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Effects of antibiotics, hospitalisation and surgical complications on self-reported immunological vulnerability following paediatric open-heart surgery and thymectomy: a single-centre retrospective cohort study

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ABSTRACT

Background Partial or complete thymectomy is routinely performed in paediatric open-heart surgeries when treating congenital heart defects. Whether or not thymectomised children require systematic immunological monitoring later in life is unknown. The objective of this study was to investigate the effects of preoperatively and postoperatively used antibiotics, hospitalisation and surgical complications on self-reported immunological vulnerability in paediatric patients with early thymectomy to better recognise the patients who could benefit from immunological follow-up in the future.

Methods We conducted a retrospective cohort study, including 98 children and adolescents aged 1–15 years, who had undergone an open-heart surgery and thymectomy in infancy and who had previously answered a survey regarding different immune-mediated symptoms and diagnoses. We performed a comprehensive chart review of preoperative and postoperative factors from 1 year preceding and 1 year following the open-heart surgery and compared the participants who had self-reported symptoms of immunological vulnerability to those who had not.

Results The median age at primary open-heart surgery and thymectomy was 19.5 days in the overall study population (60% men, n=56) and thymectomies mainly partial (80%, n=78). Broad-spectrum antibiotics were more frequently used preoperatively in participants with self-reported immunological vulnerability (OR=3.05; 95% CI 1.01 to 9.23). This group also had greater overall use of antibiotics postoperatively (OR=3.21; 95% CI 1.33 to 7.76). These findings were more pronounced in the subgroup of neonatally operated children. There was no statistically significant difference in the duration of intensive care unit stay, hospitalisation time, prevalence of severe infections, surgical complications or glucocorticoid use between the main study groups.

Conclusion Antimicrobial agents were more frequently used both preoperatively and postoperatively in thymectomised children with self-reported immunological vulnerability after thymectomy. Substantial use of antimicrobial agents early in life should be considered a potential risk factor for increased immunological vulnerability when evaluating the significance of immune-mediated symptom occurrence in thymectomised paediatric patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early thymectomy seems to increase the risk for immunological alterations later in life. Whether or not thymectomised children require regular immunological follow-up after the heart surgery is not yet established.

WHAT THIS STUDY ADDS

⇒ This study found that frequent use of antibiotics before and after thymectomy is associated with increased self-reported immunological vulnerability in the years following thymectomy.

⇒ Occurrence of surgical complications was not associated with self-reported or parental-reported immunological vulnerability in thymectomised paediatric patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Substantial use of antibiotics early in life should be considered a potential risk factor when assessing the need for regular immunological follow-up of thymectomised paediatric patients.

INTRODUCTION

Thymus is a primary lymphoid organ accounting for the maturation of T lymphocytes of adaptive immune system. Located posterior to sternum and anterior to heart while reaching its maximum neonatal size approximately at fourth month of life,[1] it

