

## Case Report

# Integrative Pediatrics and Child Care

## Isolated Congenital Alacrima in a Child with Autism Spectrum Disorder

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### Abstract

Isolated congenital absence of lacrimal glands is a very rare condition in children, only few cases were reported so far. Its symptoms can be quite variable depending on the other associated factors like absence of accessory lacrimal glands and/or salivary glands. Children with isolated absence of lacrimal glands can have normal tear film but lack tear production upon emotional stimuli. Although, alacrima can be a part of other rare syndromes, isolated absence has never been reported in the literature in association with autism spectrum disorder. With increasing recognition of autism spectrum disorder, it is important to report common and rare association of other clinical co-morbidities as this may influence the initial presentation posing diagnostic challenges to the diagnosticians. In this case the lack of tears with the emotional stimuli was considered exclusively caused by the lack of social-emotional reciprocity, which is one of the core symptoms of autism spectrum disorder.

**Keywords:** Alacrima, Lacrimal glands, Autism

**Abbreviations:** ASD: Autism Spectrum Disorder; ICA: Isolated Congenital Alacrima; AAAS: Adrenal Insufficiency, Achalasia, and Alacrima; CT scan: Computed Tomography; ALSG: Autosomal dominant Aplasia of Lacrimal and Salivary Glands; OMIM: Online Mendelian Inheritance in Man

### Introduction

The recognition of autism spectrum disorder (ASD), which is prevalent worldwide across the race and gender, is on the rise worldwide with the current estimation rate being as high as 1 in 59 children [1]. In children with autism, the core symptoms of social communication and interaction difficulty along with restricted and repetitive behaviour are often associated with other internalising and externalising behaviour such as anxiety, sensory processing disorder and ADHD. Intellectual disability is common and seen in nearly a third of the children. The diagnosis of autism is quite complex and time consuming and often requires multidisciplinary assessment with the help of other allied health care professionals like occupational therapist, speech pathologist, and

psychologist. Nearly, 10-15% of children with autism underlying genetic causes are identified particularly when associated with intellectual disability. The frequency of *de novo* copy number variants has been reported in 3-19% case of ASD from simplex and multiplex families, compared to approximately 1% in healthy controls [2]. Wide range of symptoms variability is the norm; therefore, the word 'spectrum disorder' is added to the name. Children with autism, in addition to the behavioural symptoms and developmental delay often show other physical symptoms. Gastrointestinal symptoms are not uncommon and seen in nearly one third of children with autism which includes constipation, gastro-oesophageal reflux, vomiting, feeding difficulty and recurrent abdominal pain. Similarly, there is increased incidence

of seizures. Awareness of these associated symptoms is very important as these are some of the common reason for the primary referral , masking the core symptoms of ASD.

In this article we present a 3-year-old girl with alacrima, who was initially referred for further assessment because of lack of tears with emotional stimuli. She fulfilled the diagnostic criteria for autism spectrum disorder as per DSM V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) after rigorous multidisciplinary assessment. It is important to increase our knowledge base about associated physical symptoms in children with autism. We have not found similar association in the literature before.

