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Review Article

A review of adenotonsillar hypertrophy and adenotonsillectomy in children after solid organ transplantation

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ABSTRACT

Objective: Paediatric solid organ transplantation is an increasingly successful treatment. Improved survival is paralleled by increased secondary complications of immunosuppression, including post-transplant lymphoproliferative disease (PTLD). PTLD frequently presents in Waldeyer's lymphatic ring. Adenotonsillar hypertrophy (ATH) is common in children, however in children after transplant, ATH may indicate PTLD. We review the literature on ATH and the role of adenotonsillectomy in children after transplantation.

Methods: A comprehensive literature search was performed on the 26 th September 2017 of Ovid Medline (1996–September 2017), Embase (1996–2017) and EBM reviews (Cochrane database of systematic reviews 2005–September 20 th 2017). Results were limited to English language publications within the last 20 years. Abstracts were screened for relevance to PTLD and ATH in the paediatric solid organ transplantation population. Screening of the bibliographies identified further articles.

Results: 85 unique articles were screened to yield 18 relevant publications. 10 were retrospective studies and 8 were prospective studies.

Conclusion: In children, we report a PTLD incidence of up to 15%, with up to 63% of cases presenting in the head and neck. Histological examination of adenotonsillectomy specimens found PTLD in a mean 5.7% (range 0–39%). We found a lack of prospective studies into this topic and further high quality research is needed. Clinical assessment of ATH in children after transplantation and when to perform a diagnostic adenotonsillectomy remains challenging. Children with ATH warrant prompt further investigation and support from colleagues in transplantation and oncology is required.

1. Introduction

Paediatric solid organ transplantation of the heart, lungs, kidney or liver is an increasingly successful treatment with more than 80% of children surviving into early adulthood [1]. Internationally, the exact incidence of paediatric solid organ transplantation is unknown. Combination figures for adult and paediatric solid organ transplants amounted to 97,851 performed between 2015 and 2016 [2]. Between 1 April 2015 to 31 March 2016, 177 paediatric deceased donor solid organ transplants were performed in the UK [3]. The improved survival from solid organ transplantation has been paralleled by increased long-term secondary complications of iatrogenic immunosuppression, including secondary malignancies, which affect up to 20% of paediatric transplant recipients by 10 years after transplant [4–8]. Post-transplant lymphoproliferative disease (PTLD) is the most common paediatric secondary malignancy [1,9–11].

PTLD is most frequently associated with Epstein Barr Virus (EBV) seroconversion or reactivation [12–15]. In the immunocompromised patient, defects in T cell regulation allow uncontrolled proliferation of B and T lymphocytes in response to EBV infection and subsequent unregulated lymphoproliferation [16,17]. PTLD is frequently categorised into hyperplastic early lesions, polymorphic or monomorphic [18,19]. The hyperplastic early lesions can be indolent, isolated lesions and are represented by plasma cell hyperplasia or infectious mononucleosis-like histopathological subtypes. The polymorphic PTLD cases are comprised of polyclonal or monoclonal subtypes and the most aggressive monomorphic PTLD can be seen to represent B or T cell lymphoma, myeloma or Hodgkin's disease [19].

Prompt diagnosis is critical as early hyperplastic PTLD is amenable to reduced immunosuppression treatment, increasing the immune

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system's activity to target and destroy the hyperplastic cells [18]. The most severe monomorphic subtypes of PTLD are extremely resistant to treatment and have poorer prognoses. Overall childhood PTLD mortality remains high at between 10 and 20% [20–23].

The clinical presentation of PTLD is variable and can often present with non-specific symptoms such as fever, lethargy or weight loss [13,24]. If specific organ systems are involved, symptoms may relate to that organ, such as gastrointestinal or respiratory symptoms [13,24]. However, many children may be asymptomatic, particularly in the early stages of the disease. Waldeyer's lymphatic ring is the gateway of the respiratory and alimentary tracts and primarily consists of the palatine tonsils, adenoid and lingual tonsils [25]. Lymphoid hypertrophy is an important indicative sign of PTLD and a common site of PTLD lymphoid hypertrophy is Waldeyer's lymphatic ring [24,26]. Adenotonsillar hypertrophy (ATH) is however extremely common in children making differentiation between benign lymphoid hyperplasia and a new presentation of PTLD difficult. Deciding when it is appropriate to perform diagnostic adenotonsillectomy in this group of children is especially challenging [4–7,13,21,24].

The aim of this review was to evaluate the literature on ATH, PTLD and the role of adenotonsillectomy in children after solid organ transplantation.