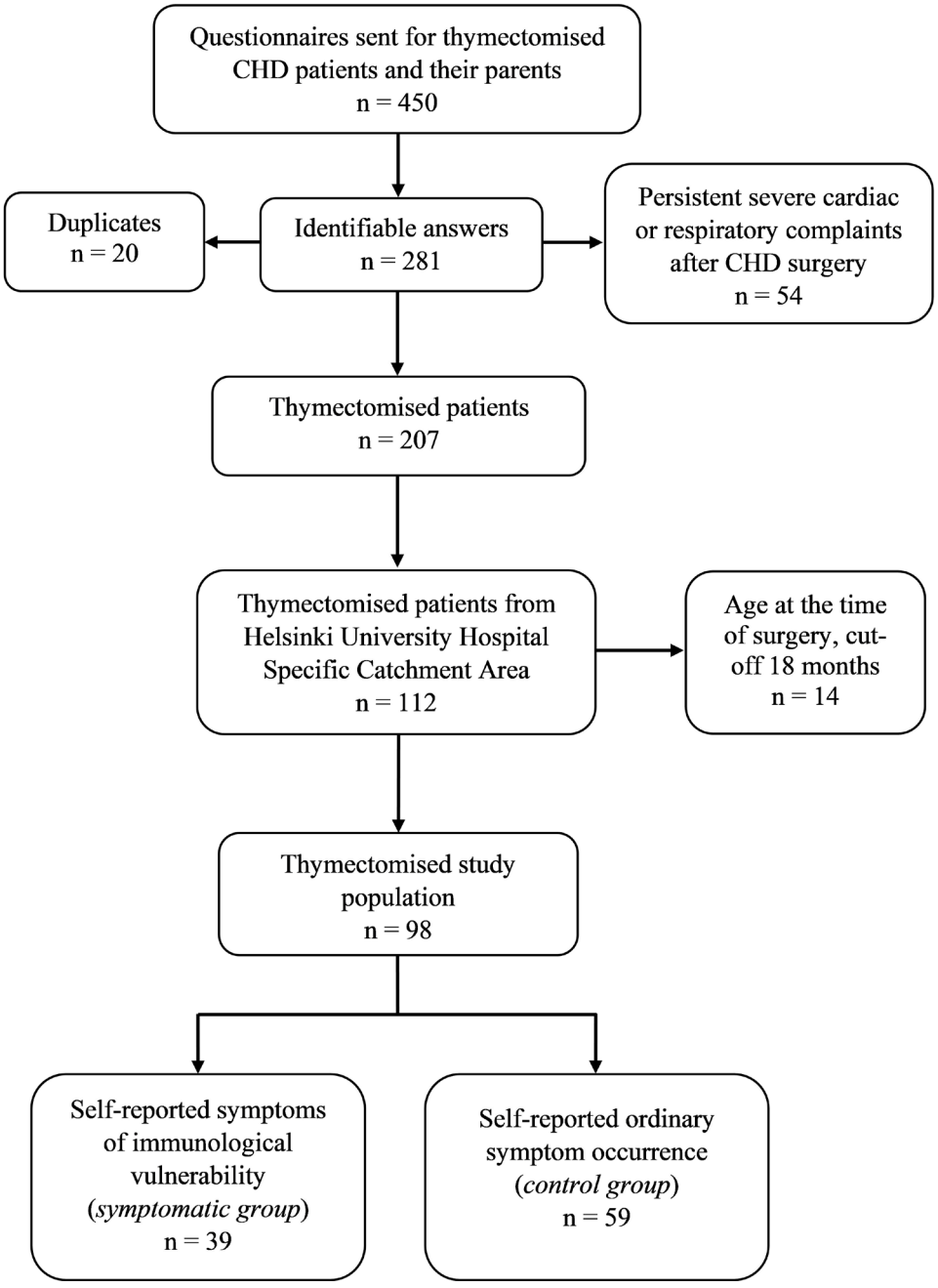

Figure 1 Flowchart of patient selection and grouping. CHD, congenital heart defect.

poses an anatomical challenge for paediatric cardiac surgeons. Partial or complete thymectomy is, therefore, routinely performed to gain better surgical visualisation of heart and major vessels when operating a congenital heart defect (CHD).

Early thymic function is essential for establishing competent adaptive immunity and congenital perturbation of fetal thymic development can result in clinical immunodeficiency, as seen in 22q11.2 deletion syndrome (DiGeorge syndrome). Early thymectomy affects T lymphocyte levels by decreasing the count of CD3+, CD4+, CD8+ and naïve T lymphocytes post-thymectomy while the effect on memory T cells remains unclear.[2–7] Delayed antibody response to vaccination has also been reported and overall immunological profile skews towards premature immunological ageing after early thymectomy.[4 8 9] Due to these adverse effects, it is recommended to resect as little thymic tissue as possible when operating a CHD while maintaining necessary exposure of the surgical field.[2 3 9–11]

Despite alterations in T cell compartment, only a few studies have found signs of possible immunocompromise later in life. Early thymectomy has been associated with longer infection-related hospitalisations, increased infections, autoimmune diseases, atopy and cancer later in life.[3 10] Our recent study[12] showed that thymectomised children's parents reported and adolescents self-reported more frequent lower respiratory tract

