Brief Communication

ACTH Resistance Syndrome: An Experience of Three Cases

Alpesh Goyal, Hiya Boro, Deepak Khandelwal[1], Rajesh Khadgawat

Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, [1]Department of Endocrinology and Metabolism, Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi, India

Abstract

The term adrenocorticotropin (ACTH) resistance syndrome is used for a group of rare inherited disorders, which present with primary adrenal insufficiency during childhood. The syndrome includes two disorders inherited in an autosomal recessive fashion – familial glucocorticoid deficiency and triple A syndrome. Herein, we report our experience of three cases with ACTH resistance syndrome, highlighting the approach to diagnosis and management in such patients.

Keywords: ACTH resistance syndrome, adrenal insufficiency, familial glucocorticoid deficiency, isolated glucocorticoid deficiency, triple A syndrome

Introduction

Primary adrenal insufficiency in children is a relatively uncommon but potentially lethal condition. The most common causes of primary adrenal insufficiency in children are congenital adrenal hyperplasia and autoimmune adrenalitis (either alone or in association with autoimmune polyglandular syndrome).[1] Adrenocorticotropin (ACTH) resistance syndrome is a rare cause of primary adrenal insufficiency in childhood. It is an inherited disorder; however, in a rare instance of a patient with autoimmune adrenalitis who develops ACTH receptor blocking antibodies, it may present as an acquired disorder.[2] Inherited ACTH resistance syndrome comprises two disorders – familial glucocorticoid deficiency (FGD) and triple A syndrome (also known as Allgrove syndrome).

FGD (OMIM 202200), also known as hereditary unresponsiveness to ACTH, adrenal unresponsiveness to ACTH, or isolated glucocorticoid deficiency, is a rare autosomal recessive disorder characterized by severe cortisol deficiency, high plasma ACTH levels, and typically a well-preserved renin–angiotensin–aldosterone axis.[2] FGD is caused by mutation in the gene for ACTH receptor (melanocortin 2 receptor, *MC2R*) and melanocortin 2 receptor accessory protein (*MRAP*). Triple A syndrome (OMIM 231550) is a rare autosomal recessive disorder characterized by a triad of adrenal insufficiency, alacrima, and achalasia cardia.[3] It is caused by mutation in the gene *AAAS*, encoding the nuclear pore complex protein ALADIN (ALacrima Achalasia aDrenal Insufficiency Neurological disorder) protein. The disorder may have a highly variable presentation, manifesting as only two of the three cardinal manifestations in some cases.[2] The cardinal manifestations of the syndrome may be accompanied by autonomic dysfunction in some cases, earning it a designation of "4 A syndrome" in the literature.[4] Here, we are presenting our experience of this uncommon disease in three cases who presented to us during childhood.

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Case Presentation

Cases 1 and 2

A 3½-year-old male child of Asian-Indian origin was brought to the outpatient department with complaints of diffuse hyperpigmentation of the body, noticed by the parents for the past 6 months. Hyperpigmentation initially started in face, hands, and thighs, and later on involved gums, tongue, and buccal mucosa. Eventually, he had diffuse hyperpigmentation all over the body. The parents initially consulted dermatology outdoor, where after ruling out dermatological causes, estimation of plasma ACTH level was advised. Plasma ACTH level was

Address for correspondence: Dr. Deepak Khandelwal, Department of Endocrinology and Metabolism, Maharaja Agrasen Hospital, Punjabi Bagh, New Delhi -110 026, India.
E-mail: khandelwalaiims@gmail.com

