

# Factors associated with recurrence of tracheoesophageal fistula

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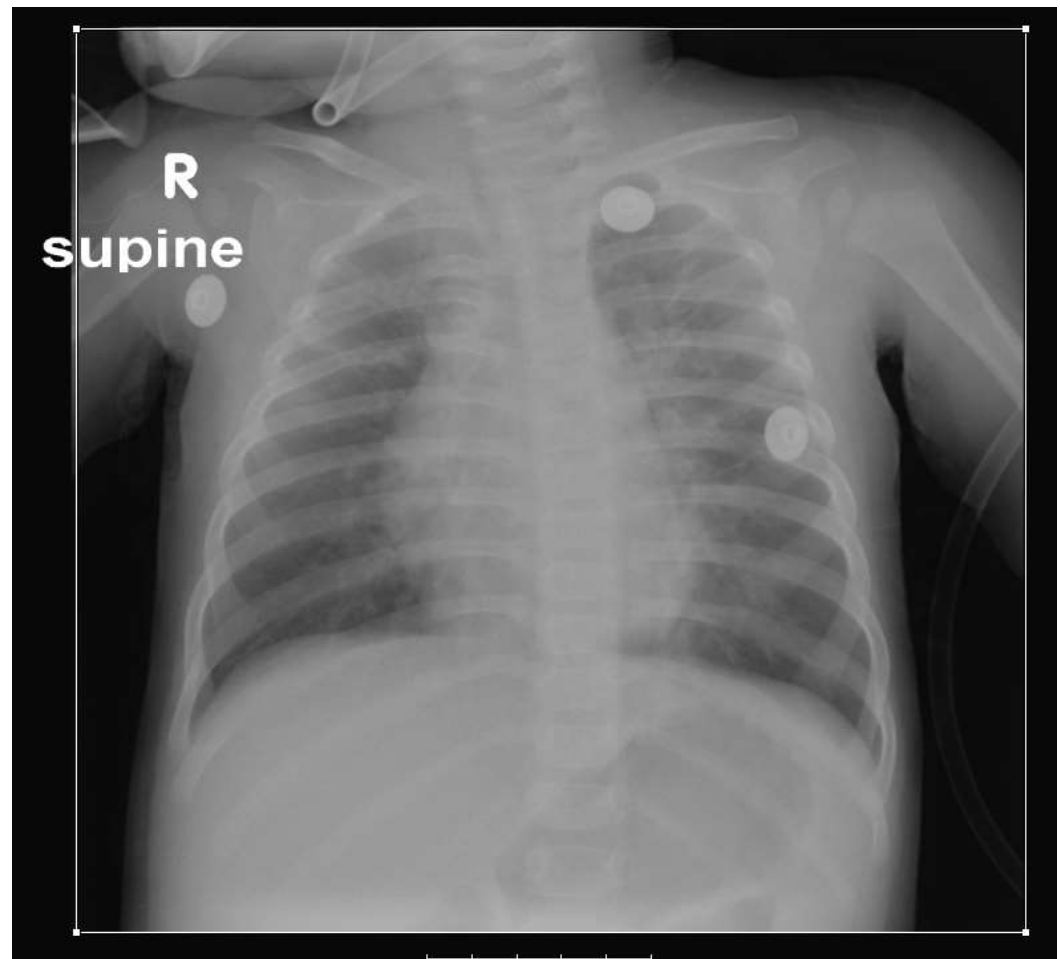
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- 9 months old boy
- Past history of tracheoesophageal fistula that was operated on at age of 1 day
- A few episodes of inhalations
- Excellent growth and development
- Admitted to the hospital due to high fever, cough and dyspnea

- On examination:
  - Temp: 38.6
  - Respiratory rate: 60 bpm
  - Saturation: 93% in room air
- On auscultation: bilateral rhonchi, prolonged expiration, bilateral wheeze



PCR positive for adenovirus  
Diagnosis: viral bronchiolitis

- Prolonged course of disease, treated with inhalations, systemic steroids and antibiotics
- 3 weeks later due to lack of improvement – bronchoscopy:
- TEF 3 cms above the carina (same location)
- Coincidence?

