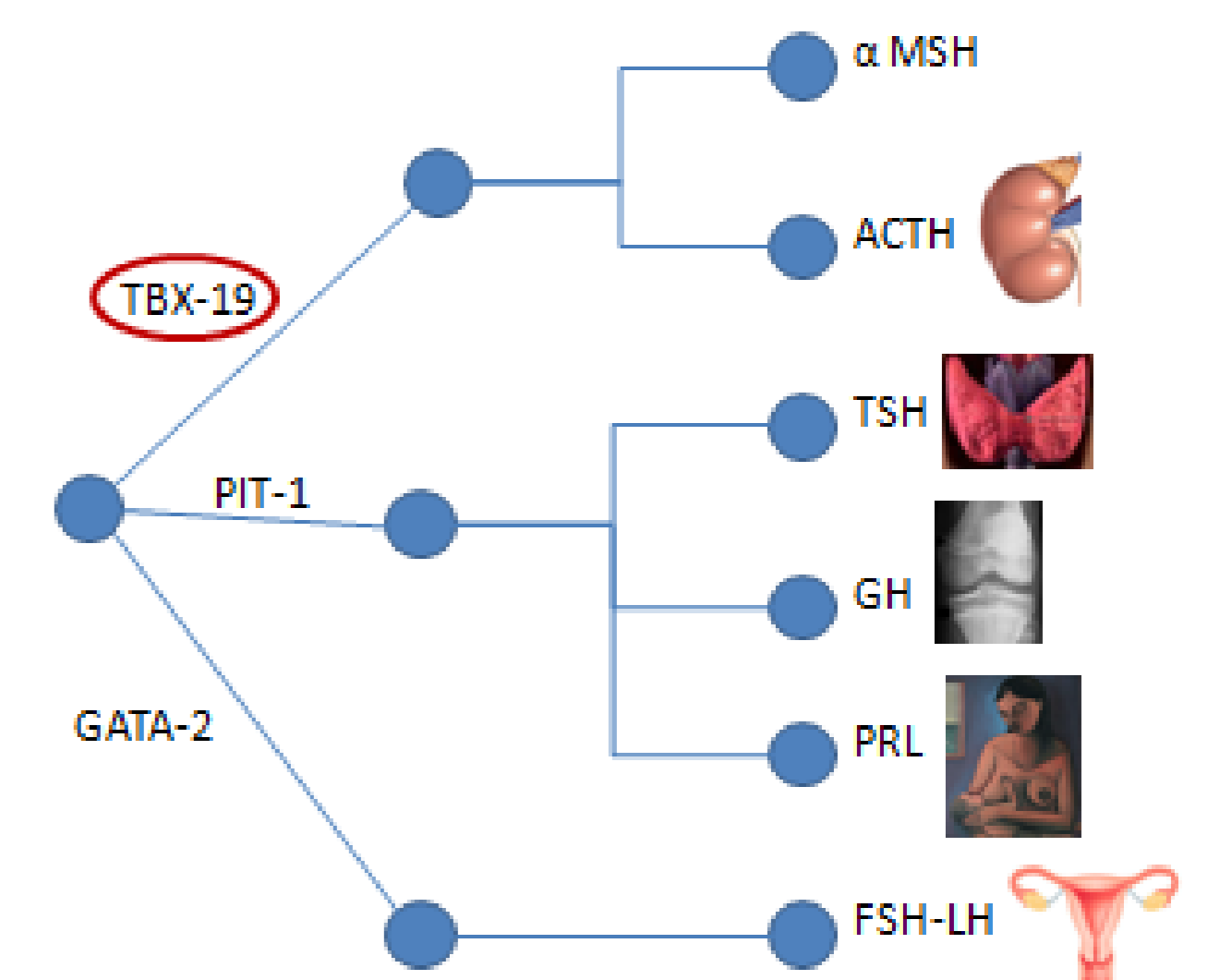
<sup>1</sup> Université Pierre et Marie Curie, AP-HP, Hôpital Trousseau, Paris, France

<sup>2</sup> Université Aix-Marseille, CRN2M-7286, CNRS, Faculté de Médecine Nord, Marseille, France

<sup>3</sup> Université René Descartes, AP-HP, Hôpital Necker enfants malades, Paris, France

## BACKGROUND

**Congenital isolated ACTH deficiency (IAD) is a rare inherited disorder that is clinically and genetically heterogeneous. Patients are characterized by low or absent cortisol production secondary to low plasma ACTH despite normal secretion of other pituitary hormones and the absence of structural pituitary defects. Mutations in the TBX19 gene, a T-box factor selectively expressed in developing corticotroph cells, have been identified so far only in cases of neonatal-onset complete IAD.**