Table 1 Demographics of the symptomatic and control groups

	Symptomatic group n=39	Control group n=59	Total n=98	P value
Sex				
Male	19 (49%)	37 (63%)	56 (60%)	0.171
Female	20 (51%)	22 (37%)	42 (40%)	
Age group (age at the time of survey)				0.894
1–3 years	12 (31%)	19 (32%)	31 (32%)	
5–7 years	17 (43%)	23 (39%)	40 (41%)	
13–15 years	10 (26%)	17 (29%)	27 (27%)	
Birth information				
Preterm birth (< 37 weeks)	2 (5%)	4 (7%)	6 (6%)	0.739
Birth weight (g), mean (SD)*	3210 (582)	3320 (735)	3270 (674)	0.426
Birth height (cm), mean (SD)†	49 (2.1)	49 (3.2)	49 (2.8)	0.401
Gestational age-adjusted SD score, mean (SD)‡	−0.77 (1.2)	−0.58 (1.4)	−0.66 (1.4)	0.532
Twin pregnancy	1 (3%)	4 (7%)	5 (5%)	0.353
Time of operation				0.326
< 1 months of age	22 (56%)	29 (49%)	51 (52%)	
1–12 months of age	12 (31%)	26 (44%)	38 (39%)	
> 12 months of age	5 (13%)	4 (7%)	9 (9%)	
Age (days) at time of surgery, median (IQR)	17 (5.5, 149.5)	50 (7, 141.5)	19.5 (6, 143.8)	0.655
Urgency				
Urgent	10 (25%)	12 (20%)	22 (22%)	0.538
Elective	29 (75%)	47 (80%)	76 (78%)	
Thymectomy§				
Partial	30 (77%)	48 (81%)	78 (80%)	0.480
Total	4 (10%)	10 (17%)	14 (14%)	
Additional open-heart surgeries during the follow-up period				
None	30 (77%)	50 (85%)	80 (82%)	0.328
One	8 (20%)	7 (12%)	15 (15%)	0.245
Two	1 (3%)	2 (3%)	3 (3%)	0.816

*N/A for 2 cases in the symptomatic group and for 8 in the control group.
† N/A for 3 cases in the symptomatic group and for 18 in the control group.
‡ N/A for 6 cases in the symptomatic group and for 13 in the control group.
§N/A for 5 cases in the symptomatic group and for 1 in the control group.

infections, wheezing and asthma compared with healthy non-thymectomised children. However, the study did not assess the effect of factors apart from thymectomy.

We conducted a retrospective cohort study, including a subset of thymectomised paediatric patients enrolled in our previous nationwide cohort study.[12] We reviewed and compared the preoperative and postoperative use of antibiotics and glucocorticoids, hospitalisation time and occurrences of surgical complications of the participants who had self-reported symptoms of immunological vulnerability to those who had not. The aim of this study was to assess the effects of pre- and postoperative factors on immunological vulnerability emerging after thymectomy to better identify the children and adolescents who would benefit from more robust immunological follow-up later in life.

METHODS

Study design and population

This retrospective cohort study included a subset of thymectomised children who had participated in our previous nationwide cohort study[12] and who resided at the Helsinki University Hospital Specific Catchment Area. Patients were derived from The Research Registry of Pediatric Cardiac Surgery (Helsinki, Finland) maintained by

Table 2 Cardiac diagnoses of the study groups

	Symptomatic group n=39	Control group n=59	P value
Primary heart defect			0.214
UVH	5 (13%)	3 (5%)	
TGA	6 (15%)	12 (20%)	
TOF	3 (8%)	8 (14%)	
Outflow tract obstructions	13 (33%)	11 (19%)	
Shunt lesions	12 (31%)	22 (37%)	
Other	0 (0%)	3 (5%)	
Complex* and mild defects			0.386
Complex	17 (44%)	31 (53%)	
Mild	22 (56%)	28 (47%)	
All cardiac diagnoses present in the study population			
VSD	21 (54%)	28 (48%)	0.536
ASD or PFO	13 (33%)	10 (17%)	0.061
CoA	11 (28%)	8 (14%)	0.073
TGA	6 (15%)	12 (20%)	0.535
HAA	5 (13%)	6 (10%)	0.684
TOF	3 (8%)	8 (14%)	0.368
PDA	3 (8%)	6 (10%)	0.678
UVH	5 (13%)	3 (5%)	0.171
LSVC	0 (0%)	6 (10%)	0.040
APW	2 (5%)	3 (5%)	0.992
AVSD	4 (10%)	1 (2%)	0.059
DORV	2 (5%)	3 (5%)	0.992
TAPVR or PAPVR	1 (3%)	3 (5%)	0.537
IAA	1 (3%)	2 (3%)	0.816
PA	1 (3%)	2 (3%)	0.816
ALCAPA	0 (0%)	2 (3%)	0.245
Dextrocardia	1 (3%)	0 (0%)	0.216
Ebstein's anomaly	0 (0%)	1 (2%)	0.414

