International Journal of Multidisciplinary Research and Modern Education (IJMRME)
International Peer Reviewed - Refereed Research Journal, Website: www.crystalpen.in
Impact Factor: 7.315, ISSN (Online): 2454 - 6119, Volume 12, Issue 1, January - June, 2026

ALLGROVE SYNDROME (TRIPLE A SYNDROME): A REVIEW

N. Sakthi Bharathi* & G. Sarojini**
* Associate Professor, Meenakshi College of Nursing, Madurai, Tamil Nadu, India
** Professor, Sacred Heart Nursing College, Madurai, Tamil Nadu, India

Cite This Article: N. Sakthi Bharathi & G. Sarojini, "Allgrove Syndrome (Triple A Syndrome): A Review", International Journal of Multidisciplinary Research and Modern Education, Volume 12, Issue 1, January - June, Page Number 81-83, 2026.

Type of Review: Peer Reviewed as per |C|O|P|E| Guidance.

DOI: https://doi.org/10.5281/zenodo.20671654

Abstract:

Allgrove syndrome, commonly referred to as Triple A (AAA) syndrome, is a rare autosomal recessive multisystem disorder characterized by the triad of achalasia, alacrima, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. The syndrome results from mutations in the AAAS gene, which encodes the ALADIN protein involved in nuclear pore complex function. Clinical manifestations vary widely and may include neurological, autonomic, endocrine, ophthalmologic, and gastrointestinal abnormalities. Due to its progressive nature, diagnosis is often delayed until multiple characteristic features become apparent. Early recognition and multidisciplinary management are essential to prevent life-threatening complications and improve quality of life. This review summarizes the etiology, clinical manifestations, diagnostic approaches, management strategies, nursing care, and complications associated with Allgrove syndrome.

Key Words: Allgrove Syndrome, Triple A Syndrome, Achalasia, Alacrima, Adrenal Insufficiency, ACTH Resistance, AAAS Gene.

Introduction:

Allgrove syndrome, also known as Triple A (AAA) syndrome, is a rare inherited disorder first described by Jeremy Allgrove and colleagues in 1978. The syndrome is characterized by the classical triad of achalasia, alacrima, and ACTH-resistant adrenal insufficiency. It is a slowly progressive multisystem disease, and the complete clinical picture may take several years to develop.

The disorder is caused by mutations in the AAAS gene, located on chromosome 12q13, which encodes the ALADIN (Alacrima-Achalasia-Adrenal Insufficiency Neurologic Disorder) protein. Inheritance follows an autosomal recessive pattern, with a higher prevalence reported among consanguineous families.[1,2]

Etiology and Risk Factors:

Allgrove syndrome is a rare genetic disorder caused primarily by mutations in the AAAS gene, which is located on chromosome 12q13 and encodes the ALADIN (Alacrima-Achalasia-Adrenal Insufficiency Neurologic Disorder) protein. The disease follows an autosomal recessive pattern of inheritance, meaning that an affected individual must inherit two mutated copies of the gene, one from each parent. The syndrome is more commonly observed in families with a history of consanguineous marriages, which increase the likelihood of inheriting recessive genetic mutations. Dysfunction of the ALADIN protein disrupts the normal transport of molecules across the nuclear pore complex, resulting in cellular abnormalities affecting multiple organ systems. A positive family history of the disorder and the presence of affected siblings may further increase the risk of developing the syndrome. Although the condition is rare, early genetic identification and family screening are essential for timely diagnosis and management.[3]

Clinical Manifestations:

The clinical presentation of Allgrove syndrome is highly variable and often progresses gradually over time. Endocrine manifestations commonly include ACTH-resistant adrenal insufficiency, which may present with fatigue, weakness, recurrent hypoglycemia, hyperpigmentation of the skin, and impaired growth. Gastrointestinal involvement is characterized by achalasia, a disorder of esophageal motility that leads to dysphagia, recurrent vomiting, feeding difficulties, weight loss, and failure to thrive. Ophthalmological abnormalities are frequently among the earliest signs and include alacrima, dry eyes, keratopathy, and corneal ulceration resulting from inadequate tear production.

Neurological and autonomic dysfunction are also prominent features of the syndrome. Patients may experience peripheral neuropathy, developmental delay, speech impairment, muscle weakness, gait disturbances, ataxia, postural hypotension, anisocoria, abnormal sweating, and reduced sensory perception. Additional manifestations include hyperkeratosis, short stature, osteoporosis, sensorineural hearing loss, sexual dysfunction, and varying degrees of cognitive impairment. The severity and progression of symptoms differ considerably among affected individuals, making comprehensive clinical evaluation essential for diagnosis and long-term management.[4]

Diagnostic Evaluation:

The diagnosis of Allgrove syndrome is based on a combination of clinical findings, laboratory investigations, and genetic testing. During clinical assessment, patients may exhibit characteristic physical features such as a long and narrow face, prominent philtrum, thin upper lip, downward-curved mouth, and microcephaly. Other findings may include hyperpigmentation, orthostatic hypotension, corneal abnormalities, and reduced heart rate variability during the Valsalva maneuver, indicating autonomic nervous system dysfunction.