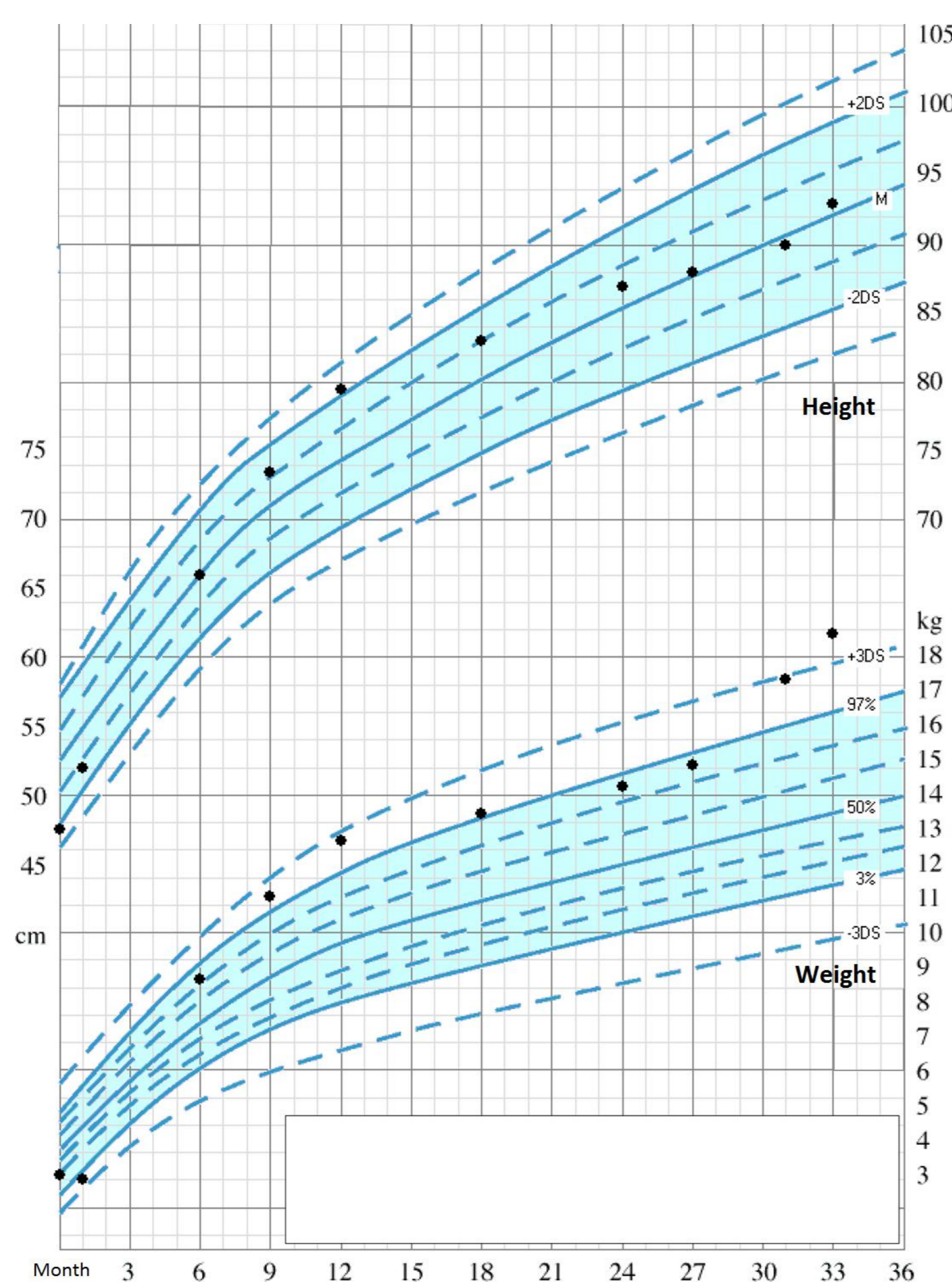
## CASE REPORT

The patient was born full term from related Tunisian parents. The mother had gestational diabetes. He had an asymptomatic hypoglycemia episode, a few hours after the delivery, thought to be secondary to the gestational diabetes with no detected recurrence in the first months of life.

He had a medical history of asthma with multiple hospitalizations, including one at 15 months with a long-fasting hypoglycemia noted without any clinical symptom.

He has a regular growth.

His older brother was diagnosed with a combined pituitary hormone deficiency at 2 months (hypoglycemia with seizure) and deceased at 24 months in a probable context of hypoglycemia.



