T-Cell Receptor Excision Circles in Newborns with Congenital Heart Disease

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Objectives To determine if children with congenital heart disease (CHD) have lower newborn T-cell receptor excision circles (TREC) levels than the general population and to evaluate if low TREC levels in newborns with CHD are associated with clinical complications such as hospitalization for infection.

Study design The Connecticut Newborn Screening Program reported TREC levels for newborns with CHD delivered between October 2011 and September 2016 at 2 major Connecticut children's hospitals. TREC levels for children with CHD were compared with the general population. TREC levels and outcome measures, including hospitalization for infection, were compared.

Results We enrolled 575 participants with CHD in the study. The median TREC level for newborns with CHD was lower than the general population (180.1 copies/μL vs 312.5 copies/μL; $P < .01$). patients with CHD requiring hospitalization for infection had lower median TREC levels than their counterparts (143.0 copies/μL vs 186.7 copies/μL; $P < .01$). The combination of prematurity and low TREC level had a strong relationship to hospitalization for infection (area under the receiver operative characteristic curve of 0.89). There was no association between TREC level and CHD severity.

Conclusions Newborns with CHD demonstrated lower TREC levels than the general population. Low TREC levels were associated with hospitalization for infection in preterm children with CHD. Study limitations include that this was a retrospective chart review. These findings may help to identify newborns with CHD at highest risk for infection, allowing for potential opportunities for intervention. *(J Pediatr 2019;213:96-102)*.

Childhood infections in children with congenital heart disease (CHD) are a major risk factor for morbidity and mortality.[1-5] Children with CHD are at higher risk for complications associated with infection, such as hospitalization, pediatric intensive care unit admission, mechanical ventilation, longer postoperative length of hospital stay, and mortality.[6-13] Complications of infection may be linked to an inadequate immune response in a subset of patients with heart disease. Genetic syndromes, such as 22q11.2 microdeletion (DiGeorge) syndrome, are associated with both cardiac disease and thymic abnormalities resulting in immunodeficiency.[14,15] This association suggests a common mechanistic link leading to abnormal development and function of both organ systems. Cumulative events, including surgical interventions with partial or complete thymus removal and physiologic changes such as congestive heart failure, can exacerbate underlying abnormalities in immune function in children with CHD and result in negative consequences as they grow and mature.[13,16-21]

T-cell receptor excision circles (TRECs) are small circular pieces of DNA that are byproducts of T-cell maturation in the thymus.[22] They are an established biomarker of T-cell lymphopoiesis. Very low TREC levels are a marker for severe combined immunodeficiency (SCID).[22-25] SCID is caused by mutations in ≥1 genes leading to abnormal naïve T-cell development, resulting in dysfunction of cell-mediated immunity and subsequent abnormalities in humoral immunity. This in turn results in life-threatening viral and bacterial infections if left untreated. Since 2008, TREC assays have been used as a population-based newborn screen to detect SCID and are now included in the newborn screen programs in 48 states across the United States.[24-27] A high percentage of newborns with false-positive SCID screening have CHD; the reason is unknown. Data analysis from 10 states, including Connecticut and the Navajo Nation, identified 411 infants with severely decreased TREC levels who screened positive for SCID but did not have the disease upon further testing.[28] In a subgroup of 117 infants with false-positive screens without genetic syndromes, 26% had congenital cardiac

AUC	Area under the receiver operative characteristic curve
CHD	Congenital heart disease
TREC	T-cell receptor excision circles
SCID	Severe combined immunodeficiency

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anomalies. An additional 136 newborns with a false-positive SCID screen had genetic syndromes, many of which are associated with CHD, including DiGeorge, trisomy 21, trisomy 18, Noonan, Jacobsen, and CHARGE syndromes.

The newborn screen data suggest a possible association between immunodeficiency and CHD. We hypothesized that low TREC levels are more prevalent in newborns with congenital cardiac malformations. In addition, we hypothesized that children with CHD and low TREC levels are at increased risk for infection as compared with newborns with CHD and normal TREC levels. In this study we examined children born with CHD in the State of Connecticut who underwent newborn TREC screening and evaluated their clinical history of hospitalization for infection.