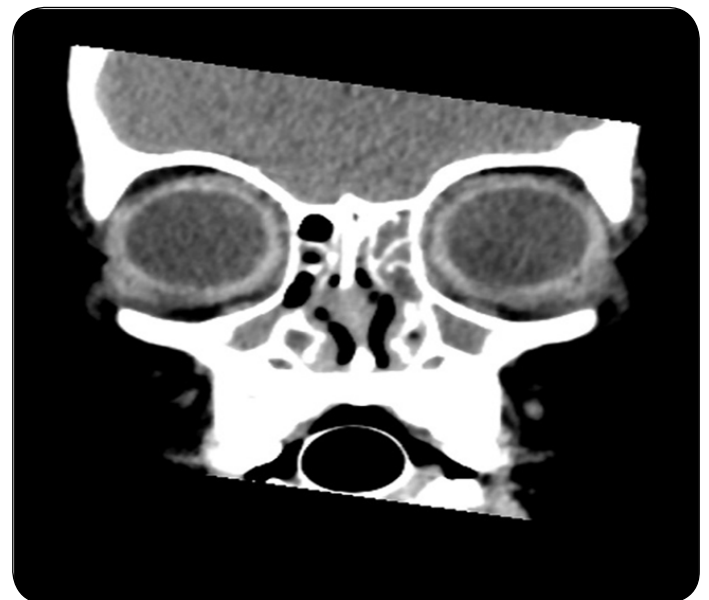
### Case report

A three-year old girl underwent comprehensive assessment by the speech pathologist and psychologist due to the maternal concern of her difficult behaviour and delayed speech in the context of complete absence of tears even at the height of emotional stimuli. She was her mother's second child. The pregnancy was uneventful. There was no medical or any developmental disorder on both sides of the family. She was reported to be very "moody" and did not produce tears on both eyes when cried even at the time of significant meltdowns. The following tools were used for assessment: Autism Diagnostic Observation Schedule – Toddler (ADOS-T), Mullen Scales of Early Learning (MSEL), Autism Diagnostic Interview- Revised (ADI-R) and Vineland Adaptive Behaviour Scales – Second Edition (VABS-II). She met sufficient criteria for the diagnosis of ASD (DSM-V). During the pediatrician's assessment she was found to have normal tear films on both eyes at rest. There was no tear flow through the indentation supposed to be the lacrimal punctum and no evidence of conjunctival xerosis. The rest of the ophthalmological examination including extraocular muscles and fundus were normal. She had normal salivation and there was no abnormality on her teeth, hair and skin. Her growth parameters were on 50th centile on the CDC growth chart. Systemic examination including the neurology was normal. She had no facial dysmorphism or any swallowing difficulty. The newborn screening test was normal. No clinically significant copy number variants was identified by SNP microarray genetic testing (Illumina CytoSNP-850K Genome-wide SNP array analysed with 'Bluefuse-Multi' software). Other laboratory studies ruled out any biochemical evidence of adrenal insufficiency. The lacrimal glands were not visualized on the orbital CT scan, however, extraocular muscles and

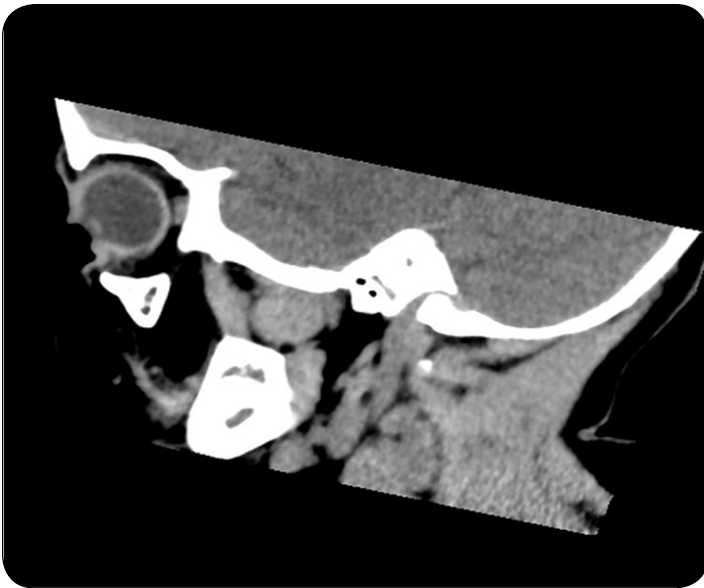
the optic nerves appear unremarkable with normal retro-orbital fat (Figures 1-4). The parotid glands were normal bilaterally. Parents did not consent for the MRI brain scan as it would require to be done under general anesthesia. In the absence of dry eyes, no specific ophthalmological treatment strategies were required for this girl.



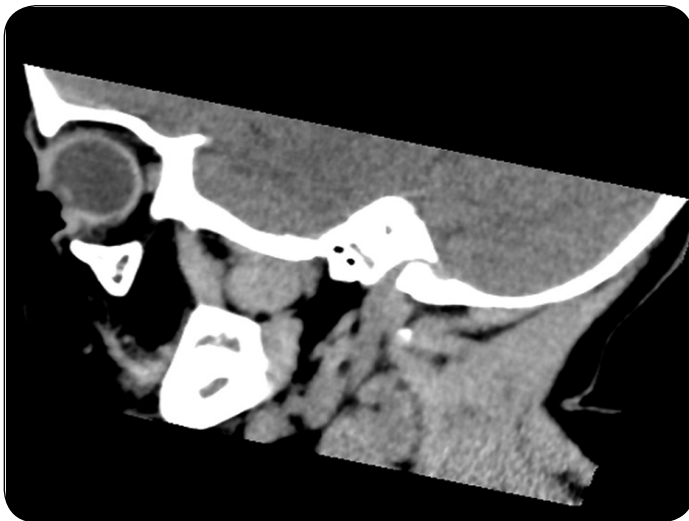
**Figure 1:** Clinical picture of right eye with presence of lacrimal punctum but no tears flowing.



