Impact of newborn screening for SCID on the management of congenital athymia

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Abstract

Background: Newborn screening (NBS) programmes for severe combined immunodeficiency (SCID) facilitate early SCID diagnosis and promote early treatment with haematopoietic stem cell transplantation, resulting in improved clinical outcomes. Infants with congenital athymia are also identified through NBS due to severe T-cell lymphopaenia. With the expanding introduction of NBS programmes, referrals of athymic patients for treatment with thymus transplantation have recently increased at Great Ormond Street Hospital (GOSH), London, United Kingdom.

Objective: We studied the impact of NBS on timely diagnosis and treatment of athymic infants with thymus transplantation at GOSH.

Methods: We compared the age at referral and complications between athymic infants diagnosed after clinical presentation (N=25) and patients identified through NBS (N=19), referred for thymus transplantation at GOSH between 10/2019 and 02/2023. We assessed whether age at time of treatment influences thymic output at 6 and 12 months after transplantation.

Results: Infants referred after NBS identification were significantly younger and had less complications, in particular less infections. All deaths occurred in the non-NBS group, including six patients before and two after thymus transplantation because of pre-existing infections. In the absence of significant co-morbidities or diagnostic uncertainties, timely treatment was more frequently achieved after NBS. Treatment at <4 months of age was associated with higher thymic output at 6- and 12-months post-transplantation.

Conclusion: NBS contributes to earlier recognition of congenital athymia, promoting referral of athymic patients for thymus transplantation prior to acquiring infections or other complications, and facilitating treatment at younger age, thus playing an important role in improving their outcomes.

Clinical implications:

- NBS facilitates early diagnosis of congenital athymia and timely treatment before patients develop complications.
- Treatment at a younger age is associated with quicker immune reconstitution due to earlier thymopoiesis and increase in T-cell counts after thymus transplantation.

Capsule summary: Newborn screening for severe combined immunodeficiency and T-cell lymphopaenia promotes early diagnosis of congenital athymia and timely treatment with thymus transplantation, contributing to improving outcomes for athymic infants.

Key words: Thymus transplantation, newborn screening, severe combined immunodeficiency, DiGeorge syndrome, athymia

Abbreviations: NBS newborn screening, SCID severe combined immunodeficiency, HSCT haematopoietic stem cell transplantation, TREC T-cell receptor excision circle, cDGS complete DiGeorge Syndrome, OS Omenn syndrome

Introduction

The introduction of newborn screening (NBS) for severe combined immunodeficiency (SCID) and T-cell lymphopaenia is increasingly recognised as improving clinical outcomes for infants with SCID by promoting early initiation of protective and prophylactic measures, and early referral for corrective treatment with haematopoietic stem cell transplantation (HSCT) (1-3). Delivery of HSCT before the age of 4 months results in high survival rates regardless of donor type (3, 4). Infants with thymic aplasia and hypoplasia are also identified through these NBS programmes which are based on the enumeration of T-cell receptor excision circles (TRECs) on dried blood spots (5, 6). Athymic infants require treatment with thymus transplantation, which is available at Great Ormond Street Hospital (GOSH) in London, United Kingdom (UK) (7) or Duke University Hospital, United States (US) (8). Athymia is most commonly associated with complete DiGeorge Syndrome (cDGS) due to 22q11.2 deletion syndrome (22q11.2DS) or CHARGE syndrome but has also been diagnosed in other rare disorders (9). Athymic patients frequently have syndromic co-morbidities requiring acute medical attention and/or corrective surgery (10, 11). In the absence of NBS, recognition of their SCID phenotype may be delayed, increasing their risk of infections and other complications before referral for thymus transplantation (11, 12). Universal and pilot NBS programmes are being implemented in an increasing number of countries (13). In October 2019, a 19-day-old cDGS patient was the first infant identified by NBS to be referred for thymus transplantation at GOSH, receiving the procedure less than 4 weeks later (6). Since then, we have seen a steady increase in referrals for patients identified through NBS. Over the period from October 2019 to February 2023, 44 patients were referred, including 19 infants (43%) diagnosed through NBS programmes in eleven countries. The purpose of this brief report is to highlight the benefits of NBS for athymic patients in terms of timely diagnosis and referral for corrective treatment, including the improved kinetics of T-cell count recovery after thymus transplantation in younger patients.