Methods

We conducted a multicenter, retrospective cohort study at Connecticut Children's Medical Center and Yale-New Haven Children's Hospital in collaboration with the Connecticut Newborn Screening Program. As the only 2 hospitals in the state where pediatric cardiothoracic surgery is performed, Connecticut Children's Medical Center and Yale-New Haven Children's Hospital provide most of the care to children with structural CHD born in Connecticut. Approval for the study was obtained at Connecticut Children's and Yale-New Haven's Institutional Review Board and the Human Investigations Committee at the State of Connecticut Department of Public Health.

Children with a diagnosis of structural CHD born in Connecticut between October 2011, when newborn TREC screening began in Connecticut, and April 2016 were eligible for enrollment. Enrollment with informed consent took place from September of 2015 through February of 2017. Children with heart lesions considered to be a variant of normal or remnants of the normal fetal circulation, such as patent ductus arteriosus or patent foramen ovale, were excluded. Potential participants with structural CHD were identified by chart review using *International Classification of Diseases*, 9th edition, codes as well as nurse and physician referrals from cardiology clinics. After obtaining informed consent, newborn TREC levels were obtained for participants from the Connecticut Newborn Screen Program. A retrospective chart review was subsequently performed to obtain demographic information, patient characteristics, and outcome measures, including hospitalization for infection as a primary outcome. Secondary outcome measures included number of hospitalizations for infection, timing of infection with relation to cardiac intervention, postoperative measures including length of pediatric intensive care unit stay, length of hospitalization, development of wound infection, and postoperative bacteremia, as well as mortality.

Primary CHD types were grouped into eight anatomically based categories for analysis (**Table I**). CHD severity was assigned by CHD class designation (1 for 2 ventricles without arch obstruction, 2 for 2 ventricles with arch obstruction, 3 for a single ventricle without arch obstruction, and 4 for a single ventricle with arch obstruction) for all participants, intervention status (cardiac catheterization and/or operative intervention vs no cardiac intervention), as well as by Risk Adjustment for Congenital Heart Surgery-1 scores for children who underwent surgical intervention.[29,30] Deidentified population TREC data collected in 37 101 newborns from January 1, 2016, to December 31, 2016, were provided by the Connecticut Newborn Screen Program and used as general population data for comparison with the CHD study group. Initial criteria for positive SCID screens used by the Connecticut Newborn Screen program were TREC levels of <40 copies/μL in October of 2011; to limit false positives, this level was later changed to <25 copies/μL for preterm babies and <30 copies/μL for term babies in late

Table I. Demographics and median TREC values of the participant Group (n = 575)

Characteristics	n (%)	TREC (copies/μL), median range
Gestational age, mean ± SD	37.6 ± 3.1	180.2 (5.2-839.7)
Birth weight (g), mean ± SD	3002 ± 773	180.2 (5.2-839.7)
Sex*		
Male	286 (49.7)	159 (9.5-839.7)
Female	289 (50.3)	205.2 (5.2-837.7)
Genetic syndrome identified*		
Yes + suspected	92 (16.7)	139.0 (5.2-518.4)
No	459 (83.3)	190.6 (11.8-839.7)
Prenatal diagnosis of CHD		
Yes	123 (21.5)	174.7 (9.5-837.7)
No	450 (78.5)	181.6 (5.2-839.7)
Immunodeficiency identified in participant		
Yes	3 (0.5)	139.2 (51.3-470.7)
No	564 (99.5)	180.1 (5.2-839.7)
Documented complete blood count with lymphopenia (Absolute Lymphocyte Count <3000)*		
Yes	228 (55.3)	156.7 (5.2-721.7)
No	184 (44.7)	208.7 (9.5-837.7)
Primary CHD type		
Right-sided obstructive lesions	40 (7.0)	172.0 (17.4-555.8)
Left-sided obstructive lesions	61 (10.6)	156.9 (23.9-715.3)
Conotruncal defects and aortic arch anomalies	76 (13.2)	192.9 (36-721.7)
Atrioventricular canal defects	26 (4.5)	146.8 (36.2-837.7)
Single ventricle	24 (4.2)	177.5 (9.54-518.4)
Septal defects	324 (56.3)	190.6 (5.18-839.7)
Venous anomalies	11 (1.9)	198.8 (61.1-461.9)
Other	12 (2.1)	113.1 (34.6-303.5)
CHD class		
I	484 (84.8)	180.7 (5.2-839.7)
II	64 (11.2)	210.8 (20.6-715.3)
III	16 (2.8)	172.1 (9.5-337.7)
IV	7 (1.2)	174.7 (49.3-354.6)
Prostaglandins started		
Yes	76 (13.5)	186.9 (20.6-715.3)
No	488 (86.5)	180.8 (5.2-839.7)
Preoperative death*		
Yes	12 (2.1)	94.3 (5.2-446.6)
No	555 (97.9)	181.6 (12.2-839.7)
Intervention (operation/catheterization/ preoperative death)		
Yes	225 (39.8)	185.2 (5.2-839.7)
No	335 (59.8)	176.2 (12.2-837.7)

