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Idiopathic T cell lymphopenia identified in New York State Newborn Screening

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ABSTRACT

Quantification of T-cell receptor excision circles (TRECs) for newborn screening for SCID has advanced the diagnosis of severe combined immune deficiency (SCID). However, it has led to the identification of infants with T cell lymphopenia without known cause. The clinical characteristics, appropriate laboratory monitoring, and outcomes of patients remain unclear. We performed a retrospective review of clinical and laboratory studies for 26 infants collected from 7 New York State referral centers from 2010 to 2016 with low TRECs (mean, 70 copies/μl) and subnormal CD3 counts (mean, 1150/cubic mm). Over time absolute CD3 counts increased in 17 and decreased in 9; 22 (85%) have done well clinically regardless of absolute T cell values. Additional infants with TCL will continue to be identified in newborn screening panels. While most patients seem to do well clinically, parameters for diagnosis and monitoring have yet to be formalized, and additional information needs to be collected, causes and outcomes reported.

1. Introduction

The method of evaluating T-cell receptor excision circles (TRECs) to universally screen infants for a profound deficiency in T cells in the newborn period was established in Wisconsin and Massachusetts in 2009, based on methodology developed by Puck [1–5]. This practice has now been extended to the majority of states and the success of this approach in identifying infants with severe combined immunodeficiency (SCID) and other forms of severe T cell impairment, has been proven [3,4,6–9]. As the method does not discriminate between the underlying causes of T cell reduction, prematurity, birth defects, and a variety of other medical reasons can also lead to abnormally low TREC values and T cell deficiency. For example, Wisconsin identified 33 infants with T cell lymphopenia of varying degrees through newborn screening between 2008 and 2011. Nineteen infants had secondary causes of T cell lymphopenia, such as anatomic, metabolic, and chromosomal abnormalities. Fourteen infants had primary causes of T cell lymphopenia, including 5 infants with SCID, 4 infants with the 22q11.2 deletion syndrome; however 5 other infants with T cell lymphopenia, not considered to have genetic or medical causes, were considered to have idiopathic T cell lymphopenia [10]. Comeau et al. in the Massachusetts study, noted that of 51 infants referred for additional testing, 9 infants had idiopathic T cell lymphopenia and remained under the care of an immunologist [3].

Newborn screening for SCID began in New York State in September 2010; infants with low TRECs were originally referred to one of 8 referral centers, based on location of birth: Albany Medical Center, Long Island Jewish Health System, Montefiore Medical Center, Mount Sinai Hospital, New York Medical College, University of Rochester Medical Center, Upstate Medical University, and Women's & Children's Hospital of Buffalo. At these tertiary centers, complete blood cell counts and flow cytometry were performed to identify infants with potentially severe T cell defects. As in other reports, infants in New York State were

Abbreviations: TCL, T cell lymphopenia; SCID, severe combined immunodeficiency; TREC, T-cell receptor excision circle.

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identified with SCID, DiGeorge syndrome or other genetic anomaly, or other clinically significant, non-SCID abnormalities leading to loss of T cells [8]. In this earlier report 30 infants were classified as having idiopathic T cell lymphopenia (TCL), defined as infants without SCID, other genetic defect, or another medical syndrome that required ongoing monitoring or treatment [8]. The laboratory parameters and clinical treatment were variable for the infants in this report; 6 (20%) were treated with antibiotics, and fewer than half (N = 11; 37.9%), were said to have resolution of the flow cytometry abnormalities by around 12 months of age. However, for 19 infants, the lymphopenia had not resolved in the two year period and no immunologic or follow-up data on these subjects was presented. In this report we provide demographic, clinical and laboratory information on 26 infants with CD3 lymphopenia identified between 2010 and 2016, 24 of them not included in the prior report. For all infants we collected longer term data, revealing additional medical complexities in some of the infants followed and persistence of lymphopenia in many after a number of months to years of follow-up.

2. Methods

Dried blood spots were collected at birth through standardized newborn screening practices. DNA was extracted and TREC levels were quantified using real-time quantitative polymerase chain reaction as described [8]. The initial cut off TREC value of <200 copies/μl was originally chosen in NYS based on parameters derived from both normal infants and infants with SCID; this was subsequently reduced to <125 copies/μl for referral to specialized centers. Infants were evaluated with complete blood counts and flow cytometry to assess T, B, and NK cell numbers. There was no uniform protocol for each center to follow for investigation of abnormal values. Naïve and memory T cells were not routinely collected. Infants with absolute lymphocyte counts <2500/cubic mm^3 [9,11] without evidence of prematurity (<37 weeks gestation), birth defect, or other identifiable causes of lymphopenia are included in this report. Infants were followed for additional visits, at intervals defined by each center, for ongoing monitoring and/or diagnostic testing as requested by each center director. Statistical analysis was performed utilizing GraphPad Prism (Graphpad Software, La Jolla CA); all tests were performed using a level of significance of <0.05.