Results

Among these 44 infants, 31 (71%) were diagnosed with congenital athymia due to 22q11.2DS (n=17) or CHARGE Syndrome (n=14), and 7 patients were diagnosed with athymia due to rare thymic stromal cell defects, including TBX1 (n=4), FOXN1 (n=1) and PAX1 (n=2) deficiency (Table 1). No known defect previously associated with SCID or athymia was identified in the remaining 6 patients. The median age at referral for the 19 NBS patients was 31 days (d) (range: 5-205d), compared to 105d (range: 10-534d) for the 25 patients diagnosed through clinical presentation ($p \leq 0.001$, Mann-Whitney U test) (Figure 1). At the time of referral, infants diagnosed through NBS had less invasive infections (n=3/19, 16%)

than the non-NBS infants (n=12/25, 48%) (p≤0.05, Fisher's exact test) (Table 2). Two NBS infants acquired post-natal CMV infections, including one patient who presented clinically with hypocalcaemic seizures at 6 weeks old after becoming lost to follow up despite a positive NBS result. Six patients died from systemic viral infections before treatment (Table 2); all of whom were in the non-NBS group (n=6/25, 24%). Athymic patients are at risk of developing Omenn syndrome (OS) over time (7, 8). 4/19 (21%) NBS patients and 9/25 (36%) non-NBS patients had OS-like symptoms before thymus transplantation (Table 2), including one non-NBS patient with progressive inflammatory disease who died before transplantation. Because of complex co-morbidities, corrective treatment was not pursued in an additional 8/44 (18%) patients, equally distributed between NBS and non-NBS groups (Table 2). At the time of data collection, 26/44 (59%) patients had received thymus transplantation (Table 1) with an overall median referral-to-treatment time of 119d (3.9 months (m)) (range: 25-392d). Three recently referred patients are awaiting treatment. As a result of earlier referral, 40% of the NBS infants (n=6/15) were transplanted at <4 months of age compared to 18% (n=2/11) of the non-NBS patients. Of the 9/15 (60%) NBS patients transplanted at a later age (median: 225d, range: 137-597d), two were treated at just (17 and 22 days) over the 4 months cut-off for logistical reasons, whilst the other seven were delayed for clinical reasons including the need for surgery for congenital heart disease (n=2) or respiratory tract anomaly (n=1), and novel or undefined causes of T-cell lymphopaenia (n=4) requiring additional investigations and a period of observation to determine that the T-cell lymphopaenia was due to athymia (Table 1).

With an overall median follow up time after transplantation of 18m (range 4-42m) by 05/2023, all but three patients are alive (n=23/26, 88%). All three deaths were from the non-NBS group. Two patients had pre-existing viral infections, dying at 8 and 9m after thymus transplantation without establishment of thymopoiesis. The third patient had treatment-refractory autoimmune haemolytic anaemia and died 3 years post-transplantation from complications of immunosuppressive therapy. Regular immunological monitoring was performed in all transplanted patients. Assessment of thymic output included measurement of $CD4^+CD27^+CD45RA^+$ naïve ($nCD4^+$) T-cells. At 6 ±1 months post-transplantation (data available in 22 patients), patients treated at <4 months of age had higher absolute counts and proportions of $nCD4^+$ T-cells (median: 100 cells/µL, range: 50-1680 cells/µL; median: 37.4% of $CD4^+$ T-cells, range: 11.5-92.6%) than those treated at >4 months old (median: 20 cells/µL, range: 0-170 cells/µL; median: 6.8%, range: 0-96.8%) (respectively p= 0.011 and p=0.017, Mann-Whitney U test) (Figure 2). Due to a history of OS, 8/15 patients in the older group were receiving immunosuppression with ciclosporin compared to only 1/7 patients in the younger group. At 12±1 months post-transplantation (data available in 19 patients), only one patient in the older group remained on weaning ciclosporin treatment. Two patients with autoimmune complications,