*$P < .05$ when comparing median TREC levels.

2012. Connecticut uses an in situ real-time quantitative polymerase chain reaction method for the dried blood spot analysis of TREC for SCID testing, adapted from the Centers for Disease Control and Prevention to evaluate dried blood spot reference materials and refined for use in the Connecticut laboratory.

Analyses were conducted using STATA 14.2 software (StataCorp LLC, College Station, Texas) and R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to report numbers, proportions, or means and standard deviations as well as medians. A P value of <.05 was considered significant. Preterm was defined as a gestational age of <37 weeks at birth. The preterm group was compared with the term group using the χ^2 test or the Fisher exact test. Quartile analyses were conducted to assess whether lower TREC levels were associated with various health outcomes, including hospitalization for infection. Nonparametric analysis using a boosting classification tree was used to evaluate the association between TREC levels and hospitalization for infection in preterm infants.[31] To avoid overfitting the data, cross-validation was used to choose an optimal boosting iteration. The diagnostic test accuracy of the boosting models was evaluated using the area under the receiver operative characteristic curve (AUC).

Results

Of the 197 571 newborns with TREC screens performed in Connecticut 696 (0.4%) were identified with CHD at 1 of the 2 participating centers. Of these, 575 participants (83%) were enrolled in the study (375 children from Connecticut Children's and 200 from Yale New-Haven) and form the study population (Table I). At the time of study enrollment closure, surviving children had been followed from 10 months to 3 years of age; 225 participants (40% of the study population) underwent a cardiac catheterization intervention and/or cardiac surgery. Of the 575 children in the study group, 117 were born prematurely (20.45%), which is higher than the general population of the United States in 2016 (9.9%) and the Connecticut population in 2016 (9.4%; Centers for Disease Control and Prevention; $P < .0001$ and $P < .0001$, respectively).[32] A genetic syndrome was identified in 86 of the infants with CHD (15%) and was suspected in an additional 11 (2%).

The median TREC level of the CHD study population was lower than that of the general Connecticut newborn population (180.2 copies/μL vs 312.5 copies/μL; $P < .001$; Figure 1). Preterm newborns with CHD had lower median TREC levels than term newborns with CHD (104.8 vs 200.4 copies/μL; $P < .0001$). When preterm newborns were excluded, term CHD children continued to have a significantly lower newborn median TREC level in comparison with the general Connecticut population (200.4 copies/μL vs 312.5 copies/μL; $P < .0001$). TREC levels did not vary by CHD type. There was no association between TREC level and the severity of CHD as determined by CHD class, Risk Adjustment for Congenital Heart Surgery-1 score in 197 operative patients or by intervention status, which included operations, cardiac catheterizations, and preoperative death. In the small group of participants who died before surgery (n = 12; 2.1% of the study group), the median TREC level was significantly lower than the remainder of the study group (94.3 copies/μL vs 181.6 copies/μL; $P < .05$). Owing to the potential influence of hydrops on TREC values, we analyzed the final fetal echocardiogram performed before delivery in 123 participants who