Note that a patient can have multiple different cardiac defect diagnoses simultaneously, that is, the absolute nor the proportional values do not add up to the total number of participants nor 100%.
*Complex defects include UVH, TGA, TOF, TAPVR, IAA, DORV, PA with VSD, and Ebstein's anomaly.
ALCAPA, anomalous left coronary artery from the pulmonary artery; APW, aortopulmonary window; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of aorta; DORV, double-outlet right ventricle; HAA, hypoplastic aortic arch; IAA, interrupted aortic arch; LSVC, persistent left superior vena cava; PA, pulmonary atresia; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defects; VSD, ventricular septal defect.

New Children's Hospital, Helsinki. As part of the previous nationwide study, the thymectomised participants and healthy age-matched controls had answered an electronic survey focusing on their immunological health. Surveys were sent for three separate age groups (1–3, 5–7 and 13–15 years) based on the recommended guidelines for investigating immunological function in paediatric patients with 22q11.2 deletion syndrome.[13] Adolescents over 13 years of age responded either themselves or with the help of their parents, whereas the parents answered the survey for participants under 13 years of age. For this study, we divided the thymectomised participants from the previous survey study by Rantanen *et al*[12] into two groups based on their answers in the electronic questionnaire. All thymectomised participants who had self-reported or parent-reported any of the clinically used warning signs to detect primary and secondary immunodeficiencies, or immune-mediated symptoms associated with thymectomy based on the current scientific literature (recurrent infectious events including pneumonia, otitis media, herpes infections, non-specific fever, prolonged cough or mucous cough; hospital admissions related to infectious or respiratory or dermatologic diseases; autoimmune diseases or unspecific gastrointestinal symptoms)[10 14 15] in the survey, were considered immunologically vulnerable and thus included in the *symptomatic group*, while all thymectomised participants who did not self-report any of these symptoms formed the *healthy thymectomised control group*. These criteria for the group allocation were decided by the paediatricians and infectious disease specialists before conducting the previous questionnaire study. Patients born with low birth weight (≤1499 g), or before 28th gestational week, or diagnosed with 22q11.2 deletion syndrome, Down syndrome, Noonan syndrome, KAT6A syndrome, Milroy syndrome, Mulibrey nanism or chromosome 18 translocation, were excluded from the study since these conditions affect the immune system independently. All patients had undergone an open-heart surgery in Helsinki University Children's Hospital between June 2006 and December 2019.

Data collection and definitions

The information on study subjects' demographics (sex, gestational age, birth weight and height, possible twin pregnancy, and heart defect types) and preoperative and postoperative factors relevant to the study question (antibiotic and glucocorticoid use, surgical complications, hospitalisation and time in intensive care unit (ICU)) was retrieved from the medical records of tertiary healthcare. Details related to the cardiac operation and thymectomy (age at the time of operation, whether the thymectomy was complete or partial, was the operation performed urgently or as elective, and the number of open-heart surgeries during 1-year follow-up) were derived from the operative reports. Surgical complications that could have impact on either immune or cardiopulmonary system (infections, chylous leakage, arrhythmia, severe bleeding and prolonged mechanical ventilation) were also reviewed from the medical records and operative notes. Preoperative data were collected from medical records dating back to subjects' birth, and postoperative data until 1 year from subject's first open-heart surgery.

Antibiotics were classified as either narrow-spectrum or broad-spectrum depending on their antimicrobial

Table 3 Preoperative factors, complications and postoperative factors of the symptomatic and control groups