both in the older group, were receiving steroids and were excluded from this analysis. Thymic output increased in both groups (Figure 2). Absolute counts and proportions of $nCD4^+$ T-cells remained higher in patients treated at <4 months (median: 334 cells/µL, range: 130-2000 cells/µL; median: 68.5%, range: 48.7-87.9%) than in those treated at >4 months (median: 90 cells/µL, range: 4-480 cells/µL; median: 27.4%, range: 2.1-77.5%) (respectively p=0.015 and p=0.010, Mann-Whitney U test) (Figure 2). Three patients in the older group did not show any evidence of beginning thymopoiesis at 12 months post-transplantation (Figure 2.B). All three patients suffered from viral infections (CMV in n=2 and EBV in n=1). Differences in thymic output between both groups remained statistically significant upon exclusion of these 3 patients (data not shown). Where measured, counts of $CD4^+CD45RA^+CD31^+$ recent thymic emigrants and levels of TRECs/10^6 T-cells, as additional parameters of thymic output, were consistent with the numbers of naïve $CD4^+$ T-cells (data not shown). 12/18 (67%) transplanted patients with at least 12 months follow-up have discontinued immunoglobulin replacement treatment upon recovery of satisfactory T-cell counts.

Overall, these results suggest that treatment at a younger age is associated with better immune reconstitution due to more efficient initial thymopoiesis and greater recovery of T-cell numbers after thymus transplantation.

Discussion

Both centres offering thymus transplantation have reported an overall survival of 75-80% (7, 8). Infections before immune reconstitution are the main cause of death. Despite NBS, the Primary Immune Deficiency Treatment Consortium reported infections prior to HSCT in 55% of SCID patients (14). We also see infections in 16% of athymic children identified through NBS. Nevertheless, these patients benefit from close monitoring and early interventions increasing their chances of a successful outcome despite pre-existing infections. In Europe, coverage by NBS for SCID is still limited and existing programmes are in their infancy, with implementation differing across and within countries (6, 15). Even with NBS, there is still a risk for infants to be lost in follow-up and to develop serious infection (6, 14, 15), as seen in our series. Identification of strategies to further reduce the incidence of infections in infants diagnosed through NBS will improve outcomes for athymic infants. Systemic viral infections, in particular, remain challenging because recovery of T-cell immunity after transplantation typically requires several months (7, 8). Patients who develop OS prior to thymus transplantation require immunosuppressive treatment with ciclosporin and anti-thymocyte globulin (7, 8). This has not been reported to adversely affect clinical outcomes after transplantation but avoiding this complication with earlier corrective treatment has multiple benefits including a reduced

risk of drug toxicity, shorter hospital inpatient stays with reduction in healthcare costs, and improved patient and family experience.

Congenital athymia is characterised by profound T-cell lymphopaenia and absent thymic output (7-9). Absolute $CD3^+$ T-cell counts are generally <50 cells/μL, unless patients have developed OS-like features, which are associated with higher $CD3^+$ T-cell counts. The proportion of naïve T-cells, a measure of thymic output, is negligible (<5% of T-cells) in all athymic patients. Circulating naïve T-cells appear 5-6 months after treatment and progressively increase over time, but typically remain subnormal (7, 8). In the context of the expanding implementation of NBS for SCID, athymic patients have increasingly been treated at a younger age at GOSH, and we aimed to investigate the impact of this on thymic output. We here show for the first time that treatment at a younger age (<4 months) is associated with higher thymic output in the first year after transplantation. Whether earlier treatment results in superior thymic output, sustained over time, and overall better immunological outcomes, will need to be confirmed through long-term follow up of this growing cohort of patients.