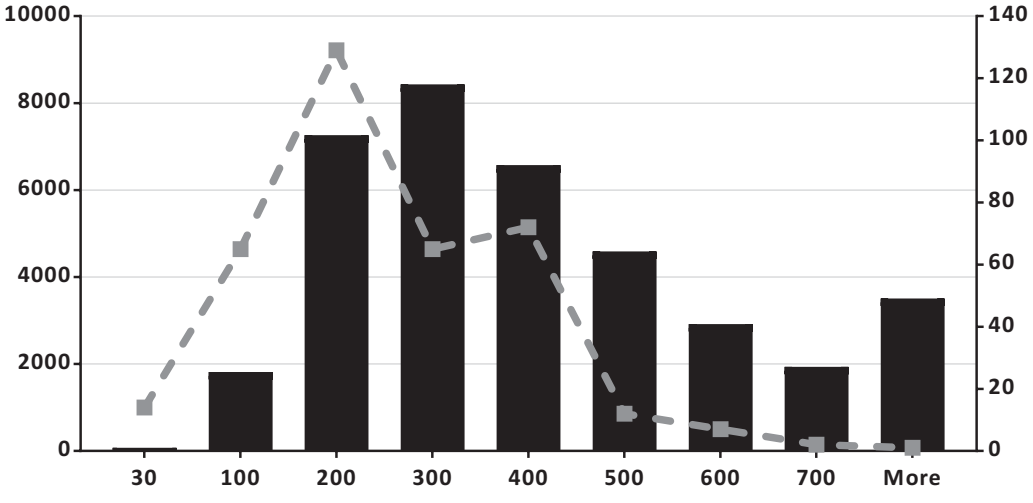

Figure 1. TREC level distribution for participants with CHD vs the general population. Superimposed graphs of distribution of TREC copies/μL for 37 101 samples from the general population (bar graph, left *y*-axis) vs 575 samples from newborns with CHD (*dotted line*, right *y*-axis).

underwent prenatal cardiac evaluation. Hydrops was not present in any of these cases. Newborn screening panels in which TREC levels were obtained in our study population were performed before any cardiac surgery; therefore, third spacing and chylous effusion related to cardiac surgery would not affect the TREC levels evaluated in this study.

One hundred children (18% of the total CHD group) were hospitalized for an infection as the primary cause (**Table II**). More than one-half (61%) of hospitalizations for infection occurred before surgical or cardiac catheterization intervention, 26% occurred after intervention, and 13% occurred in between a series of interventions. Bronchiolitis and upper respiratory infections were the most common type of infection resulting in hospitalization, followed by pneumonia, bacteremia, urinary tract infection, and necrotizing enterocolitis. There were 12 postoperative wound infections reported in the operative group. Eight children experienced bacteremia with positive blood cultures postoperatively. Infants with CHD hospitalized for infection had a lower median TREC level than their counterparts (143 copies/μL vs 186.7 copies/μL; $P < .01$).

TREC levels within the study group were lower in children with premature birth and in children with genetic syndromes ($P = .001$ and $P = .0001$, respectively), consistent with findings in the published TREC literature (**Table I** and **Table III** [available at www.jpeds.com]).[28] When adjusted for the presence of a genetic syndrome, the odds of hospitalization for infection in the lowest TREC quartile were 2.2 times greater than the highest quartile (95% CI, 1.17-4.23; $P = .02$). Premature newborns hospitalized for infection had lower median TREC levels in comparison with premature newborns who did not require hospitalization for infection (91.1 copies/μL vs 119.3 copies/μL; $P = .02$). When controlled for prematurity, TREC levels were not lower in term children who required hospitalization for infection ($P = .69$). TREC levels were highly correlated with prematurity and increased as gestational age increased ($P < .0001$). In our study group, the median TREC level was 62.2 copies/μL for newborns <32 weeks of gestation, 125.3 copies/μL for newborns between 32 and 36 weeks of gestation, and 200.4 copies/μL for newborns 37 weeks or greater. Statistical modeling demonstrated that prematurity contributed independently to the risk of hospitalization for infection in patients with CHD (AUC of 0.64). However, the combination of prematurity and low TREC level had a much stronger relationship to hospitalization for infection (AUC of 0.89). These findings indicate that TREC levels are a biomarker for hospitalization for infection in preterm children with CHD (**Figure 2**). TREC levels were not associated with any of the secondary postoperative outcome measures, including length of pediatric intensive care unit stay, wound infection, bacteremia, or mortality.

