Indian Experience with TBX-19 Mutation- A Single Centre Experience

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Abstract:
Objective: The objective of this case series is to highlight the workup of adrenal insufficiency as cause of hypoglycaemia with recurrent seizures. **Case series:** We report 4 cases of IAD presenting at 5-month, 27-month, 4 month and 6 months of age with lethargy, hypoglycaemia and recurrent seizures. All patients had documented cortisol deficiency and TBX-19 mutation. All were treated with oral steroids along with resolution of symptoms and catch-up growth. **Conclusion:** IAD Isolated ACTH deficiency (IAD) is a rare cause of adrenocortical insufficiency, characterized by low ACTH and cortisol levels, which causes early and severe secondary adrenal insufficiency without other pituitary defects. High suspicion with genetic diagnosis with timely treatment with steroids is the key to improve morbidity and mortality.
Key words: Hypoglycaemia, Isolated ACTH deficiency (IAD), TBX-19 mutation

Introduction

Adrenocortical insufficiency (primary or secondary) is one of the life-threatening conditions requiring early diagnosis and treatment. Isolated ACTH deficiency (IAD)[1], although rare, presents as persistent hypoglycaemia, prolonged cholestatic jaundice and seizures and families frequently have a history of neonatal death. Couture et al[1] reported TBX 19 mutation in 60 percent of IAD cases in case series of 91 patients, representing other pathogenic mutations for the deficiency. Although IAD, commonly manifest in neonatal and infantile age but delayed diagnosis hinders early appropriate intervention. We report 4 cases of TBX 19 mutation with their early age of manifestation and time of diagnosis with their outcome. Early detection of TBX19 mutations is crucial to ensure rapid management at birth and avoid neonatal mortality. The TBX19 gene (formerly known as TPIT) codes for a T-box transcription factor found in pro-opiomelanocortin (POMC) expressing pituitary cells [2]. TBX19 is required for the terminal differentiation of these cells and the expression of the POMC gene. TBX19 is located on chromosome 1q24.2 and its main transcript is composed of 8 exons (NM 005149.3)[3].

Details of demographics and investigations are described in table-1 and anthropometric parameters at first visit and 1 year follow up are given in table-2.

Case 1

A 5 days old girl presented with lethargy and hypoglycaemia which was noticed first on day 3rd of life. Baby was born term (birth weight 2.8 kg) with unremarkable antenatal or natal events with negative septic screen; she had no dysmorphism, no organomegaly and normal genitals. Critical sample was sent which was suggestive of hypocortisolemia with a low ACTH (Table-1). Clinical exome confirmed homozygous mutation in TBX-19. Baby is growing well on oral hydrocortisone (10 mg/m²/ day) with no hypoglycaemia till date.

Case 2

2 years 3 months old girl, first born of a non-consanguineous marriage with birth weight of 3 kg was referred for recurrent seizure episodes (at 6 months, 1 years and 2.3 years). She had unremarkable birth and family history with normal general examination. She was started on 2 anti-epileptic medications with normal EEG and MRI Brain. She was not growing well (Table-2), blood sugars were not documented in the first 2episodes and hypoglycaemia were documented in the 3rd episode of seizure at 2.3 years of age.Critical sample was suggestive of low cortisol levels and ACTH levels. Free T4 andProlactin was normal. Iv hydrocortisone was administered and genetic test confirmed TBx-19 mutation. She was gradually shifted to oral hydrocortisone with normal growth velocity on follow-up and no further seizure episode.

Case 3

A 4 months old girl was referred to endocrine unit with excessive weight gain. She had history of hypoglycaemic seizure at 25th DOL, was admitted in NICU, was diagnosed as congenital adrenal hyperplasia and started on oral steroids @ 20 mg/m2/day. No electrolyte abnormality was documented during NICU stay and 17 hydroxy progesterone was borderline elevated (12 ng/ml) with a low cortisol (4.3 mcg/dl). At 4 months (at time of referral), her weight gain was excessive with faltering in length gain and examination showed signs of steroid toxicity. With history of low cortisol with hypoglycaemia, steroids were not stopped but the dose was gradually tapered off to 10 mg/m 2 /day and genetic test was sent. It confirmed the diagnosis of TBX-19 mutation. Hydrocortisone was continued at 10 mg/m 2 /dayand catch-up growth (length and head circumference) was documented during follow-up.

Case4

A 6 months boy (3rd born of a third-degree consanguineous marriage) was referred toendocrine unit with history of recurrent seizures (7thday of life, 1month and 5 months of age). Low sugar (25 mg/dl) was documented with first seizure episode and was

attributed to poor feeding butcritical sample was not sent. He was started on antiepileptics since EEG showed multiple discharges. Parents had history of 2 sibling deaths (at 2nd month and 1st month with lethargy and seizures). He was under care of neurology unit with a possible diagnosis of genetic epilepsy since there was no response to 3 antiepileptics. Genetic test was sent to confirm the diagnosis which confirmed a mutation in TBX-19 gene. Cortisol and ACTH sample was sent before starting steroids which were low but had normal free T4 and Prolactin. He is growing well with no further seizure episodes, gradually antiepileptics were tapered off and been continued on oral hydrocortisone at 10 mg/m²/day.