	Symptomatic group n=39	Control group n=59	P value	OR (95% CI)
Preoperative factors				
Antibiotic use				
Any	16 (41%)	16 (27%)	0.151	1.87 (0.79 to 4.41)
Narrow-spectrum	13 (33%)	13 (22%)	0.215	1.77 (0.71 to 4.38)
Broad-spectrum	10 (26%)	6 (10%)	0.043	3.05 (1.01 to 9.23)
Infections	5 (13%)	4 (7%)	0.311	2.02 (0.51 to 8.06)
ICU stay (days), median (IQR)	1(0, 4.5)	0(0, 2.5)	0.057	
Glucocorticoid treatment	6 (15%)	12 (20%)	0.535	0.71 (0.24 to 2.09)
Complications				
Infections	15 (39%)	18 (31%)	0.415	1.42 (0.61 to 3.33)
Arrhythmia	10 (26%)	11 (19%)	0.409	1.50 (0.57 to 3.98)
Excessive bleeding	1 (3%)	2 (3%)	0.816	0.75 (0.07 to 8.56)
Reoperation (≤ 30 days)	1 (3%)	1 (2%)	0.766	1.53 (0.09 to 25.15)
Chylous leakage	7 (18%)	5 (9%)	0.161	2.36 (0.69 to 8.07)
Mechanical ventilation after first open-heart surgery			0.469	
No PMV (0–1 day)	14 (36%)	22 (37%)		
Mild PMV (2–3 days)	6 (15%)	14 (24%)		
Medium PMV (4–7 days)	12 (31%)	18 (31%)		
Extended PMV (> 7 days)	7 (18%)	5 (9%)		
Mechanical ventilation time during the 1 year follow-up (d), median (IQR)	4(0, 9)	3(1, 5)	0.621	
Postoperative factors				
Antibiotic use				
Any	29 (74%)	28 (48%)	0.008	3.21 (1.33 to 7.76)
Narrow-spectrum	26 (67%)	28 (48%)	0.061	2.21 (0.96 to 5.13)
Broad-spectrum	16 (41%)	15 (25%)	0.104	2.04 (0.86 to 4.85)
Hospitalisation time after first open-heart surgery (days), median (IQR)	14(9, 22)	10(7, 15)	0.074	
Time spent ICU during the 1 year follow-up (days), median (IQR)	6(3, 11.5)	5(2.5, 8)	0.540	
Glucocorticoid treatment	11 (28%)	17 (29%)	0.948	0.97 (0.40 to 2.38)

ICU, intensive care unit; PMV, prolonged mechanical ventilation.

effect. First and second-generation cephalosporins, phenoxymethylpenicillin, benzylpenicillin, ampicillin, amoxicillin, cloxacillin and nitrofurantoin were classified as narrow-spectrum antibiotics whereas all the other used antibiotics (ceftriaxone, carbapenems, aminoglycosides, macrolides, clindamycin, metronidazole, vancomycin, trimethoprim-sulfadiazine, piperacillin and aztreonam) were classified as broad-spectrum. Arrhythmias requiring antiarrhythmic drugs or pacemaker treatment after the cardiac procedure was considered a surgical complication. Operations performed in 30 days since the last operation were classified as reoperations. Time of hospitalisation was determined from the date the subject ended up in hospital care leading to thymectomy until the date of discharge. The stay in ICU was assessed as the total time spent in ICU during the preoperative and 1-year postoperative period, meaning if the patient ended up in the ICU multiple times during our study window, all days in ICU were included. The duration of mechanical ventilation was measured as number of days intubated during the original open-heart surgery as well as during the 1-year study window.

Statistical analysis

Statistical analysis was performed using R statistical computing software, V.4.2.1,[16] using *tableone* package.[17] Continuous data were summarised as mean and SD when normally distributed and as median and IQR when non-normally distributed. Student's t-test was used for normally distributed data, Mann-Whitney U test for

Table 4 General overview of complications reported in the study population

	Symptomatic group n=39	Control group n=59
Infections		
Preoperative	► Viral gastroenteritis ► Viral bronchiolitis ► Acute respiratory infection ► Urinary tract infection ► Surgical site infection following balloon angioplasty for coarctation of aorta	► Bacteraemia ► Viral bronchiolitis ► Unspecified infection focus after catheter procedure
Postoperative	► Sepsis ► Catheter-related bloodstream infection (CRBSI) ► Operation area infection ► Viral gastroenteritis ► Pneumonia	► Sepsis ► Catheter-related bloodstream infection (CRBSI) ► Operation area infection ► Unspecific infection focus ► Urinary tract infection ► *Clostridioides difficile* gastroenteritis ► Acute respiratory infection
Bleeding complications	► Surgical site haemorrhage	► Haemothorax ► Cerebral haemorrhage
Arrhythmic complications	► Junctional ectopic tachycardia ► Supraventricular tachycardia ► Atrial flutter	► Junctional ectopic tachycardia ► Supraventricular tachycardia ► Atrial flutter

non-normally distributed data and χ^2 test for categorical data. A p value ≤0.05 was considered statistically significant. In addition, ORs and 95% CIs were assessed by cross-tabulation for categorical variables.