# TEF

- The prevalence is 1 per 2500 live births
  - Prevalence remaining constant over the years
  - Still, prenatal diagnosis not good enough
  - But genetic progression:
  - Among 375 patients with TEF, 167 genetic defects of copy number variations (CNVs) (frequency $<0.0005$ ) were reported, suggesting they can act as a modifier in a multiple hit model, or as the second hit in a recessive condition
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- Brosens E, Marsch F, de Jong EM, Zaveri HP, Hilger AC, Choinitzki VG, Hölscher A, Hoffmann P, Herms S, Boemers TM, et al. Copy number variations in 375 patients with oesophageal atresia and/or tracheoesophageal fistula. European Journal of Human Genetics. 2016 24(12):1715–1723.

# Recurrence of TEF

- Reported rates: 8-20%
- Mostly 2-18 months after the initial repair
- The term includes:
  - Recurrence of fistula in the same location
  - Acquired *de novo* fistula in a different location,
  - Second fistula that may have been missed prior to the first operation

# Difficulties in diagnosis

- Pouch vs. true fistula
  - Flexible bronchoscopy:
    - Air flow
    - Methylene blue
  - Gastroscopy
  - Barium swallow
  - Contrast injection
- Still not always unequivocal



# Known risk factors for recurrence

- Anastamotic leak
- Esophageal stenosis
- Long gap atresia
- No differences in short-term complication rates, anastomotic leak, or anastomotic stricture were found between the thoracoscopic and open approaches

- We have encountered several patients in whom recurrence of TEF was diagnosed concurrently or shortly after viral bronchiolitis
- Such an association has not been reported to date
- The objective of this study was to describe the incidence and the risk factors of recurrent TEF

# Methods

- A retrospective review of patients with a previous surgery for tracheoesophageal fistula who were followed in the Pediatric Pulmonary Institute of our hospital between January 2007 and December 2016
- Patients were excluded if the information in the hospital medical record was insufficient

# Results

- 77 patients previously operated for TEF were identified
- 3 patients were excluded due to insufficient data in the medical records
- 9 (12%) patients experienced a recurrence of TEF, eight of whom suffered a single recurrence
- 1 (1.3%) patient died at 17 years of age due to respiratory insufficiency and sepsis, after three episodes of recurrent TEF

# Results – patients' characteristics

|  |   |
|--|---|
| <b>Mean age<math>\pm</math>SD (median,range)</b> | <b>8.2<math>\pm</math>5.67 (8,0.5-28)</b>   |
| <b>Sex (M)</b>                                   | <b>41 (55%)</b>   |
| <b>Concurrent anomalies</b>                      | <b>VACTERL – 29 (39%)<br/>CHARGE – 1 (1.3%)<br/>Feingold syndrome – 1 (1.3%)<br/>Concurrent CPAM – 1 (1.3%)</b> |
| <b>Recurrence of fistula</b>                     | <b>9 (12%)</b>  |
| <b>Died</b>                                      | <b>1 (1.3%)</b>   |
| <b>FEV1 (% predicted) n=15</b>                   |   |
| <b>Mean<math>\pm</math>SD</b>                    | <b>68<math>\pm</math>20.7</b>   |
| <b>Median (range)</b>                            | <b>74 (30-96)</b>   |

**CT (n=20)**

**Normal lung fields – 6**

**Bilateral bronchiectasis – 6**

**Uneven ventilation and  
atelectasis - 4**

**Mediastinal collection – 1**

**Post lobar resection – 1**

**Bilateral infiltrates – 2**



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# Comparison of patients with and without recurrence of TEF

|  | No recurrence of TEF (n=65) | Recurrence of TEF (n=9) | P value |
|--|-----------------------------|-------------------------|---------|
| <b>Age</b>   | 7 (4-11)                    | 8 (1.5-11.5)            | 0.97    |
| <b>Gender (M)</b>                                      | 36 (55%)                    | 5 (56%)                 | 1.00    |
| <b>Patients hospitalized with respiratory symptoms</b> | 32 (49%)                    | 7 (77%)                 | 0.16    |
| <b>VACTERL association</b>                             | 27 (42%)                    | 2 (22%)                 | 0.46    |
| <b>FEV1% predicted (mean±SD)</b>                       | 69.7(±22.6)<br>n=14         | 62 (±17)<br>n=3         | 0.51    |
| <b><u>Surgery</u></b>                                  |                             |                         |         |
| <b>Open</b>  | 42 (65%)                    | 5 (56%)                 | 0.72    |
| <b>Thoracoscopy</b>                                    | 23 (35%)                    | 4 (44%)                 |         |
| <b>Prolonged respiratory assistance</b>                | 18/61 (30%)                 | 1/7 (14%)               | 0.66    |
| <b>Gastrointestinal symptoms</b>                       | 40 (62%)                    | 6 (67%)                 | 1.00    |
| <b>Anatomic abnormality (c type)</b>                   | 60 (92%)                    | 9 (100%)                | 1.00    |
| <b>Atretic gap (cm)</b>                                | 1.56 (0-4)<br>n=42          | 1.6 (1-3)<br>n=5        | 1.00    |