Discussion

Adrenal insufficiency (primary or secondary) present with constellation of symptoms like anorexia, nausea, fatigue or weakness, prolonged neonatal jaundice, hypoglycaemia or electrolyte imbalance. Hypoglycaemia and recurrent seizures were main presentation of the children that are reported in the study. Hypoglycaemia and hypocortisolemia should be ruled out in all cases of seizures presenting early in life.

All our cases presented early although the diagnosis was delayed in 2nd and 4th case till 2.3 years and 6 months respectively. Similarly, the age of presentation was in early (infancy) [4,5,6] though the diagnosis was delayed to 4.8-year and 2.7 years in the cases reported by Abali et al[7] and Weijing et al[8]. Hypoglycaemic seizures were present in all our cases as also been reported by Unal et al[9], Kardalen et al[10]. Adrenal insufficiency presenting as recurrent chest infections and neonatal cholestasis was noted in Vieira et al[11] and Alsaleem et al[12] repsectively.

Other associated features were also reported in various reports, like fast growth and thyroid function derangement were reported by Weijing et al[8]. Chiari malformation, low BMD and microcephaly with dysmorphism were reported in 2 siblings by Kardelen et al[10]. Developmental delay was reported in one of the 2 siblings by Unal et al[9] which might be attributed to hypoglycaemic insult. None of our patients had any other associated factors. The presence of other features reported in various studies might be a co-incidence rather than direct association to the primary condition.

All our patients exhibit homozygous deletion in TBX-19 gene (Exon 3,8,2 respectively). Charnay et al[5] reported 4 patients with homozygous deletion in the same region of the gene; compound heterozygous mutations were reported by Akcan et al[4] and Vieira et al[11]. Couture et al[1] with the largest series had reported most cases with homozygous mutation but one of their cases was symptomatic with heterozygous mutation by genomic sequencing; they decoded the gene by Q-PCR to find a large heterozygous deletion in the gene consistent with mother and grandfather mutations. It should be kept in mind in symptomatic patients with heterozygous mutation that a large mutation might have been missed and can be evaluated by family gene sequencing.

Improved growth velocity was noticed in all of our patients, notably in our 3rd case as she was on a higher dose of steroids while physiological replacement doses are

recommended in cases of secondary adrenal insufficiency. She had a catch-up growth after decreasing the dose of steroid to physiological replacement doses. Improvement in weight z-scores was also documented in all cases except the 3rd case where a catch down weight was noticed in the patient after decreasing steroid dose. No further symptoms were noticed in follow up in various reports[4,10] (Akcan, Vieira)

Conclusion: Isolated ACTH deficiency should be kept in mind with symptomatic hypoglycaemia especially in the early onset presentation.

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Conflict of interest: None

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TABLE-1: Demographics and Investigations:

	Case-1	Case-2	Case-3	Case-4
Age at presentation	5th DOL	6 months	25th DOL	7th DOL
Age at diagnosis	7th DOL	2.3 years	4 months	6 months
Gender	Female	Female	Female	Male
Presentation	Lethargy and hypoglycaemia	Recurrent seizures	Hypoglycaemia seizure	Recurrent seizures
Seizures	No	Yes	Yes	Yes
Consanguinity	No	No	No	Yes
H/O sibling death	No	No	Yes	Yes
Investigations				
S.Cortisol N- > 18 mcg/dl with hypoglycaemia	2.3 mcg/dl (Low)	1.8 mcg/dl (Low)	4.3 mcg/dl (Low)	2.6 mcg/dl (Low)
ACTH N- 15-72 pg/ml	5.1 pg/ml (Low)	8.1 pg/ml (Low)	NA	4.8 pg/ml (Low)
S.Insulin N- <2 IU/L	0.4 IU/L (Normal)	NA	NA	NA

with hypoglycaemia				
Growth Hormone	11 ng/ml (Normal)	NA	NA	NA
S. Ammonia	12 mcg/l (Normal)	43 mcg/l (normal)	NA	34 mcg/l (Normal)
Free T4	1.2 ng /dl (Normal)	1.18 ng/dl (Normal)	1.3 ng/dl (Normal)	1.1 ng/dl (Normal)
TSH	4.8 IU/L (Normal)	2.9 IU/L (Normal)	1.2 IU/L (Normal)	4.1 IU/L (Normal)
Prolactin	NA	16 ng/ml (Normal)	NA	22 ng/ml (Normal)
Genetic test (Next generation whole exome sequencing)	Homozygous mutation TBX-19 (Exon 3; c.586 G>C) (p.Ala196Pro)	Homozygous mutation TBX-19 (Exon 3; c.524G>T (p.Gly175Val)	Homozygous mutation TBX-19 (Exon 8; c.1060C>T) (p.Pro354Ser)	Homozygous mutation TBX-19 (Exon 2; c.377C>T) (p.Pro126Leu)

TABLE-2: Anthropometry at first visit and follow up after 1 year:

	Weight (SD)		Height (SD)		Head circumference (SD)	
	First visit	Follow up	First visit	Follow up	First visit	Follow up
Case-1	-1.3 SD	-1.2 SD	0.09 SD	0.08 SD	1.2 SD	1.0 SD
Case-2	0.2 SD	-0.4 SD	-1.5 SD	-1.0 SD	-0.9 SD	-0.7 SD
Case-3	1.5 SD	-1.3 SD	-3.5 SD	-0.7 SD	-3.2 SD	-2.0 SD
Case-4	-3.2 SD	-0.6 SD	-1.8 SD	-0.8 SD	-1.7 SD	-0.6 SD