Thymus transplantation should be undertaken as soon as possible, however the recommendation for proceeding with corrective treatment by four months of age, as in SCID infants with haematopoeitic cell-intrinsic defects identified through NBS, should not be the benchmark for timely delivery of thymus transplantation in all infants. As seen in this report, athymic patients often have major co-morbidities (10, 11). Palliative care is considered and provided in patients with life-limiting co-morbid conditions, including severe complex heart defects and severe neurological impairment. For patients in whom thymus transplantation can be lifesaving, it may be necessary to first proceed with other procedures to achieve clinical stability (11). Furthermore, despite increasing access to next-generation-sequencing, a significant number of patients with a SCID phenotype do not have a genetic variant in any of the known SCID genes (16). Infants with genetically undefined $T^-B^+NK^+$ SCID and T-cell lymphopaenia require significant additional diagnostic work, including broader genetics and *ex vivo* T-cell differentiation assays before a therapeutic decision can be made (17-19). Whilst most patients have haematopoietic-cell intrinsic defects, which can be treated by HSCT, an increasing number of patients are found to have congenital athymia and require thymus transplantation. In some infants, particularly those with novel thymic stromal cell defects with variable penetrance, it may not be immediately clear whether athymia is complete, and a period of observation may be required to determine whether thymus transplantation is indicated (11). For these multiple reasons, delay in treatment may be necessary despite early diagnosis on NBS.

In conclusion, our experience over the past three years highlights the benefits of NBS for athymic patients, due to earlier recognition and referral for thymus transplantation prior to acquiring infections or developing other complications. Despite being the only thymus transplantation centre in

Europe, timely treatment is accessible at GOSH, and in our cohort, earlier treatment was associated with more efficient early thymopoiesis and immune reconstitution.

Ethics: This work was completed under research ethics approval from London Bloomsbury Research Ethics committee (07/Q0508/43).

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Table 1: Athymic patients referred for thymus transplantation at GOSH:

Diagnosis		**Number of infants** (n=44)	**Number identified by NBS** (n=19)	**Number transplanted** (n= 26)	**Number transplanted at <4months** (n=8)	**Median age at transplantation (Range, in days)**	
cDGS	22q11.2DS	17 (39%)	8/17 (47%)	12/17 (71%)	5	170d (44-301)	142d (44-381)
	CHARGE syndrome	14 (32%)	6/14 (43%)	6/14 (43%)	2	133.5d (82-381)	
	TBX1 deficiency	4 (9%)	0/4 (0%)	1/4 (25%)	0	271d	
Nude SCID	FOXN1 deficiency	1 (2%)	0/1 (0%)	0/1 (0%)	0	NA	NA
Other	PAX1 deficiency	2 (4.5%)	1/2 (50%)	1/2 (50%)	0	338d	225d (110-597)
	Undefined*	6 (13.5%)	4/6 (67%)	6/6 (100%)	1	217d (110-597)	

Table 2: Complications in athymic patients referred for consideration of thymus transplantation:

	Infections	**Omenn Syndrome**	**Death before transplantation**	**Palliation for co-morbidities**
NBS (n=19)	3[#] (15.7%)	4 (21%)	0	4 (21%)
Non-NBS (n=25)	12**(48%)	9 (36%)	6(24%)	4 (16%)

Figure Legends:

Figure 1: Age at referral for consideration of thymus transplantation: Box plots showing the differences in age at referral for 44 athymic infants identified after clinical presentation (N=25) or diagnosed via a NBS programme (N=19). Age at referral is indicated in days. * $p \leq 0.001$.

Figure 2: Thymic output at 6 and 12 months after thymus transplantation: Box plots showing the differences in absolute counts (**A**) and proportions of naïve $CD27^+CD45RA^+$ T-cells (% of $CD4^+$ T-cells) (**B**) at 6- and 12-months post-treatment in patients, who either received thymus transplantation at <4 months of age or who were treated at >4 months of age. *$p \leq 0.05$. N indicates number of patients with evaluable data at 6±1m and 12±1m.

Table 1: Athymic patients referred for thymus transplantation at GOSH:

Summary of the number of patients identified by NBS and the number of patients transplanted among the athymic patients referred for thymus transplantation at GOSH with a diagnosis of cDGS, Nude SCID or other thymic stromal cell defects. Median age at time of transplantation is indicated in days. NA: not applicable; *including 4 patients with genetic defects under investigation and putatively associated with athymia.

Table 2: Complications in athymic patients referred for consideration of thymus transplantation: Overview of the number of patients with infections, OS or life-limiting co-morbidities at the time of referral for thymus transplantation, including number of deaths prior to transfer for corrective treatment. Infections: #Cytomegalovirus (CMV) (n=2), Parainfluenza virus type 3 (Paraflu3) (n=1); **Adenovirus (n=3), Paraflu3 (n=1), Rotavirus (n=1), CMV (n=6), Astrovirus (n=1), Epstein Barr Virus (n=1 in addition to CMV).