RESULTS

Of the nationwide study cohort, we included participants from every age group who resided in the Helsinki University Hospital Specific Catchment Area (n=112). The symptomatic group included 43 patients and the control group 69 patients. We excluded 14 patients who had had open-heart surgery significantly later in life than their study peers (aged 18 months or older). Final study population consisted of 98 subjects with 39 subjects in the symptomatic group and 59 subjects in the control group. Patient selection algorithm is shown in figure 1.

Patient demographics

The demographic data are shown in table 1. Median age at thymectomy in the symptomatic group was 17 days ((IQR from 5.5 to 149.5 days) and in the control group 50 days (IQR from 7 to 141.5 days; p=0.655). 56% of the symptomatic group and 49% of the control group participants were operated within the first month of life.

Most open-heart surgeries were classified as elective (75% vs 80%) and thymectomies as partial (77% vs 81%). The information about the grade of thymectomy was missing for 6% of the study population. Eighteen children had multiple heart operations during our follow-up period (15 patients had two operations and 3 patients three operations) due to the complexity of the heart defect (eg, univentricular heart (UVH) defect requiring staged palliation) or to reoperation if the original procedure did not suffice.

Cardiac defects

Cardiac diagnoses are shown in table 2. Primary cardiac defects were similar between the two groups (p=0.214). Most common primary defects were outflow tract obstructions (33% vs 19%) and shunt lesions (31% vs 37%). We additionally classified the defect types either mild or complex to further evaluate the effect of the cardiac condition. Cyanotic defects, including UVH defects, transposition of the great arteries (TGA), tetralogy of Fallot (TOF), total anomalous pulmonary venous return (TAPVR), interrupted aortic arch, double-outlet right ventricle, pulmonary atresia with ventricular septal defect and Ebstein's anomaly,[18] were classified as complex. Other heart defects were categorised as mild. There was no statistically significant difference in the prevalence of complex heart defects (p=0.386) between the groups.

Preoperative antibiotics, ICU stay and glucocorticoid treatments

We found a statistically significant difference in the preoperative use of broad-spectrum antibiotics (26% vs 10%; p=0.043; OR 3.05; 95% CI 1.01 to 9.23, table 3) between the groups. Narrow-spectrum antibiotics and antibiotic treatment of any type were also more frequently used in the symptomatic group than in the control group (33% vs 22%; 41% vs 27%, respectively), but the differences were not statistically significant (p=0.215 and p=0.151, table 3). Severe infections requiring hospital care before thymectomy were apparent in five symptomatic group subjects and in four control subjects (13% vs 7%;

Table 5 Subgroup analysis of participants who had first open-heart surgery and thymectomy during the first month of life, and those operated 1–12 months after birth

	Less than 1 month after birth			1–12 months after birth		
	Symptomatic group n=22	Control group n=29	P value	Symptomatic group n=12	Control group n=26	P value
Sex						
Male	12 (55%)	20 (69%)	0.291	5 (42%)	14 (54%)	0.485
Female	10 (45%)	9 (31%)		7 (58%)	12 (46%)	
Heart defect severity						
Mild	8 (36%)	7 (24%)	0.343	10 (83%)	17 (65%)	0.257
Complex	14 (64%)	22 (76%)		2 (17%)	9 (35%)	
Age (days) at time of surgery, median (IQR)	6(4, 10)	7(5, 10)	0.522	126.5(98, 252)	134(81, 207)	0.520
Hospitalisation after first open-heart surgery (days), median (IQR)	17(14, 25)	11(10, 16)	0.003	10(8, 13)	7(7, 14)	0.515
Preoperative antibiotic use						
Any	9 (41%)	9 (31%)	0.465	5 (42%)	5 (19%)	0.144
Narrow-spectrum	7 (32%)	7 (24%)	0.543	4 (33%)	4 (15%)	0.207
Broad-spectrum	5 (23%)	6 (21%)	0.861	4 (33%)	0 (0%)	0.002
Postoperative antibiotic use						
Any	19 (86%)	13 (45%)	0.002	7 (58%)	13 (50%)	0.632
Narrow-spectrum	16 (73%)	13 (45%)	0.046	7 (58%)	13 (50%)	0.632
Broad-spectrum	12 (55%)	7 (24%)	0.026	4 (33%)	8 (31%)	0.874

