LETTER TO THE EDITOR

Neonatal abstinence syndrome is a potential cause of low TREC copy number

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Abstract

Severe combined immunodeficiency (SCID) is a rare genetic condition characterized by significant T cell lymphopenia and impaired T cell function. Many jurisdictions use the quantitation of T cell receptor excision circles (TRECs) to screen for SCID in newborns, but false positives may be seen in several conditions. We report 3 newborns with neonatal abstinence syndrome who presented with decreased TREC copy number.

Keywords: SCID, Primary immunodeficiency, TRECs, Opiates, Neonatal abstinence syndrome

We report three neonates who were referred by the Ontario NBS program to a tertiary care Pediatric centre in Hamilton, Ontario for low TREC copy number between 2014 and 2017 who had neonatal abstinence syndrome (Table 1). Repeat TREC enumeration and T cell immunophenotyping on day 13 of life were normal, and all patients had normal 22q11.2 FISH and normal serum purine concentrations. The patients had no other medical comorbidities to explain their transient T cell lymphopenia. The mothers of the neonates tested negative for HIV and had no history of immunosuppressant medication use. Patients 1 and 3 were preterm, but late preterm newborns typically have very similar TREC copy numbers to those born at term [4]. Patients 2 and 3 had low birthweight, which was attributed to maternal recreational drug use.

Opioids including methadone and heroin readily cross the placental barrier [5]. We therefore posit that maternal opioid use during pregnancy may cause or contribute to transient T cell lymphopenia in the newborn. The specific mechanisms by which this could occur are unclear, but perinatal stress associated with neonatal abstinence syndrome seems a plausible explanation. Data from animal models also show that opioids may directly affect T cells lymphocytes. Opioids can cause thymic and splenic atrophy [6], significantly decreased thymus cellularity [6, 7], and decreased mitogen responses [8]. Flow cytometry of thymocytes from mice exposed to...
Morphine showed depletion of double negative T cells [7], which would be expected to cause decreased TREC numbers since this cell population has not undergone V(D)J recombination.

In the USA, antepartum opioid use is estimated at nearly 6 per 1000 hospital births [5], but the rate of low TRECs is approximately 1 per 1000 newborns screened, many of whom have alternate explanations for capture [3]. We speculate that this discrepancy is multifactorial, including the potential need for chronic, perhaps high-dose opioid exposure during the third trimester, leading to neonatal abstinence syndrome, and additional genetic or environmental factors to contribute to transient neonatal T cell lymphopenia. There may also be contributions from other recreational drug exposures.

The potential for maternal opioid use to decrease TREC values is of significant public health import. Jurisdictions such as ours with a higher rate of illicit drug use may have a higher number of false positive screening results causing unnecessary follow up testing, cost, and parental psychological stress. During the period of study, the Ontario NBS program used a threshold of less than 75 copies/µL to identify abnormal results. Adjusting the TREC cutoff to <25 copies/µL, which is used by numerous states in the USA [3], would reclassify all 3 cases as negative for SCID. Importantly, lowering TREC thresholds to 20–25 copies/microliter does not appear to increase the number of false negative results [3, 9].

In summary, we report a series of 3 neonates presenting with neonatal abstinence syndrome and low TREC copy numbers in the absence of SCID. To our knowledge, this is the first report associating maternal opioid use with transiently low T cells in newborns. We hypothesize that antenatal opioid exposure may contribute to T cell lymphopenia in the newborn period and may be the sole cause in a small subset of cases. The possibility of broad immune effects from antenatal opioid exposure based on animal data indicate that follow-up of infants with low TREC values should be continued even when the possible etiology is NAS. Given that SCID is a rare condition and TREC enumeration is a recent addition to NBS in many areas, additional non-SCID causes of low TREC numbers are likely to be identified in the future. Consideration of these aetiologies is important when evaluating individual cases and for the optimization of nascent SCID screening programs.

Abbreviations
CS: Caesarean section; GA: Gestational age at birth; IUGR: Intrauterine growth restriction; SVD: Spontaneous vaginal delivery; TREC: T cell receptor excision circle.

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Authors’ contributions
AA and LL wrote the initial draft; PC, LB, and RB reviewed the manuscript, suggested changes, and approved the final version. All authors read and approved the final manuscript.

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Availability of data and materials
All data are contained within the manuscript.
Declarations

Ethics approval and consent to participate
This study was approved by the Hamilton Integrated Research Ethics Board.

Consent for publication
Consent was waived by the ethics board as these patients are no longer followed in clinic.

Competing interests
AA, LL, PC, and LB do not have any conflicts of interest to report. RB reports honoraria from Takeda and Sanofi-Genzyme, outside the submitted work.

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