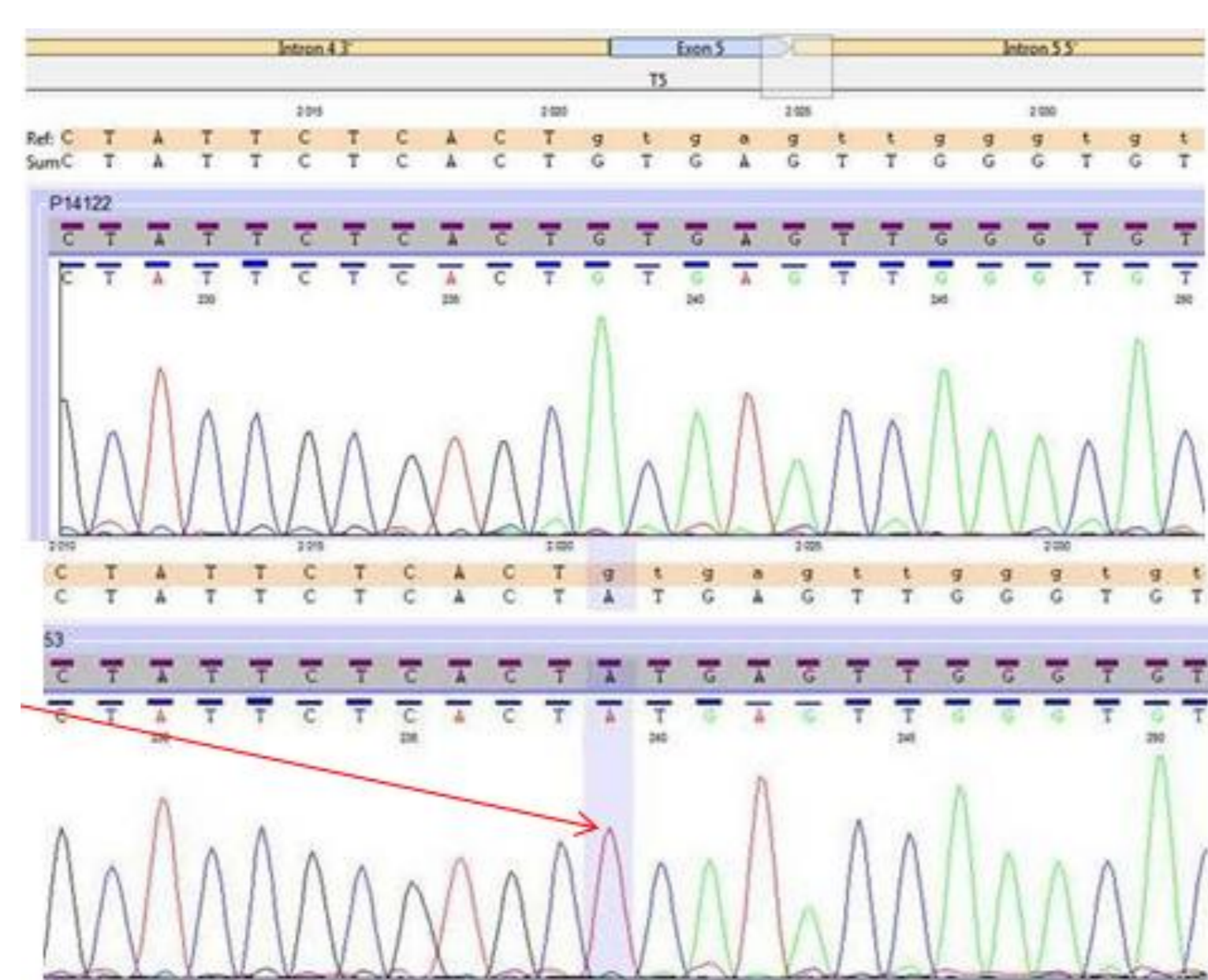
At 23-month-old he presented an episode of severe hypoglycemia with generalized seizure during a viral episode with fever and vomiting. His cortisol and ACTH were undetectable. Other pituitary hormones were in the normal range and the brain MRI showed no pituitary defect.

Hydrocortisone was introduced without recurrence of hypoglycemia.

### Work-up during hypoglycemia

Cortisol (µg/dL)	< 0,35
ACTH (ng/mL)	< 1

IGF1 (µg/l)	26
FT4 (pmol/l)	8,6
TSH (mUI/L)	6,6



The *TBX19* gene direct sequencing showed a homozygous recessive splicing site mutation previously described: IVS5+1G>A, leading to mRNA targeted for nonsense mediated decay and absence of protein expression. The sequencing of his parents' DNA showed the mutation at the heterozygous state.

## DISCUSSION

Usually *TBX19* mutation have been described in neonates with a very homogenous phenotype of severe recurrent hypoglycemia. Here the complete isolated ACTH-deficiency with *TBX19* mutation was diagnosed at nearly 2 years old, without symptomatic hypoglycemia event until his hypoglycemic seizure. The brain MRI showed no sign of severe and recurrent hypoglycemia.

## CONCLUSION

**This is a rare case with a late IAD diagnosis secondary to a *TBX19* mutation. A *TBX19* anomaly should not be ruled out in patients without a neonatal diagnosis of IAD. This diagnosis is of major importance since the severity of the ACTH deficiency is life threatening.**