p=0.311). Even though we found a difference in preoperative broad-spectrum antibiotic use, the incidence of preoperative severe infections did not differ between the groups (p=0.311). Preoperative median ICU stay in the symptomatic group was 1 day (IQR 0–4.5 days) and in the control group 0 days (IQR 0–2.5 days). There was no difference in the use of glucocorticoids neither preoperatively (p=0.535) nor postoperatively (p=0.948).

Surgical complications

Fifteen symptomatic subjects (39%) and 18 controls (31%) suffered from postoperative infection following open-heart surgery and thymectomy (p=0.415). Most common infections were surgical site bacterial infection and catheter-related bloodstream infections. Postoperative complications reported in our study population are listed in table 4.

Mechanical ventilation is a risk factor for neonatal lung injury,[19] and in the long-term, it can damage the tissues of respiratory system.[20] Median length of mechanical ventilation did not differ significantly between the groups (4 days (IQR 0–9) vs 3 days (IQR 1–5); p=0.621). The symptomatic group had slightly more patients with extended mechanical ventilation (defined as mechanical ventilation lasting longer than 7 days[21]; 18% vs 9%), but the difference was not statistically significant.

Chylous leakage can occur after open-heart surgery if the lymphatic ducts are surgically severed during the procedure or if the outcome of the surgery alters the lymphatic flow (such as in Fontan circulation).[22] As chyle is rich in lymphocytes and immunoglobulins, chylothorax, chylopericardium or chylous ascites can result in immunological malfunction.[23 24] In this study, chylous leakage was more common in the symptomatic group (seven subjects, 18%) than in the control group (five subjects, 9%), but this difference was not statistically significant (p=0.161). We could not detect statistically significant differences in other surgical complications either (table 3).

Postoperative antibiotics and hospitalisation time

Postoperatively, the overall antibiotic use was more frequent in the symptomatic group subjects (74% vs 48%; p=0.008; OR 3.21; 95% CI 1.33 to 7.76). When considering different types of antibiotics separately, there were no statistically significant differences in postoperative narrow-spectrum and broad-spectrum antibiotic use (67% vs 48%, p=0.061 and 41% vs 25%, p=0.104).

Median hospitalisation time following the initial open-heart surgery tended to be slightly longer in the symptomatic group (14 days (IQR 9–22) vs 10 days (IQR 7–15)) as well as the median stay in ICU (6 days (IQR 3–11.5) vs 5 days (IQR 2.5–8)). However, these differences did not reach statistical significance (p=0.074 and p=0.540, respectively).

Impact of the age at surgery

We conducted a subpopulation analysis in children who were operated within the first month of life and in those operated 1–12 months after birth (table 5). The

children and adolescents of the symptomatic group who were operated during the first month of life had received more postoperative antibiotics compared with the control group regardless of the antibiotic spectrum (86% vs 45%, p=0.002). Additionally, these participants had longer hospitalisation times (17 days (IQR 14, 25) vs 11 days (IQR 10, 16), p=0.003). There was statistically significant difference in preoperative antibiotic use within the symptomatic and control group participants operated 1–12 months after birth (33%, n=4 vs 0%, n=0; p=0.002).

DISCUSSION

In this study, we found that thymectomised paediatric patients who self-reported symptoms of immunological vulnerability years after thymectomy had received more often antimicrobial treatments before and within 1 year after thymectomy and this effect was prominent especially in children operated in neonatal period. We could not detect statistically significant differences in the incidence of surgical complications or the severity of cardiac condition between the two main study groups.

Whether early thymectomy could cause clinically relevant immunological malfunction during childhood is unclear. Karazisi *et al*[25] found an association with early cardiac surgery and increased cancer risk in children, but several other studies have not found clinically relevant effects during childhood and adolescence following early thymectomy.[5 11 26] Our previous national questionnaire study found that, on average, thymectomised children and adolescents self-reported more frequently pneumonia, wheezing and asthma.[12] However, not all thymectomised participants self-reported symptom occurrence. Thus, we aimed to seek factors that might contribute to immunological vulnerability in thymectomised children.