**Figure 2:** CT scan of orbit: coronal view of left eye showing no lacrimal gland in the socket.



**Figure 3:** CT scan of orbit: sagittal view of right eye showing no lacrimal gland in the socket.



**Figure 4:** CT scan of orbits: sagittal view of both eyes showing no lacrimal glands in the supero-temporal region.

## Discussion

Alacrima refers to a wide spectrum of lacrimal secretory disorders that are mostly congenital in origin characterized by aplasia or hypoplasia of the lacrimal gland. Exact incidence of alacrima is not known. It is usually inherited in an autosomal recessive fashion, but dominant pedigrees have been described in the literature [3][4]. The main lacrimal gland is normally situated superotemporally in the orbit within the lacrimal fossa of the frontal bone and is responsible for the reflex tear production. The accessory lacrimal glands of Kraus and Wolfring develop slightly later, which are responsible for basal tear secretion. There are three stages of lacrimal

gland morphogenesis which continues till 9-16 weeks of gestation, however, full differentiation may take up to 3-5 years to complete [3]. Interaction between epithelial and mesenchymal cells is necessary for proper lacrimal gland development. Any disarrangement in very early intrauterine life may cause lacrimal gland agenesis. Lacrimal gland agenesis may occur as an isolated condition or it may accompany salivary gland agenesis and atresia of lacrimal drainage system. No specific cause or risk factor has been identified to cause isolated congenital absence of lacrimal glands.

The symptoms of isolated absence of lacrimal gland can be variable ranging from a complete absence to reduced secretion of tears in response to emotional stimulation but a normal secretory response on normal blinking to complete dry eyes. This is due to the presence of accessory lacrimal glands which causes normal tear films. It can be an isolated problem in Isolated congenital alacrima (ICA) or a part of other syndromes like Riley-Day syndrome, Sjögren syndrome, Allgrove (or triple-A) syndrome, anhidrotic ectodermal dysplasia, Christ-Siemens-Touraine Syndrome. There are only few case reports of congenital alacrima in different parts of the world including Saudi Arabia, Tunisia and Brazil [5-13].

The prognosis of isolated congenital alacrima is generally good and they are expected to live a normal life. However, it depends on the severity of symptoms particularly when it is associated with absence of accessory lacrimal glands causing persistent ocular surface dryness which can be very difficult to manage. Autosomal dominant aplasia of lacrimal and salivary glands (ALSG), caused by heterozygous mutation in the FGF10 gene (OMIM # 602115) on chromosome 5p12, have been reported with very few cases [6].

Allgrove Syndrome, one of the most notable syndromes associated with alacrima is an autosomal recessive disease characterized by the triad of adrenal insufficiency, achalasia, and alacrima [5]. Mutations in the AAAS gene on chromosome band 12q13 have been described in several pedigrees with Allgrove (or triple-A) syndrome. The AAAS gene encodes a 547-amino acid protein named ALADIN (for alacrima-achalasia-adrenal insufficiency-neurologic disorder), which belongs to the family of regulatory proteins involved in intracellular protein transport. Mixed pattern of upper and lower motor neuropathy, sensory impairment, autonomic neuropathy, and mental retardation are reported. The association or coexistence of congenital alacrima and

the Pierre Robin sequence has been described in one case report [6]. SNP microarray in our case ruled out any clinically relevant micro deletion. Also, none of the syndromes mentioned above has higher incidence of autism.

Congenital lacrimal gland agenesis is rare but should be considered in young patients with long history of dry eyes and chronic aseptic ulcer. CT and MRI of the orbit are generally sufficient to identify defect [12]. The Schirmer test must be done in all cases of chronic corneal ulcers. In 2016, three adults in a same Tunisian family were diagnosed with bilateral absence of lacrimal glands but no specific genetic mutation identified.

Lifelong tear supplementation may be necessary when it is associated with dry eyes. In extremely severe symptomatic cases perforation can happen [14][15] [16]. For example, a 9-month-old infant with congenital alacrima had bilateral corneal opacity which subsequently perforated with collapsed anterior chambers. Therapeutic soft contact lenses with daily application of ofloxacin ointment were successful sealing perforation in 1 week [11].

## Conclusion

This is the first reported case to our knowledge identifying an atypical co-morbidity of autism spectrum disorder which is very closely related the core symptoms of social-emotional reciprocity. Although several similar reports will be necessary to establish any association between these two, it is important that clinicians are aware of this uncommon feature, therefore, not to miss any underlying physical co-morbidity. Fortunately, for this child no specific treatment is required at this stage and a further follow up will be required to monitor her progress.

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