References:

1. Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017;130(25):2718-27.
2. van der Burg M, Mahlaoui N, Gaspar HB, Pai SY. Universal Newborn Screening for Severe Combined Immunodeficiency (SCID). Front Pediatr. 2019;7:373.
3. Thakar MS, Logan BR, Puck JM, Dunn EA, Buckley RH, Cowan MJ, et al. Measuring the effect of newborn screening on survival after haematopoietic cell transplantation for severe combined immunodeficiency: a 36-year longitudinal study from the Primary Immune Deficiency Treatment Consortium. Lancet. 2023;402(10396):129-40.
4. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med. 2014;371(5):434-46.
5. Martin-Nalda A, Cueto-Gonzalez AM, Argudo-Ramirez A, Marin-Soria JL, Martinez-Gallo M, Colobran R, et al. Identification of 22q11.2 deletion syndrome via newborn screening for severe combined immunodeficiency. Two years' experience in Catalonia (Spain). Mol Genet Genomic Med. 2019;7(12):e1016.
6. Speckmann C, Nennstiel U, Honig M, Albert MH, Ghosh S, Schuetz C, et al. Prospective Newborn Screening for SCID in Germany: A First Analysis by the Pediatric Immunology Working Group (API). J Clin Immunol. 2023:1-14.
7. Davies EG, Cheung M, Gilmour K, Maimaris J, Curry J, Furmanski A, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol. 2017;140(6):1660-70 e16.
8. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. J Allergy Clin Immunol. 2022;149(2):747-57.
9. Kreins AY, Maio S, Dhalla F. Inborn errors of thymic stromal cell development and function. Semin Immunopathol. 2021;43(1):85-100.
10. Gupton SE, McCarthy EA, Markert ML. Care of Children with DiGeorge Before and After Cultured Thymus Tissue Implantation. J Clin Immunol. 2021;41(5):896-905.
11. Howley E, Davies EG, Kreins AY. Congenital Athymia: Unmet Needs and Practical Guidance. Ther Clin Risk Manag. 2023;19:239-54.
12. Kreins AY, Worth A, Ghosh S, Mohammed RW, Davies EG. First Use of Thymus Transplantation in PAX1 Deficiency. J Clin Immunol. 2023.
13. Meyts I, Bousfiha A, Duff C, Singh S, Lau YL, Condino-Neto A, et al. Primary Immunodeficiencies: A Decade of Progress and a Promising Future. Front Immunol. 2020;11:625753.
14. Dorsey MJ, Wright NAM, Chaimowitz NS, Davila Saldana BJ, Miller H, Keller MD, et al. Infections in Infants with SCID: Isolation, Infection Screening, and Prophylaxis in PIDTC Centers. J Clin Immunol. 2021;41(1):38-50.
15. Blom M, Zetterstrom RH, Stray-Pedersen A, Gilmour K, Gennery AR, Puck JM, et al. Recommendations for uniform definitions used in newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol. 2022;149(4):1428-36.
16. Dvorak CC, Haddad E, Buckley RH, Cowan MJ, Logan B, Griffith LM, et al. The genetic landscape of severe combined immunodeficiency in the United States and Canada in the current era (2010-2018). J Allergy Clin Immunol. 2019;143(1):405-7.
17. Kreins AY, Bonfanti P, Davies EG. Current and Future Therapeutic Approaches for Thymic Stromal Cell Defects. Front Immunol. 2021;12:655354.
18. Bosticardo M, Pala F, Calzoni E, Delmonte OM, Dobbs K, Gardner CL, et al. Artificial thymic organoids represent a reliable tool to study T-cell differentiation in patients with severe T-cell lymphopenia. Blood Adv. 2020;4(12):2611-6.
19. Bifsha P, Leiding JW, Pai SY, Colamartino ABL, Hartog N, Church JA, et al. Diagnostic assay to assist clinical decisions for unclassified severe combined immune deficiency. Blood Adv. 2020;4(12):2606-10.