Of the study group, 514 participants (81%) had ≥1 year of follow-up data. To adjust for the variability in follow-up time in the larger study group, a subgroup analysis was performed. Hospitalizations for infection were analyzed in the first year of life alone. Results from this subgroup were similar to results for the larger study population. Specifically, children requiring hospitalization for infection in the first year of life had significantly lower median TREC levels than their counterparts (131.7 copies/μL vs 187.3 copies/μL; $P = .006$). Results evaluating the relationship between TREC level and gestational age in relation to hospitalization for infection in preterm children were similar to that of the larger study group, demonstrating a higher AUC of 0.83

Table II. Characteristics of participants requiring hospitalization for infection (n = 100)

Characteristics	n (%)	TREC (copies/μL), median (range)
Hospitalization for infection as primary cause*		
Yes	100 (17.5)	143 (12.2-715.3)
No	471 (82.5)	187.2 (5.2-839.7)
Timing of infection with relation to cardiac intervention		
Before CHD surgery or catheterization intervention	59 (60.8)	132.9 (12.2-555.8)
After definitive CHD surgery or catheterization intervention	25 (25.8)	139.2 (20.6-518.4)
Between series of CHD surgeries or catheterization interventions	13 (13.4)	180.2 (17.4-715.3)
Type of infections		
Upper respiratory infection/bronchiolitis	49 (49.0)	156.8 (12.2-573.9)
Pneumonia	22 (22.0)	141.3 (41.6-555.8)
Urinary tract infection	4 (4.0)	96.4 (29.3-518.4)
Bacteremia	5 (5.0)	121.2 (17.4-151.3)
Necrotizing enterocolitis	3 (3.0)	51.8 (19.0-79.9)
Other	17 (17.0)	182.3 (17.2-715.3)
Number of hospitalization for primary infectious purpose		
0	471 (83.1)	186.2 (5.2 - 839.7)
1	71 (12.5)	154.4 (17.2-715.3)
2	16 (2.8)	100.5 (12.2-497.8)
≥3	9 (1.6)	142.6 (51.3-461.9)
Postoperative wound infection		
Yes	12 (6.2)	189.5 (85.2-623.5)
No	182 (93.8)	186.9 (20.6-721.7)

*$P < .05$ when comparing median TREC levels.

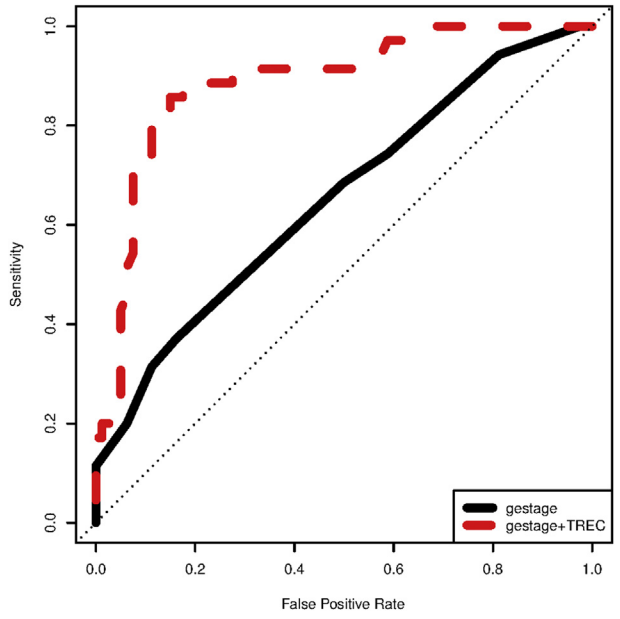

Figure 2. ROC curve for hospitalization for infection to analyze relationship of TREC level and gestational age to hospitalization for infection in preterm infants (*dotted line*) vs gestational age alone (*solid line*; AUC of 0.89 vs 0.64).

when evaluating for TREC with gestational age than gestational age alone (AUC of 0.61).

Ten newborns with CHD in our study population had very low TREC levels triggering a positive screen for SCID under the current criteria. Nine cases were false positives for the disease on further testing and one patient passed away before confirmatory testing (**Table IV**; available at www.jpeds.com). The median gestational age for this group was 34 weeks of gestation with a range of 26-37 weeks. Four of these infants had genetic syndromes. Eight of the 9 patients who survived to undergo additional testing had negative follow-up testing for SCID by repeat TREC analysis. A patient with tetralogy of Fallot with pulmonary atresia and Renpenning syndrome demonstrated T-cell and B-cell lymphopenia not consistent with SCID, but concerning for an immunocompromised state, although lymphocyte proliferation/mitogen studies were within normal limits. Three children in this group died before an operative intervention. Of the 9 children with positive initial screening tests who survived to discharge from the hospital after birth, 4 (44%) were subsequently hospitalized for infection as a primary problem. Three patients within the study group who had a negative initial screen for SCID were later identified with immunodeficiencies. These immunodeficiencies included autoimmune neutropenia, combined immunodeficiency, and self-resolving febrile neutropenia with newborn TREC values of 51.3, 139.2, and 470.7 copies/μL, respectively.