3. Results

Data on a group of 26 infants with abnormally low TRECs and CD3 T cell counts lower than 2500/cubic mm were collected from 6 of the NYS referral centers. These infants were assigned a case dispensation of "non SCID" and had no identified genetic defect or identifiable medical cause that could lead to lymphopenia (Tables 1 and 2). Aside from baseline counts for Cases #13 and #21, these data do not overlap with the prior report [8]. The median triplicate TREC value for these infants was 66.5 (range 0–171; 25 to 75% = 27.3–107.8). The mean absolute CD3 count for these infants was 1150/cubic mm (range 24 to 2439 cubic mm); three of the infants (patient #2, #10 and #26) also had low B cells counts and two of them, low NK cells at baseline. While the TREC level for referral was reduced from 200 to 125 copies/μl over time, the initial TREC values were positively correlated to the absolute CD3 counts from the first blood test ($r_s = 0.62$, $p < 0.0001$) (Fig. 1). (Table 1) However, this was not always predictive, as a TREC triplicate average of 22 copies/μl correlated with an absolute CD3 count of 1125/cubic mm in one infant, while a TREC triplicate average of 46 copies/μl correlated with an absolute CD3 count of 254/cubic mm in another infant. While there was and still is, no consensus protocol for continuing to test or follow lymphopenic infants with no known genetic or medical reason for low levels, the 26 newborns discussed here had been recalled for clinical follow-up by the referral center, and had at least one, and in some cases, a number of additional flow cytometry tests performed over time. These showed that absolute CD3 counts had increased in 17 infants but decreased in 9, in a period of 6 months to 66 months of follow-up. (Table 1) Fig. 2 shows the most recent counts for these infants.

Interestingly, there were 4 infants, all males, with newborn TREC triplicate averages of "0" who are included in this cohort. Three had quite low absolute CD3 counts (212, 544, 377, 895/cubic mm). All are clinically stable (up to now age 5.5 years), and have had 2 to 7

Table 1
Infants with T cell lymphopenia identified by New York State Newborn Screening.

Pt. #	Gender	Center	TREC Avg	CD3 (2500–5500)*	CD19 (300 − 2000)	CD16/56 (170–1100)	CD4 (1600–4000)	CD8 (560–1700)	CD4/CD8	LAST CD3
1	Female	Buffalo	143	741	1097	414	613	117	5.24	324
2	Male	Buffalo	46	254	53	101	124	116	1.07	2054
3	Female	LIJ	29	1360	1139	771	861	487	1.77	1434
4	Female	LIJ	58	1438	1525	1046	1222	255	4.79	1186
5	Male	LIJ	0	544	977	1046	444	89	4.99	558
6	Male	LIJ	44	2129	2392	195	1525	548	2.78	2145
7	Female	LIJ	171	1371	688	134	909	439	2.07	2715
8	Male	Monte	110	2439	N/A	N/A	1864	649	2.87	3392
9	Male	Monte	146	1846	N/A	N/A	1308	502	2.61	2232
10	Male	Monte	94	1991	298	578	2212	1533	1.44	2382
11	Female	Monte	143	1641	1778	546	1335	320	4.17	1453
12	Female	Monte	88	1215	303	786	818	339	2.41	2242
13	Male	NYMC#	118	2237	1785	387	1593	545	2.92	1564
14	Male	NYMC	58	1149	932	489	778	345	2.26	975
15	Male	UPS	0	377	816	942	289	78	3.71	742
16	Male	UPS	0	212	654	514	169	42	4.02	921
17	Female	MSSM	107	918	1742	557	455	347	1.31	1965
18	Female	MSSM	75	617	682	971	424	193	2.20	301
19	Female	MSSM	77	860	344	387	645	194	3.32	986
20	Female	MSSM	18	393	2058	349	292	68	4.29	559
21	Male	MSSM#	79	1166	1722	220	717	434	1.65	1509
22	Male	MSSM	103	1650	481	851	1032	607	1.70	1284
23	Female	MSSM	22	1125	770	146	769	314	2.45	1774
24	Male	MSSM	0	895	269	824	534	269	1.99	679
25	Female	MSSM	47	1170	456	376	781	347	2.25	1650
26	Female	MSSM	49	74	6	72	45	19	2.37	2800

* Reference normals (9) # initial data included in Table VI in reference (6).