Several diagnostic investigations are useful in confirming the diagnosis. The Schirmer test is commonly employed to assess tear production and confirm alacrima. A slit-lamp examination can identify corneal lesions, keratopathy, and other ocular abnormalities. Hormonal studies, including serum cortisol and ACTH measurements, are important for evaluating adrenal function and detecting adrenal insufficiency. Esophageal manometry remains the gold-standard diagnostic test for achalasia, while imaging studies such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) may provide supportive information regarding associated abnormalities. Definitive diagnosis is achieved through genetic testing, which identifies pathogenic mutations in the AAAS gene.[1]

Management:

Management of Allgrove syndrome requires a comprehensive and multidisciplinary approach involving endocrinologists, gastroenterologists, neurologists, ophthalmologists, nutritionists, and nursing professionals. Because the disorder affects multiple body systems, treatment is primarily directed toward symptom control, prevention of complications, and improvement of quality of life. Regular follow-up and individualized treatment plans are essential to address the progressive nature of the disease and optimize long-term outcomes.

Medical Management:

The cornerstone of medical treatment is the management of adrenal insufficiency through lifelong glucocorticoid replacement therapy. Hydrocortisone is generally the preferred medication, although alternative glucocorticoids such as prednisone or dexamethasone may be prescribed when clinically indicated. Appropriate hormone replacement helps prevent adrenal crises and maintains normal metabolic function. Ocular manifestations are managed with frequent administration of artificial tears, lubricating eye drops, and protective eye care measures to prevent corneal damage. Regular ophthalmologic evaluations are necessary to monitor disease progression and preserve visual function. Nutritional support and management of associated neurological symptoms may also be required depending on the patient's clinical status.[5]

Surgical Management:

Surgical intervention is primarily indicated for patients with symptomatic achalasia who do not respond adequately to conservative treatment. Pneumatic dilation of the lower esophageal sphincter is commonly performed to relieve obstruction and improve swallowing. Patients with persistent or recurrent symptoms may require Heller's myotomy, a surgical procedure that involves cutting the muscles of the lower esophageal sphincter to facilitate esophageal emptying. More recently, Peroral Endoscopic Myotomy (POEM) has emerged as a minimally invasive and effective alternative to conventional surgery, offering significant symptom relief and improved quality of life for many patients. The choice of intervention depends on patient characteristics, disease severity, and institutional expertise.[6]

Nursing Management:

Nurses play a vital role in the holistic care and long-term management of individuals with Allgrove syndrome. Continuous monitoring of growth parameters, nutritional status, hydration, and developmental milestones is essential, particularly in pediatric patients. Nurses are responsible for assessing medication adherence, administering prescribed therapies, and monitoring for adverse effects associated with long-term glucocorticoid use. Eye care management includes educating patients and caregivers regarding the regular use of artificial tears and ocular lubricants, maintaining ocular hygiene, and recognizing early signs of corneal injury or infection.

Patient and family education is a critical component of nursing care. Nurses should provide counseling regarding lifelong hormone replacement therapy, stress-dose steroid administration during illness, and recognition of symptoms suggestive of adrenal crisis. Coordination of multidisciplinary follow-up appointments and psychosocial support services can help improve treatment adherence and overall quality of life. Furthermore, nurses play a key role in early identification of complications, facilitating timely intervention and reducing morbidity associated with this rare multisystem disorder.[1]

Complications:

Allgrove syndrome can lead to a wide range of complications involving multiple organ systems. Ocular complications commonly include keratoconjunctivitis sicca, resulting from chronic alacrima, which may progress to corneal ulceration and subsequent visual impairment if left untreated. Endocrine complications are primarily related to adrenal insufficiency and may include adrenal crisis, a life-threatening condition characterized by severe hypotension and hypoglycemia. Long-term glucocorticoid therapy may also contribute to growth suppression and the development of Cushing syndrome when administered in excessive doses. Gastrointestinal complications associated with achalasia include aspiration pneumonia, recurrent choking episodes, and respiratory tract infections due to aspiration of food or liquids. Neurological complications may develop progressively and include autonomic neuropathy, ataxia, developmental delay, cognitive impairment, and progressive neurological deterioration, all of which can significantly affect functional independence and quality of life.[7]

Conclusion:

Allgrove syndrome is a rare, progressive multisystem genetic disorder characterized by the triad of achalasia, alacrima, and ACTH-resistant adrenal insufficiency. Because clinical manifestations often develop gradually, early diagnosis can be challenging. Prompt recognition, comprehensive evaluation, and multidisciplinary management are essential to reduce morbidity and improve long-term outcomes. Nursing professionals play a pivotal role in monitoring, patient education, symptom management, and prevention of complications.

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