# Patients hospitalized for respiratory symptoms

|  | No recurrence of TEF (n=32/65) | Recurrence of TEF (n=7/9) | P value |
|--|--------------------------------|---------------------------|---------|
| No. of hospitalizations                                | 57                             | 34                        |         |
| No. of hospitalizations per patient (median, 25-75%)   | 1.5 (1-2)                      | 3 (2-6)                   | 0.011   |
| No. of patients with bronchiolitis                     | 19/32                          | 7/7                       | 0.073   |
| Episodes of bronchiolitis per patient (median, 25-75%) | 1 (1-2)                        | 3 (2-6)                   | <0.0001 |
| Episodes of positive PCR during bronchiolitis          | 15/30                          | 9/24                      | 0.42    |
| No. of positive PCR per patient (median, 25-75%)       | 0 (0-1)                        | 1 (1-2)                   | 0.009   |



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# Results

- 6/7 patients with recurrent TEF had a positive PCR for at least one respiratory virus
- 11/32 patients without recurrent TEF had a positive PCR for at least one respiratory virus
- PCR panel includes parainfluenza, influenza A&B, RSV, HMPV and adenovirus
- Adenovirus was the most frequent virus, identified in 6 patients with and 3 patients without recurrent TEF
- Patients with recurrence of TEF had significantly more episodes of positive PCR for viruses ( $p=0.009$ )

# Discussion

- In this retrospective study, we assessed the factors associated with recurrence of TEF
- Recurrence of TEF was associated with more hospitalizations for respiratory infections, more hospitalizations for bronchiolitis and a higher rate of positive PCR for viruses
- Such an association has not been reported yet

# Discussion

- Recurrence of TEF is not always easy to diagnose
- Requires additional corrective surgery
- Over the past years a few alternative methods, such as injections of fibrin glue and bio-absorbable patches have been developed

# Discussion

- We found higher episodes of positive PCR for viruses per patient in the patients with recurrent TEF
- The term “recurrence of TEF” referred to all the patients who had a fistula after prior surgery
- This may include recurrence of fistula in the same location as the original fistula, fistula *de novo* in a different location, and a second fistula that may have been missed prior to the first operation

# Discussion

- An association between *de novo* fistula and infectious agents has been reported in immunosuppressed patients:
  - A renal transplant patient following *Mycobacterium tuberculosis* infection
  - A patient with HIV-1 who had necrotizing candidiasis of the trachea that resulted in the formation of a TEF
  - A patient with aplastic anemia and invasive pulmonary aspergillosis
- Samhan M, Al-mousawi M, Halim M, Nampoory MRN. Tuberculous Tracheo-Esophageal Fistula in a Renal Transplant Patient. Saudi Journal of Kidney Diseases and Transplantation. 2005;16(2):198–200.
- Rusconi S, Meroni L, Galli M. Tracheoesophageal fistula in an HIV-1-positive man due to dual infection of *Candida albicans* and cytomegalovirus. Chest. 1994;106(1):284–5.
- Yu Y, Zhu C, Qian X, Gao Y. Tracheoesophageal fistula induced by invasive pulmonary aspergillosis. Ann Transl Med 2016;4:345.



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# Discussion

- The exact mechanism of the development of these fistulae is unknown
- The patients in our study who developed recurrence of TEF were immunologically intact
- We may postulate that, following TEF repair, the tracheoesophageal area may be more vulnerable to additional insults such as viral infections

# Discussion

- Study limitations:
  - Relatively small sample size
  - Retrospective nature
  - Not all patients underwent bronchoscopy prior to the first operation; hence, we could not clearly categorize the fistula
  - As it is merely a descriptive study, we were unable to establish the cause and effect relationships

# Discussion

- It is impossible to determine whether the bronchiolitis itself increases the risk of recurrence of TEF, or whether patients who develop recurrence of fistula are more vulnerable to common infectious agents in the process



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# Conclusion

- Patients with a history of TEF and hospitalizations for viral bronchiolitis should be carefully evaluated for the possibility of recurrent TEF
- Vaccinations against RSV and influenza for patients with a history of TEF may be beneficial
- Further larger prospective studies should be conducted in order to better understand the association between viral bronchiolitis and recurrent TEF