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found to be markedly elevated at 3320 pg/mL (normal range: 7.2-63.3 pg/mL) and he was referred to endocrinology services with provisional diagnosis of hypoadrenalism. The parents denied any history suggestive of hypoadrenalism, apart from hyperpigmentation. There was no history of fungal infection, alopecia, or tetany. There was no history of tuberculosis in the child or in the family. The child was born (birth weight 2600 g) to nonconsanguineous parents after full-term normal vaginal delivery with uneventful perinatal period. There was no history suggestive of hypoglycemia, seizures, salt wasting crisis, or shock in the postnatal period. The child achieved physical and mental milestones at appropriate ages. Physical examination revealed active and cheerful child with a height of 97.5 cm (between 25th and 50th centile in K.N. Agarwal's growth charts with target height also in the same centile) and a weight of 13 kg (between 5th and 10th centile in K.N. Agarwal's growth charts). His blood pressure was 100/66 mm Hg without any postural drop. There was diffuse hyperpigmentation of body, more over forehead, gums, lips, extensor surfaces, and areas of friction. Genital examination was unequivocally male with both testes descended, without axillary or pubic hair. Systemic examination including detailed neurological examination was normal. Hemogram, renal function tests, serum electrolytes, liver function tests, and fasting plasma glucose were within normal limits. Bone age (Greulich and Pyle Atlas) was consistent with chronological age. Endocrine evaluation [Table 1] revealed 8 am serum cortisol level of 5.4 μg/dL (normal range: 6.2–19.4 μg/dL) with plasma ACTH level of 3102 pg/mL (normal range: 7.2-63.3 pg/mL) (all hormones were measured on an autoanalyzer; Roche Elecsys 2010, Roche Diagnostics, Germany, using electrochemiluminescence immunoassay). Thyroid function tests were within normal limits. Based on the clinical and biochemical data, a diagnosis of primary adrenal insufficiency was entertained and further work-up for its etiology initiated. Basal 17-hydroxy progesterone level was <1 ng/mL (normal: 0.5–2.4 ng/mL), while serum dehydroepiandrosterone sulfate level was 6.0 μg/dL (normal range: 0.47–19.4 μg/dL). Basal plasma aldosterone and renin levels were within normal range. Computed tomography scan of the abdomen revealed normal size adrenal glands without any hyperplasia, atrophy, or calcification. Schirmer's test for tear production was also normal.

A diagnosis of primary glucocorticoid deficiency with preservation of aldosterone axis was made. Samples for antiadrenal antibodies and genetic studies were collected and the patient was started on oral prednisolone 2.5 mg/day with education on stress dosing. Follow-up after 2 months showed improvement in the form of decrease in hyperpigmentation (~50% improvement in skin pigmentation) with plasma ACTH level declining to 200 pg/mL. The child has been following up with us regularly and has been growing well.

Table 1: Results of hormonal investigations at the time of diagnosis in three cases

Parameter	Case 1	Case 2	Case 3	Normal
8 am serum cortisol (μg/dL)	5.4	5.2	1.53	6.2-19.4
8 am plasma ACTH (pg/mL)	3102	470	1538	7.2-63.3
Serum T4 (μg/dL)	8.7	9.2	9.5	5.1-14.1
Serum TSH (μIU/mL)	3.4	4.6	8.4	0.27-4.2

ACTH: Adrenocorticotropin; TSH: Thyroid-stimulating hormone

Family screening showed normal cortisol and ACTH levels in both parents; however, the younger sister of the index case (age 12 months) showed normal 8 am serum cortisol (9.6 μg/dL) and high plasma ACTH (260 pg/mL). The parents denied any history suggestive of hyperpigmentation or hypoadrenalism in the child. They did not agree for further investigations of the child but agreed to observe her closely for any hyperpigmentation. Approximately 15 months later, the parents noticed hyperpigmentation over face and trunk in the child and brought her for further work-up. Her hemogram, renal function tests, serum electrolytes, liver function tests, fasting plasma glucose, and thyroid function test were within normal limits. Her 8 am serum cortisol level was 5.2 μg/dL, with corresponding plasma ACTH level of 470 pg/mL [Table 1]. In view of similar illness in her elder brother, diagnosis of FGD was considered and she too was started on treatment (oral prednisolone 2.5 mg/day). There was significant improvement in terms of decrease in hyperpigmentation and decline in plasma ACTH level to 126 pg/mL after 6 months of treatment initiation. She is also following up with us at regular interval and is growing normally. Test for antiadrenal antibodies was negative in both the siblings and parents. Mutation analysis did not show any mutation in *MC2R* or *MRAP* gene.

Case 3

A 9-year-old male of Asian-Indian origin was brought to our outpatient department with complaints of progressive darkening of complexion, noted by the parents since the past 6 months. There was a history of decreased appetite along with poor height and weight gain for the same duration. There was no history of salt craving or recurrent hospitalization for intravenous fluid administration. He was born of a nonconsanguineous marriage and had an elder and younger sibling, who did not have any similar complaints. On questioning, the mother gave a history of absent tear production while crying in the child. There was no history of difficulty in deglutition to solids or liquids, retrosternal chest pain, or regurgitation of undigested food particles. He denied history of orthostatic dizziness, dryness of skin, difficulty in dark adaptation, or any other autonomic disturbances. Examination revealed a young, average built male with a height of 121 cm (at 10th centile in K.N. Agarwal's growth charts with target height also in the same centile), a weight of 22 kg (at 25th centile in K.N. Agarwal's growth charts) and body mass index of 15.0 kg/m^2. His blood pressure was 90/70 mm Hg without postural drop. He had generalized hyperpigmentation involving the knuckles, palmar crease, nail bed, extensor aspects of extremities, and mucosa of the tongue. Sexual maturity rating was Tanner stage III with testicular volume of 10 mL bilaterally. The remaining general and systemic examination including detailed neurological examination was unremarkable.