We hypothesised the early use of antimicrobial treatments as such factor, as the use of antimicrobials after birth and in early childhood has the power to perturb the early-life development of gut microbiota.[27–30] The education of immune tolerance in infants depends on the successful colonisation of the gastrointestinal tract with commensal microbes[31] and this event is highly susceptible to perturbations caused by antibiotics, especially if broad-spectrum.[32] Early-life antibiotics results in less-diverse composition of microbiota[29] and have also been associated with increased risk for atopic dermatitis,[33] juvenile arthritis,[34] wheezing[35] and asthma,[36 37] that is, manifestations of immunological vulnerability. Children who were thymectomised during open-heart surgery have been reported to receive longer anti-infective therapies compared with their non-thymectomised peers.[38] We found an association with self-reported immunological vulnerability and more frequent antibiotic use in early childhood among thymectomised paediatric patients. Antibiotics were more frequently used especially in neonatally operated children. Our finding, thus, suggests that there might be an additive detrimental effect of early use of antibiotics and thymectomy on the long-term health of the children undergoing cardiac surgery. Additionally, Hermes *et al*[39] found that thymectomised children suffering from gastro-oesophageal reflux had more infections compared with thymectomised children without reflux. Their study suggests the importance of comorbidity as a risk factor for immunological vulnerability after thymectomy. We propose that antimicrobial use early in life, especially during neonatal period, could act as a similar comorbid factor, hypothetically due to a dysfunctional gut microbiota.

While antimicrobial therapies were more commonly administered in the symptomatic group, the overall incidence of severe infections did not differ between the groups. This discrepancy is likely related to the fact that our data are based on the medical records of tertiary healthcare where anti-infective treatment is often administered as soon as the earliest signs of infection (eg, increased inflammation markers) appear even when the presence of an infection is unclear. The effect of cardiac condition in our study population was examined by the type of defect and the age at primary cardiac surgery. The prevalence of the complex cardiac defects such as UVH, TGA and TOF were similar between the two groups as well as the participants' age at the time of primary operation. While we did not find differences in the severity of cardiac defects between the groups, we cannot completely exclude the possibility that the differences in later health could be affected by cardiac condition, as findings by Bremer *et al*[40] suggest that complex CHDs can affect the thymic function even before thymectomy. Broad-spectrum antibiotics were already more often administered in the symptomatic group before thymectomy, which could be due to immunological effects of complex CHD or an unknown malfunction of the immune system or other simultaneous comorbidities increasing the risk for immunological vulnerability. Liberal use of antimicrobials after thymectomy could then be a consequence of otherwise compromised immune system rather than the cause of immunological malfunction.

Limitations of this study include the retrospective study design, which limits our ability to assess causal effect, limited sample size reducing statistical power and the possibility of response bias as our classification of immunological vulnerability was based on the self-reported answers in the survey. The risk for immunological compromise might be increased in patients who were excluded from this study (eg, extremely low birth weight, extreme prematurity) as thymectomised children with comorbidities seem to benefit from more rigorous immunological evaluation. We could not adequately compare the effects of total thymectomy to partial thymectomy since total thymectomies were only performed in 14% of the study population (ie, total of 14 patients), as the custom of performing a total thymectomy has lately become increasingly rare as studies have recommended avoiding the complete removal.[2 3 9–11] Focusing only on children who have undergone total thymectomy could have provided more insight into the role of thymus

removal itself, although requiring careful assessment of the possible inherent immunological effect of complex CHDs.[40]

Our findings suggest an association between self-reported immunological vulnerability and increased use of antibiotics in early childhood in thymectomised children. These findings are in accordance with recent scientific results regarding the immunological effects of early-life antibiotics in paediatric patients.[29 35–37] To evaluate the effects of gut microbiota alterations on developing immune system and to unravel the multifactorial origin of immunological vulnerability following thymectomy, further research is needed. When contemplating the need for later immunological evaluation after thymectomy, attending clinicians should recognise substantial antibiotic use early in life as a possible risk factor for increased immunological vulnerability.

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