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ORIGINAL ARTICLE

A first pilot study on the neonatal screening of primary immunodeficiencies in Spain: TRECS and KRECS identify severe T- and B-cell lymphopaenia☆

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KEYWORDS
Newborn screening;
Primary immunodeficiency diseases;
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Abstract
Introduction: Early diagnosis of primary immunodeficiency such as severe combined immunodeficiency (SCID) and X-linked agammaglobulinemia (XLA) improves outcome of affected infants/children. The measurement of T-cell receptor excision circles (TRECS) and kappa-deleting recombination excision circles (KRECS) can identify neonates with severe T or B-cell lymphopaenia.
Objectives: To determine TRECS and KRECS levels from prospectively collected dried blood spot samples (DBS) and to correctly identify severe T and B-cell lymphopaenia.

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X-linked agammaglobulinaemia;
Lymphopaenia

Material and methods: Determination of TRECS and KRECS by multiplex PCR from neonates born in two tertiary hospitals in Seville between February 2014 and May 2014. PCR cut-off levels: TRECS < 15 copies/μl, KRECS < 10 copies/μl, ACTB (β-actin) > 1000 copies/μl. Internal (XLA, ataxia telangiectasia) and external (SCID) controls were included.
Results: A total of 1068 out of 1088 neonates (mean GA 39 weeks (38–40) and BW 3238 g (2930–3520) were enrolled in the study. Mean (median, min/max) copies/μl, were as follows: TRECS 145 (132, 8/503), KRECS 82 (71, 7/381), and ACTB 2838 (2763, 284/7710). Twenty samples (1.87%) were insufficient. Resampling was needed in one neonate (0.09%), subsequently giving a normal result. When using lower cut-offs (TRECS < 8 and KRECS < 4 copies/μl), all the samples tested were normal and the internal and external controls were correctly identified.
Conclusion: This is the first prospective pilot study in Spain using TRECS/KRECS/ACTB-assay, describing the experience and applicability of this method to identify severe lymphopaenias. The ideal cut-off remains to be established in our population. Quality of sampling, storage and preparation need to be further improved.
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PALABRAS CLAVE
Cribado neonatal;
Inmunodeficiencias primarias;
Inmunodeficiencia combinada grave;
Agammaglobulinemia ligada al cromosoma C;
Linfopenia

Primer estudio piloto en España sobre el cribado neonatal de las inmunodeficiencias primarias: *TRECS* y *KRECS* identifican linfopenias T y B graves

Resumen
Introducción: El diagnóstico precoz de inmunodeficiencias primarias, como la inmunodeficiencia combinada grave (IDCG) y la agammaglobulinemia ligada al cromosoma X (ALX), mejora el pronóstico de los niños afectados. La medida de los *T-cell receptor excision circles* (TRECS) y *kappa-deleting recombination excision circles* (KRECS) puede identificar neonatos con linfopenias T y/o B graves.
Objetivo: Cuantificar los niveles de TRECS y de KRECS de manera prospectiva a partir de muestras de sangre seca de talón para identificar de manera correcta linfopenias T y/o B.
Materiales y métodos: Determinación de TRECS y de KRECS mediante reacción en cadena de polimerasa multiplex en neonatos nacidos entre febrero y mayo del 2014. Los puntos de corte empleados fueron: TRECS < 15 copias/μl, KRECS < 10 copias/μl, ACTB (β-actina) > 1.000 copias/μl. Se incluyeron controles internos (ALX, ataxia) y externos (IDCG).
Resultados: Fueron analizadas 1.068 muestras de las 1.088 recogidas (edad gestacional media: 39 semanas [38-40]; peso al nacer medio 3.238 g [2.930-3.520]). La media (mediana, min/máx) copias/μl obtenidas fueron las siguientes; TRECS 145 (132, 8/503), KRECS 82 (71, 7/381) y ACTB 2838 (2763, 284/7710). Veinte muestras (1,87%) fueron insuficientes para el análisis. El *re-test* fue necesario en un neonato (0,09%), confirmándose resultados normales posteriormente. Empleando puntos de corte inferiores (TREC < 8 y KREC < 4 copias/μl), todas las muestras resultaron normales y se identificaron los controles internos y externos correctamente.
Conclusión: Es el primer estudio prospectivo realizado en España usando el ensayo TREC/KREC/ACTB para identificar linfopenias graves. Es necesario establecer puntos de corte adecuados para nuestra población, mejorar la toma de muestras, su almacenamiento y la preparación de las mismas.
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Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of disorders comprising more than 240 different pathologies, with an approximate incidence of 1:500 live births. Congenital defects of the immune system, such as severe combined immunodeficiency (SCID) and X-linked agammaglobulinaemia (XLA) are less frequent, although they still have a considerable incidence of 1:70 000 to 1:100 000 live births.[1,2] The vast majority of neonates with severe T- and/or B-cell lymphopaenias, including those suffering from severe PIDs, have no family history of PID and are asymptomatic in the first weeks of life.[3] Due to these features, delayed diagnosis is frequent, and it is associated with considerable morbidity and mortality due to the development of severe clinical manifestations at a later point.[2–4] There are highly efficacious treatment options for the most severe forms of PID, for instance, immune globulin

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