Laboratory investigations including hemogram, renal function tests, serum electrolytes, liver function tests, and fasting plasma glucose were within normal limits. Bone age (Greulich and Pyle Atlas) was consistent with chronological age. Endocrine evaluation [Table 1] revealed 8 am serum cortisol 1.53 μg/dL (normal range: 6.2–19.4 μg/dL), plasma ACTH 1538 pg/mL (normal range: 7.2-63.3 pg/mL), serum T4 9.5 μg/dL (normal range: 5.1–14.1 μg/dL), and serum thyroid-stimulating hormone (TSH) 8.4 μIU/mL (normal range: 0.27-4.2 μIU/ml) (all hormones measured on an autoanalyzer; Roche Elecsys 2010, Roche Diagnostics, Germany, using electrochemiluminescence immunoassay). Basal plasma aldosterone and renin concentration were found to be normal at 25.14 ng/dL (normal range: 2.2–35.3 ng/dL) and 8.19 mU/L (normal range: 4.4–46.1 mU/L), respectively. Further work-up included ultrasonography of the abdomen, which revealed bilateral atrophic adrenals. Schirmer's test response was <5 mm in both eyes, suggestive of severe dry eyes. At this stage, a possibility of ACTH resistance due to triple A syndrome was entertained and the patient was investigated further for possible achalasia cardia. While a barium swallow study was normal, gastroenterologist found increased resistance at the lower end of esophagus on upper gastrointestinal endoscopy procedure, suggestive of achalasia cardia. Esophageal manometry revealed high basal lower esophageal sphincter (LES) pressure with incomplete LES relaxation on wet swallows and absent esophageal peristalsis, with few spastic peristaltic fragments, confirming the diagnosis of achalasia cardia.

He was started on physiological glucocorticoid supplementation with education on stress dosing. The treatment regimen comprised prednisolone twice daily initially, which was changed to dexamethasone once daily after epiphyseal fusion to improve the treatment compliance. Hyperpigmentation and anorexia gradually improved with treatment. TSH normalized on serial treatment with steroids without thyroxine supplementation, suggesting subclinical hypothyroidism due to glucocorticoid deficiency. For dry eyes, lubricant eye drops were prescribed, while he was followed up conservatively for achalasia, which has been asymptomatic till now. The child has been following up with us regularly and achieved a final height of 169 cm (as per the expected genetic potential).

Discussion

We have described three cases with primary adrenal insufficiency due to ACTH resistance syndrome. All the three cases had isolated primary glucocorticoid deficiency with preservation of renin–angiotensin–aldosterone axis. While cases 1 and 2 were siblings who presented with features of FGD, case 3 presented with alacrima along with primary glucocorticoid deficiency and was diagnosed as triple A syndrome.

FGD was initially described by Shepard *et al*.[5] in 1959, when they reported the disease in two sisters. The disorder affects both genders equally and the age of presentation varies from birth to 9 years, with ~50% of cases presenting during the first year of life. Patients with FGD usually present with symptoms of glucocorticoid deficiency. Symptoms include hypoglycemic seizures, recurrent infections, failure to thrive, collapse, and coma.[2] Transient neonatal hepatitis has also been described as a presenting feature.[6] There may be a family history of unexplained neonatal deaths, presence of another affected family member, and/or consanguinity. High ACTH levels acting on MC1R in cutaneous melanocytes lead to excessive skin pigmentation, a feature usually seen by 6 weeks of life in patients with FGD.[2] Many of these patients may present with hyperpigmentation alone.[7] Hyperpigmentation is considered to be highly resistant to hydrocortisone replacement.[8] However, our cases showed excellent response to steroid replacement in terms of hyperpigmentation. The typical biochemical results in FGD are a combination of low cortisol levels paired with extremely high plasma ACTH levels, in the presence of normal plasma renin and aldosterone. Steroid biosynthesis in the adrenal cortex is under the control of ACTH receptor MC2R, which is expressed in zona fasciculata and reticularis of adrenal glands. In FGD, there is defect in ACTH receptor or postreceptor signaling events. The *MC2R* gene, located on chromosome 18q11, encodes a 297-amino acid G-protein-coupled receptor. More than 30 mutations have been described in *MC2R* gene, majority of which are homozygous missense or compound heterozygous mutations.[9] Only about 25% of FGD is caused by mutations in the *MC2R* gene.[10] Recently, mutations have also been found in *MRAP* gene, which is required for MC2R expression in certain cell types, suggesting that MRAP plays a role in processing, trafficking, or function of the MC2R.[11] *MRAP* mutations account for 15%–20% of all FGD cases. However, no mutations are detected in 55%–60% of patients with FGD.[12] Our patients (cases 1 and 2) also did not show any mutation in *MC2R* or *MRAP* gene. It is important to differentiate FGD from other causes of primary hypoadrenalism in children as replacement of mineralocorticoid is not required in FGD, while mineralocorticoid replacement is generally essential and life-saving in other conditions of primary hypoadrenalism.