Discussion

This study demonstrates that newborns with CHD on average have lower TREC levels than the general population. In addition, we demonstrate that, although prematurity plays a major role in the risk of hospitalization for infection, the additional presence of low TREC levels is an independent biomarker of functionally important immunodeficiency and risk for hospitalization for infection in preterm children with cardiac anomalies. Term children with CHD and low TREC levels did not demonstrate an increased risk of hospitalization for infection compared with those with normal TREC levels. Delivery at 37 weeks of gestation or later may impart a protective effect on these children that limits the morbidity associated with the relative immune deficiency in this group. This finding may be due to increased levels of maternal antibodies present at birth in term babies providing longer term passive immunity. The findings from our study also support other literature demonstrating a link between false positive screens for SCID and CHD.[23] Ten newborns with CHD within our study group demonstrated a false-positive initial screen for SCID. Newborns who meet the screening threshold for SCID owing to low TREC levels may warrant a screening evaluation by a pediatric cardiologist to rule out cardiac anomalies in addition to the workup for immunodeficiency in the setting of a high mortality rate within the group.

The thymus is a specialized immune system organ that functions as the main site for T-cell production before the onset of puberty.[33] The development and severity of both viral and bacterial infections in certain children and young adults with CHD are likely the result of abnormalities of neural crest cell derivatives and thymus development leading to disruption of T-cell maturation, and in some cases downstream humoral immune defects. Thymectomy, which is routine at the time of neonatal surgery, may further impact the population of patients with CHD with lower TREC levels at birth. Studies suggest long term differences in T lymphocyte population in adults who underwent infant sternotomy and thymectomy as compared with controls.[16,20,34] The long-term clinical implications and potential efficacy of interventions such as thymic preservation in an identified population at risk warrants further study.

There were several limitations to this retrospective study. Follow-up time was variable for the study group of 575, ranging from 10 months to 3 years for surviving children. As a result, we included a subgroup analysis of participants with ≥1 year of follow-up to evaluate hospitalization for infection in the first year of life with no significant changes in the results. Although children seen at Connecticut Children's Medical Center and Yale New-Haven Children's Hospital are a majority of patients with CHD in the state, a small percentage of patients born at other institutions outside the state were not approached to enroll in the study. We also looked only at hospitalization for infection and could not accurately assess infections that may not have resulted in

hospitalization. As a result, we could not determine infection prevalence in our study group. The TREC levels of the general population of Connecticut could not be compared with other states owing to differences in the assays used across the country. TREC level was not associated with outcome measures such as postoperative wound infection and mortality; however, the number of enrolled patients with these complications was low, limiting the power to detect a significant difference.

TREC levels provide an opportunity for risk stratification to identify those at highest risk for morbidity from infection in the CHD population. Premature babies with CHD and identified immunodeficiency may benefit from interventions such as surgical thymic preservation, a lower threshold to initiate antibiotic prophylaxis and palivizumab use in the first year of life, revaccination if antibody titers are inadequate, as well as increased vigilance in the assessment of the need for intravenous immunoglobulin treatment. In addition, there could be a role for vaccination in mothers of fetuses with identified CHD before delivery to provide passive immunity for the prevention of illness before surgical repair. Further prospective, multi-institutional research is needed to explore the clinical importance and biological mechanisms of low TREC levels and immunodeficiency in children with CHD and potentially lead to targeted strategies for prevention and treatment within this vulnerable population. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

