Received: 30 December 2023 | Accepted: 30 April 2024

DOI: 10.1002/jpr3.12084

CASE REPORT

Gastroenterology

# Achalasia in Klinefelter syndrome: A suspected pediatric case as well as prevalence analysis suggesting increased risk in this population

**Lacey Miller**[1] | **Hyung-Gyo Cho**[2] | **Charlotte Banayan**[2] | **Vivian Vega Lemus**[3] | **Shagun Sharma**[3] | **Thomas Wallach**[3]

[1]A.T. Still University School of Osteopathic Medicine, Mesa, Arizona, USA

[2]Department of Pediatrics, SUNY Downstate Health Sciences University, Brooklyn, New York, USA

[3]Department of Pediatrics, Division of Pediatric Gastroenterology, SUNY Downstate Health Sciences University, Brooklyn, New York, USA

**Correspondence**

Thomas Wallach, MD

Email: Thomas.wallach@downstate.edu

**Funding information**

None

## Abstract

A 4-year-old male with Klinefelter syndrome (KS), speech delay, and intermittent history of coughing and choking during meals was referred for evaluation. Prior evaluation with computed tomography showed a dilated esophagus at the gastroesophageal junction. The patient was unable to tolerate a barium swallow. Upper endoscopy was performed, and an intraoperative esophagogram, demonstrated a "birds beak" appearance suggestive of achalasia. There is no documented relationship between achalasia and KS. However, we utilized TriNetX (a large-scale data clearing-house) to demonstrate a higher prevalence of achalasia in patients with KS as compared to the general population.

**KEYWORDS**

achalasia, endoscopic techniques, Kleinfelter syndrome

## 1 | INTRODUCTION

Klinefelter syndrome (KS) is a supernumerary sex chromosome aneuploidy defined by an extra copy of an X chromosome. Classic findings are small and firm testes, gynecomastia, hypogonadism, infertility, and tall stature. Symptoms generally present after puberty. In children, the earliest manifestations include speech delay and learning difficulties.[1] Recent studies suggest an increased risk of eosinophilic esophagitis (EoE) in KS.[2,3] Notably, there is currently a lack of literature addressing an association between KS and achalasia. We present a case of esophageal dilation suggestive of achalasia in a young patient with KS, as well as an analysis of a large-scale clinical database demonstrating a higher prevalence of achalasia in the KS population.

## 2 | CASE REPORT

A 4-year-old male with KS and speech delay was referred to pediatric gastroenterology for an incidental finding of a dilated esophagus at the gastroesophageal junction (GEJ) on a chest computed tomography after X-ray for an upper respiratory tract infection revealed an abnormal mediastinal silhouette. Patient's history revealed a "very picky eater," tolerating only chips, cereal, soft foods, and water with several episodes of choking or gagging on foods outside of what he typically eats. No other notable history was reported. The physical exam demonstrated a child with obesity, moderate stool burden in the left lower quadrant, and high-riding bilateral testis.

To assess potential disorders in esophageal anatomy and motility, an esophagram was attempted. However,

the patient was unable to tolerate the barium contrast. Due to concern for EoE (known to be associated with KS), an upper endoscopy was performed, which revealed a dilated distal esophagus and a small superficial erosion at the prepyloric region with resistance to intubation of the GEJ. This finding raised suspicion for possible achalasia or anatomic abnormality. Accordingly, we were able to leverage a fully protected airway to complete a partial intraoperative esophagram. We placed a nasogastric (NG) tube, introduced gastrografin (10 cc), and obtained intraoperative X-rays. This was completed in 25 min with good tolerance by the patient. The esophagram demonstrated a classic "bird beak" appearance suggestive of achalasia. (Figure 1) Proximal and distal esophageal biopsies demonstrated sparse eosinophils (<5 eos/hpf).

As our institution lacks capacity to perform motility studies, the patient was referred to a local institution for further evaluation. Unfortunately, the patient has been unable to follow up with a motility expert due to there being none in the area who work with their insurance. At this time, the family is pursuing an insurance change to be able to receive additional diagnostic and therapeutic care. Accordingly, a full diagnosis of achalasia cannot be made at this time, and further treatment would be initiated upon confirmation of diagnosis.

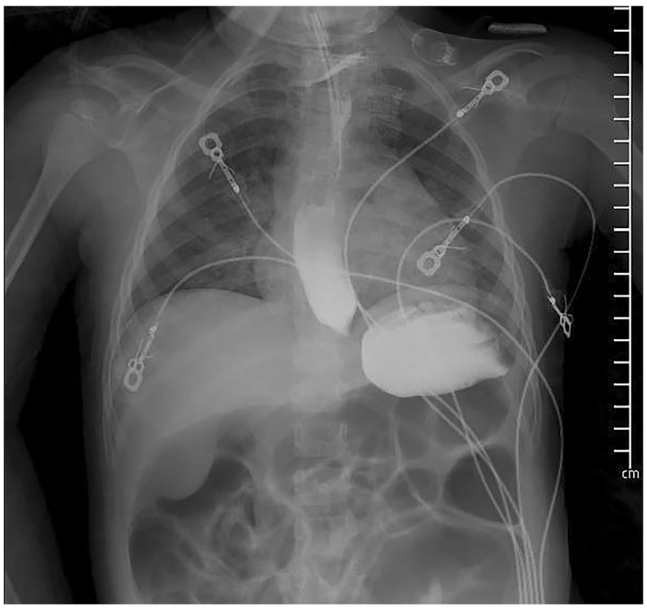


**FIGURE 1** Chest X-ray after injecting barium contrast through nasogastric tube in the operating room showing classic "Bird's-beak" appearance.

