Triple A Syndrome Presenting as Hypoglycemic Convulsions in a 3-Year-Old Boy: A Case Report

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Abstract
Triple A syndrome, characterized by the triad of alacrima, achalasia, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, is a rare and often underreported condition. We present the case of a 3-year-old boy who presented with hypoglycemic seizures unresponsive to glucose boluses. A detailed history revealed congenital alacrima. Suspicion of triple A syndrome led to the initiation of hydrocortisone therapy, which resulted in rapid resolution of symptoms and confirmed the diagnosis. Early recognition of this multisystemic genetic disorder is crucial, as delay in diagnosis can be life-threatening.

Introduction

Triple A syndrome, also known as Allgrove autosomal recessive syndrome, includes the classic triad of alacrima, achalasia and adrenocorticotropic hormone-resistant adrenal insufficiency (1). It is a rare and underreported syndrome, due to its diversity in clinical presentation, with an estimated prevalence of 1/1000000. In addition to the classic triad, a wide variety of symptoms can be associated, including neurological symptoms, dermatological problems and dental caries. The onset of symptoms may not be simultaneous. Alacrima is known to be the first symptom and is often present from birth but is not always immediately recognized. Also, not all cases present with the classic triad, complicating the diagnosis. Achalasia or adrenal crisis is often the presenting symptom.

As Triple A syndrome is a rare disease, the literature is limited and consists mostly of case reports. In this article a clinical case of Triple A syndrome is discussed, followed by a review of the literature.

Case

A 3-year-old boy presented to the emergency department of a regional hospital with symptoms of fever, vomiting, and a tonic-clonic seizure lasting more than 30 minutes. On arrival, the child was somnolent and only responsive to pain stimuli. His capillary glucose was 45 mg/dL (normal range 70-100 mg/dL), for which a glucose bolus was promptly administered. Laboratory tests revealed mild hyponatremia (132 mmol/L; normal range 135-145 mmol/L) and a moderately elevated C-reactive protein (CRP) (45 mg/L, normal range 0-5 mg/L). A brain CT scan and lumbar puncture ruled out central nervous system pathology. After initial treatment with antiepileptic medication, the child was admitted to the intensive care unit with the hypothesis of severe dehydration due to gastroenteritis and an intravenous rehydration was started.

Despite adequate rehydration and glucose supplementation, the boy's clinical status remained unchanged and hypoglycemia persisted, prompting his transfer to our center. On arrival, the blood glucose level was 54 mg/dL with a CRP of 89 mg/L, and a sodium level of 135 mmol/L. During the patient's history-taking, his mother mentioned the absence of tear production since birth, for which he had been prescribed artificial tears by an ophthalmologist. In addition, the mother reported feeding difficulties, such as gagging and dysphagia during meals.

With the differential diagnosis of Triple A syndrome in mind, an acute adrenal crisis was suspected. The patient was treated with a stress dose of intravenous hydrocortisone (2 mg/kg), followed by a stress regimen (50 mg/m²/day in four divided doses). Ceftriaxone was also administered to cover possible infectious causes. The child's symptoms resolved within hours of receiving hydrocortisone, and he was discharged three days later with oral hydrocortisone replacement therapy.

Further investigations confirmed elevated ACTH levels of 393 ng/L (normal range 7.2–63.3 ng/L) and low cortisol levels of 3.3 µg/dL (normal range 3.7–19.4 µg/dL), consistent with adrenal insufficiency. Combined with the presence of alacrima and feeding difficulties, a diagnosis of Triple A syndrome was confirmed. The patient was referred for endocrinological follow-up. Genetic testing revealed a mutation in the *AAAS* gene (c.1331+1G>A), confirming the diagnosis of triple A syndrome.

Discussion

Triple A syndrome, also known as Allgrove syndrome, is a rare autosomal recessive disorder first identified by Allgrove et al. in 1978 (1). Due to limited literature and frequent misdiagnoses,

the exact prevalence remains unclear but is estimated at approximately 1 in 1,000,000 (2-4). The syndrome is characterized by a classic triad of adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, alacrima, and achalasia. These features are pathognomonic for Triple A syndrome, though other symptoms such as autonomic dysfunction, neurological abnormalities, xerostomia, dental caries, hyperkeratosis (thickened skin), microcephaly (small head), gait disturbances, and delayed puberty can be present (2, 4-6). The clinical symptoms, time of onset and progression of the disease are highly variable, leading to the proposal of the term "4A syndrome" to include additional autonomic dysfunctions (2, 4, 7). Alternative syndromes similar to Triple A, such as AAMR (alacrima, achalasia with mental retardation), do not involve adrenal impairment (7).

Genetics and Pathophysiology

Triple A syndrome is caused by mutations in the *AAAS* gene located on chromosome 12q13, which encodes the nuclear pore protein ALADIN (2, 4, 5, 8). ALADIN plays a vital role in nucleocytoplasmic transport, essential for cellular function. The *AAAS* gene is widely expressed in various human tissues, contributing to the diverse symptomatology of the syndrome (4). High expression levels of the gene are particularly found in the adrenal glands, gastrointestinal tract, and brain (5, 9). Mutations in the *AAAS* gene are spread across all 16 exons, with the c.1331+1G>A mutation being the most common worldwide (5). Over 40 mutations have been documented, and no clear genotype-phenotype correlation has been established (2, 4, 5, 8). There is no gender difference in prevalence, and the phenotypic spectrum can vary significantly even among individuals with identical mutations. Thus, DNA studies are not particularly effective in predicting phenotype or prognosis (4).