The Clinical Spectrum and Early Diagnosis of Dawson's Encephalitis

Freeman JM. *J Pediatr* 1969;75:590-603

Dawson's encephalitis, subsequently known as subacute sclerosing panencephalitis (SSPE), was described in the 1930s as a degenerative process, suspected to be viral—possibly herpes—in origin.[1] By the late 1960s, a clear association was made with antecedent measles infection acting years later as a slow virus. Fifty years ago in *The Journal*, John Freeman at Stanford University reported 12 cases in an effort to raise clinical awareness and postulate that early treatment with pryan copolymer and 5-bromo-2-dexouyuridine might limit the disease. Freeman carefully characterized progression of the disease over weeks to months with first intellectual and personality changes, followed by myoclonic seizures, then movement disorder with dystonia, and ultimately marked rigidity and death. An addendum in that paper declared that his proposed therapy had not worked. Freeman later wrote, "There is still no useful therapy for SSPE, but the disease has virtually disappeared as measles vaccinations have become more universal."[2]

Indeed, around 1969 a definitive therapy to prevent SSPE was well underway. Widespread immunization, using an attenuated measles virus, had begun in the US. By 2000, measles had been considered to be eradicated from the US. SSPE should have been eliminated, too. However, disturbing and growing trends in vaccine exemption have now led to multiple US communities throughout the West where far more than 10% of children are unvaccinated. In 2017, a California team identified 17 SSPE cases in that state; the incidence of SSPE was 1:1367 for children <5 years of age and 1:609 for children <12 months of age at time of acute measles illness.[3]

What would Freeman say? He was my mentor who lured me from the West 31 years ago before urging me almost 10 years later to return to Stanford, where he had been at the time of this report. A self-described curmudgeon and utilitarian, John would have stood steadfast against limitless parents' rights and bluntly tell them that they must immunize their children.

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Table III. TREC level medians by identified genetic syndromes

Genetic syndromes	TREC median (copies/μL)	n
Alagille syndrome	74.0	2
DiGeorge syndrome	116.9	5
Goldenhar syndrome	270.4	1
Heterotaxy syndrome	124.6	4
Jacobsen syndrome	45.3	1
Kabuki syndrome	111.2	1
Noonan syndrome	97.7	2
Trisomy 13	134.9	2
Trisomy 18	54.6	1
Trisomy 21	140.4	37
Turner syndrome	139.5	3
Williams syndrome	227.7	5
Other	156.9	27

Table IV. Patients with CHD with positive TREC screens

Patients	TREC (copies/μL)	Gestational age (wk)	Hospitalized for infection	CHD primary diagnosis	CHD secondary diagnosis	CHD class	Preoperative death	Genetic syndrome identified	Immunodeficiency type
Patients with CHD with a positive SCID screening									
1	22.95	35	No	Ventricular septal defect	Pulmonary stenosis	I	No	No	N/A
2	9.54	39	No	Tetralogy of Fallot with pulmonary atresia	Ventricular septal defect, overriding aorta	III	Yes	Yes (Renpenning syndrome)	N/A
3	25.19	36	No	Ventricular septal defect	None	I	No	No	N/A
4	5.18	25	No	Ventricular septal defect	Atrial septal defect, bicuspid aortic valve	I	Yes	Yes (monosomy chromosome 1)	N/A
5	20.63	38	Yes	Interrupted aortic arch		II	No	Yes (DiGeorge)	N/A
6	11.77	24	N/A	Ventricular septal defect	None	I	Yes	No	N/A
7	12.18	26	Yes	Ventricular septal defect	None	I	No	No	N/A
8	17.36	32	Yes	Pulmonary Stenosis	Biventricular hypertrophy, RVOT obstruction	I	No	Yes (Noonan syndrome and RIT mutation)	N/A
9	17.23	33	Yes	Ventricular septal defect	None	I	No	No	N/A
10	29.46	37	No	Ventricular septal defect	None	I	No	No	N/A
Patients with CHD with identified immunodeficiency									
11	51.3	27	No	Other (primary hemodynamic lesion patent ductus arteriosus)	Atrial septal defect	I	No	No	Autoimmune neutropenia
12	139.2	36	Yes	Shone's complex	Atrial septal defect, bicuspid aortic valve, coarctation of aorta, ventricular septal defect, non-apex forming left ventricle, hypoplastic transverse arch	II	No	Suspected (de novo duplication of 3 p 26.3 of uncertain signifivans)	Combined immunodeficiency
13	470.7	39	No	Ventricular septal defect	None	I	No	No	Self-resolving febrile neutropenia

N/A, not applicable.