## 3 | DISCUSSION

KS is a chromosomal disorder that occurs in males, with affected individuals having more than one X chromosome. While most studies on KS focus on the disorder's reproductive consequences, limited literature exists on gastrointestinal disorders in KS. Clinical symptoms of underlying gastrointestinal disorders may include dysphagia, feeding problems, abdominal pain, and food allergies.

Achalasia is an esophageal motility disorder caused by the destruction of myenteric ganglion cells within the esophageal myenteric plexus. The damage causes reduced esophageal peristalsis and insufficient relaxation of the lower esophageal sphincter. It is rarely seen in children with an incidence of 0.11/100,000 annually.[4] Clinical symptoms include dysphagia, regurgitation (with or without food), vomiting, cough, aspiration, and chest pain. The pathophysiology of achalasia is not clearly defined, but is suspected to involve autoimmune, viral, and neurodegenerative factors.[5] The presence of neuronal autoantibodies against the myenteric plexus, antimyenteric antibodies in conjunction with inflammatory T cells, and increased inflammatory infiltrates support inflammatory and autoimmune components as being part of the pathogenesis of achalasia.[5] There is no previously reported relationship between achalasia and KS. Although limited, data suggest an increased risk of atopic diseases including asthma and allergic disorders in patients with KS likely due to supernumerary X chromosomes.[2,6]

Given the rarity of achalasia in this age range, we investigated the prevalence of achalasia within both the pediatric KS population and the general pediatric population by utilizing TriNetX. TriNetX is a real-world database consisting of electronic medical records from approximately 116 million patients across 82 healthcare organizations. The primary aim of the analysis was to discern any association of achalasia with KS. We identified 7996 individuals with KS in the pediatric population (age 2–18 years old), in whom 10 cases of achalasia were diagnosed (0.13%). In contrast, a general pediatric population of 19,051,132 individuals included 857 patients with a diagnosis of achalasia (0.004%). A $\chi^2$ test of proportion showed a statistically significant difference in prevalence between two groups ($df = 1$, $p < 0.001$), with the prevalence being 27.8 (95% confidence interval: 15.4–50.3) times higher in the KS group than that of the general group (Table 1).

**TABLE 1** Overview of the prevalence in KS and general population based on TriNetX data.

| Population | Total achalasia | Total population | Prevalence (%) | Prevalence ratio (95% CI) | $\chi^2$ test |
|---|---|---|---|---|---|
| KS in pediatric population | 10 | 7996 | 0.1251 | 27.8 (15.4–50.3) | $p < 0.001$ |
| General pediatric population | 857 | 19,051,132 | 0.0045 | | |

Abbreviations: CI, confidence interval; KS, Klinefelter syndrome.

Our database analysis demonstrates a novel and significant association between achalasia and KS. Based on these findings, further investigation into understanding the relationship between achalasia and KS is warranted. Additionally, we report an adaptive method of assessing esophageal anatomy during a fully sedated upper endoscopy for children unable to tolerate oral contrast. With the airway secured, we safely performed the esophagram using water-soluble contrast through NG placement in the supine position.

## ACKNOWLEDGMENTS

The authors have no funding to report.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ETHICS STATEMENT

Patient and parents provided permission for use of data in this case report. All data from TriNetX is deidentified in this context. Informed patient consent was obtained for publication of the case details. The parents verbally consented to the anonymous use of the patient's case for this report. Consent was documented in the patient's chart at the time of the visit.

## ORCID

*Thomas Wallach* http://orcid.org/0000-0001-6207-1363

## REFERENCES

1. Davis S, Howell S, Wilson R, et al. Advances in the interdisciplinary care of children with Klinefelter syndrome. *Adv Pediatr*. 2016;63(1):15-46. doi:10.1016/j.yapd.2016.04.020
2. Ghisa M, Savarino V, Buda A, Katzka DA, Savarino E. Toward a potential association between eosinophilic esophagitis and Klinefelter syndrome: a case series and review of the literature. *Therap Adv Gastroenterol*. 2022;15:175628482210768. doi:10.1177/17562848221076888
3. Howell S, Buchanan C, Davis SM, et al. Eosinophilic esophagitis in individuals with sex chromosome aneuploidies: clinical presentations and management implications. *Mol Genet Genomic Med*. 2021;9(12):e1833. doi:10.1002/mgg3.1833
4. Franklin AL, Petrosyan M, Kane TD. Childhood achalasia: a comprehensive review of disease, diagnosis and therapeutic management. *World J Gastrointest Endosc*. 2014;6(4):105-111. doi:10.4253/wjge.v6.i4.105
5. Furuzawa-Carballeda J, Torres-Landa S, Valdovinos MÁ, Coss-Adame E, Martín del Campo LA, Torres-Villalobos G. New insights into the pathophysiology of achalasia and implications for future treatment. *World J Gastroenterol*. 2016;22(35):7892-7907. doi:10.3748/wjg.v22.i35.7892
6. Seminog OO, Seminog AB, Yeates D, Goldacre MJ. Associations between Klinefelter's syndrome and autoimmune diseases: english national record linkage studies. *Autoimmunity*. 2015;48(2):125-128. doi:10.3109/08916934.2014.968918

**How to cite this article:** Miller L, Cho H-G, Banayan C, Vega Lemus V, Sharma S, Wallach T. Achalasia in Klinefelter syndrome: a suspected pediatric case as well as prevalence analysis suggesting increased risk in this population. *JPGN Rep*. 2024;5:374-376. doi:10.1002/jpr3.12084