Clinical Presentation

Triple A syndrome is often diagnosed in early childhood, although adult-onset cases have been reported (4). Pediatric cases usually present with alacrima or adrenal insufficiency, whereas late-onset cases may initially present with neurological symptoms (4, 5). Antenatal history is typically unremarkable, but consanguinity has been reported in 50% of cases (4). Clinical features may not appear simultaneously, with approximately one-third of patients presenting with only two symptoms and 10% presenting with only one (2)

Alacrima

Alacrima is often the earliest and most consistent finding in Triple A syndrome, though it may be overlooked due to its mild clinical significance (5, 6). Present in all patients, it often becomes evident later during diagnostic evaluations (6). This finding is attributed to parasympathetic dysfunction of the autonomic nervous system (2, 4, 10). Alacrima is rarely isolated and should prompt consideration of a congenital disorder such as Triple A syndrome, particularly when accompanied by other autonomic dysfunctions (2, 4, 7). Untreated, it can lead to serious complications like keratopathy and corneal ulceration (5).

Achalasia

Achalasia may present at any age, with symptoms including difficulty swallowing, food aversion, and prolonged mealtimes (6). Early symptoms such as dysphagia and vomiting can precede the diagnosis by years (2, 4, 5). Rarely, achalasia can be misdiagnosed as a chronic cough (2, 4). Manometric studies are the gold standard for diagnosing achalasia, revealing aperistalsis and a hypertonic lower esophageal sphincter (11). Achalasia can lead to dental caries and premature tooth loss due to xerostomia and exposure of teeth to gastric acid, making regular dental check-ups essential (2, 5, 9).

Adrenal Insufficiency

Adrenal insufficiency is the most common presenting symptom and ranges from severe manifestations such as hypoglycemia, hypotension, and ketoacidosis to milder symptoms like hyperpigmentation and poor growth (2, 4, 6, 11). This condition is present in 85% of patients, though some may never develop it (4, 5). Adrenal function may be borderline at presentation but deteriorate over time, necessitating regular monitoring of morning cortisol and ACTH levels (5). Elevated ACTH levels with a normal cortisol response on stimulation tests suggest latent adrenal failure and require close monitoring (11). Hypoglycemia from adrenal insufficiency can result in convulsions or sudden death (6, 12). Low DHEA-S (dehydroepiandrosterone sulfate) concentrations indicate involvement of the adrenal cortex layers (2, 9). Glucocorticoid deficiency is an obvious finding in patients with Triple A syndrome, whereas mineralocorticoid deficiency is rare. This suggests that the zona glomerulosa, is partially preserved in these patients (9).

Neurological and Autonomic Symptoms

Neurological dysfunctions occur in about 85% of patients, usually presenting in adolescence or adulthood (5). Rarely, neurological symptoms may precede adrenal insufficiency (4). These symptoms include developmental delay, distal weakness, sensory-motor neuropathy, intention tremors, gait imbalance, motor neuron disease, and optic atrophy (4, 5, 9). Cognitive impairment is common but not universal (6). Neurological symptoms generally progress slowly and stabilize in adulthood. Peripheral polyneuropathy is the most prevalent neurological finding (12). Autonomic disturbances, such as postural hypotension and abnormal sweating, are seen in approximately 30% of patients (4, 5, 11). The pathophysiology of these symptoms remains unclear, with ongoing debate on whether they are a primary manifestation of the disease or secondary to glucocorticoid deficiency affecting neurological development (4).

Management and Treatment

Patients with Triple A syndrome need to be medically monitored as adrenal insufficiency may not be present at diagnosis but can develop over time. Alacrima is a clinical sign of autonomic dysfunction and should always be investigated.

Treatment of adrenal insufficiency primarily involves oral hydrocortisone, with dosage adjustments during stress or illness (2, 4). Intravenous hydrocortisone may be used if oral administration is not feasible. Chronic steroid use can lead to central obesity, weight gain, and elevated hemoglobin A1c levels (5). Some studies suggest that systematic treatment may not always be necessary if glucocorticoid secretion remains borderline, but regular follow-up is crucial (10). Glucocorticoid supplementation does not significantly affect neurological symptoms, but physical therapy may improve endurance and balance (5).

Although there are no guidelines for the surveillance of patients with Triple A syndrome, it seems evident that regular follow-up is necessary. One study suggested that patients with adrenal insufficiency should be monitored every 3 months, whereas patients with borderline or no adrenal insufficiency should be monitored every 6 months or sooner if symptoms are present (5). Therefore, parents should be made aware of the possibility of developing symptoms related to adrenal insufficiency and consult promptly if those symptoms appear.

Lubricant eye drops are recommended to manage dryness and prevent ophthalmic complications associated with alacrima, with annual ophthalmological evaluations advised (2, 4, 6). Treatment for achalasia varies based on severity, from lifestyle changes to more invasive procedures such as balloon dilatation, nifedipine, or surgical myotomy (2, 6). Managing severe achalasia is essential for controlling hypoglycemia and supporting growth and development (5). DHEA supplementation may be necessary for patients with low adrenal androgen levels affecting libido and sexual function (2).

Conclusion

Triple A syndrome is a rare and potentially life-threatening condition (4, 12). It is characterized by a triad of symptoms: alacrima, achalasia and adrenal insufficiency. Although not all present simultaneously. Low glucose levels that do not normalize after an IV correction should alert the clinician to question the initial diagnosis. The importance of a thorough anamnesis in patients with an unclear medical condition should also be emphasized, as demonstrated in this case. Treatment of triple A syndrome depends on the symptoms and may include chronic hydrocortisone therapy and artificial tears. Early diagnosis of this syndrome prevents unnecessary investigations and inappropriate treatment (11).

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