Triple A syndrome was first described by Allgrove *et al.* in 1978.[3] The disorder is inherited in an autosomal recessive pattern and is caused by mutation in *AAAS* gene located on 12q13, which codes for the 546 amino acid nuclear pore complex protein ALADIN.[13] Initially, this disorder was thought to be a variant of FGD; however, later it was shown to be a separate entity which shares the features of ACTH resistance with FGD. The exact prevalence of this rare disorder is not known, as there are only scattered case reports in the literature. Classically, the syndrome presents as alacrima and ACTH-resistant adrenal failure in the first decade of life. Adrenal insufficiency occurs due to ACTH resistance and presents with an isolated glucocorticoid deficiency in most cases; however, unlike FGD, mineralocorticoid deficiency has been reported in about 15% of the patients with triple A syndrome.[14-17] Achalasia presents in the first or second decade

of life with dysphagia, especially for liquids, chest pain, and regurgitation of undigested food particles. Alacrima may be the earliest manifestation of this syndrome and is postulated to occur due to decreased basal and reflex lacrimation as a result of autonomic dysregulation.[18] Small lacrimal glands on orbital imaging and abnormal lacrimal gland histopathology have been described in these patients.[19] Some patients may have other manifestations of autonomic dysfunction, such as orthostatic hypotension, heart rate disturbances, sweating abnormality, papillary abnormality, and accommodative spasm. Owing to the association with autonomic dysfunction, the name "4 A syndrome" has been proposed in the literature.[4] Neurological features such as hyperreflexia, ataxia, dysrathria, hypernasal speech with palatopharyngeal incompetence, parkinsonism, and mental impairment have also been described.[20,21] Adrenal insufficiency may have variable severity, presenting as early as 2–3 years of age with hypoglycemic seizures to remaining asymptomatic without glucocorticoid supplementation until adolescence or adulthood.[14] Isolated alacrima and achalasia without adrenal insufficiency with proven genetic mutation of the AAAS gene have also been described in the literature (achalasia–alacrima syndrome).[22,23] Alacrima is the most consistent and earliest feature of this syndrome; however, isolated alacrima cannot be relied upon for reaching the diagnosis of this rare entity.[14] Our patient (case 3) had onset of symptoms of adrenal insufficiency and alacrima in the first decade of life; however, he was asymptomatic for achalasia. The diagnosis of adrenal insufficiency was clear on hormonal investigations, while Schirmer' test and esophageal manometry helped confirm the diagnosis of alacrima and achalasia, respectively. The management of such a patient requires a multidisciplinary team approach. Appropriate glucocorticoid supplementation should be provided with education on the increased dosage of steroids during periods of stress as injury or illness. Achalasia may be treated with botulinum toxin injection into LES or surgical intervention such as pneumatic dilatation or anterior cardiomyotomy. For alcarimia, topical lubricants should be used regularly; however, punctual occlusion may be required in cases where treatment with lubricants is unsuccessful.

Conclusion

ACTH resistance syndrome should be considered in a child presenting with primary adrenal failure and normal renin–angiotensin–aldosterone axis. FGD presents with isolated primary glucocorticoid deficiency, while additional clinical features such as alacrima, achalasia, and rarely neurological dysfunction help establish the diagnosis of triple A syndrome. Making a diagnosis of ACTH resistance syndrome is important not only in providing reassurance that mineralocorticoid replacement may be unnecessary but also for genetic prediction and counseling.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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