2. Methods

A comprehensive literature search was performed on 26 th September 2017 using Ovid Medline (1996–September 2017), Embase (1996–2017) and EBM reviews (Cochrane database of systematic reviews 2005–September 20 th 2017). The search terms used were; 'obstructive sleep apnoea' or 'adenotonsillar hypertrophy' or 'lymphoid hyperplasia' or 'swelling' or 'head and neck' or 'Waldeyer's ring' or 'tonsil' or 'adenoid' or 'palatine tonsil' or 'adenotonsillectomy' or 'tonsillectomy' or 'adenoidectomy' or 'posttransplant lymphoproliferative disease/disorder' AND 'solid organ transplant' or 'organ transplant' or 'organ transplantation' AND 'paediatrics' or 'pediatrics' or 'children'. Search results were limited to those published between 1996 and 2016 in the English language. Duplicate articles were removed. The literature search yielded 85 unique articles and abstracts were screened for study eligibility including; paediatric population, patients having undergone solid organ transplantation, studies focusing on the development of PTLD and/or ATH. Further articles were identified through screening of relevant article bibliographies and 18 were considered to meet inclusion criteria for the review. Data abstracted from the 18 articles included; title, year of publication, study design, sample size and transplanted organ. Additional data abstraction was taken from applicable papers on; reported incidence of PTLD, reported risk factors for PTLD and commentary on adenotonsillectomy undertaken within the post-transplantation population. Data was analysed where possible with a quantitative summary of pooled data from multiple small included articles. Given the nature of the review and the small number of included papers, qualitative summaries have been included where necessary.

3. Results

The literature search yielded 85 unique articles. Of which 18 were considered relevant and included in the review Table 1. Of these, 10 were retrospective studies and 8 were prospective studies.

3.1. Incidence of PTLD in children after solid organ transplantation

The number of cases of PTLD is increasing, likely due to the increasing use of more potent immunosuppression in a larger at risk population, owing to prolonged survival after transplantation [27–30]. The reported risk of developing PTLD in children varies widely in the literature, with a range from 1 to 15% [18,20,27,29]. This is higher than the rate in adults, which is in the range of 1–10% [29,31].

Pooling multiple, small, retrospective studies for paediatric renal transplant the overall incidence of PTLD developing after transplant, has been reported at 6.9% (n = 19/274), 1.2% (n = 56/4595) and 2.3% (n = 35/1537) [15,27,28]. Paediatric liver transplants are reported as 8.4% (n = 298) and 13.1% (n = 61) [24,32]. Heart or lung transplants showed an overall incidence of 6.3% in the heart recipients and 11% PTLD in lung recipients (n = 443) [26].

PTLD presentation is often categorised into early (within 12 months of transplantation) or late (beyond 12 months) and was reported in a case series of 450 paediatric patients as occurring anywhere between 6 weeks and 7 years after transplantation with 60% occurring within the first 12 months [13,18]. The often innocuous presentation of PTLD in children and the risk of development many years after transplant further compounds the diagnostic difficulties in children after transplantation.

The head and neck is a crucial site for presentation of PTLD, while reported incidence varies by study, it is described as between 25 and 62.5% of cases presenting in the head and neck, with 25–80% of PTLD that presents in the head and neck, located in Waldeyer's lymphatic ring [14,18,24,26,33–35].

3.2. PTLD and immunosuppressive regimen

The organ transplanted has a significant impact on the rates of PTLD and this is theorised to be linked to the different amounts of immunosuppression required for different transplanted organs [13,18]. Lifelong immunosuppression attempts to mitigate the risks of acute or chronic organ rejection, however with extensive immunosuppression, subsequent unregulated lymphoproliferation risks the development of PTLD [16,36]. Reported rates of rejection in the literature vary, with adult European figures reporting a 10–40% rejection rate for kidney transplants within the first 12 months, 20–50% liver, 10–40% pancreas, 50% lung and 50–80% in heart transplants in the first 6 months alone [37]. Cardiothoracic transplants are associated with the highest risk of rejection and thereby require significantly higher levels of immunosuppression which increases their risk of developing PTLD [36,37].

A recent retrospective review of the United Network for Organ Sharing (UNOS) database supports this theory, showing an increased incidence of PTLD amongst cardiothoracic transplant recipients of all ages, as opposed to other organ types [38]. The authors hypothesised that this increased risk was due to the higher level of immunosuppression required for these patients. The lowest incidence of PTLD was in patients with tacrolimus immunosuppression when compared to other immunosuppressive regimens (n = 38,861 heart, 21,857 lung) [38]. A recently published study of the kidney transplantation population found that induction with an agent other than anti-CD25 monoclonal antibody was independently associated with an increased risk of PTLD [adjusted hazard ratio 2.07 (95% CI 1.16–3.70), P = 0.01] [36].

Current pharmacological immunosuppressive therapies used in solid organ transplantation are extensive and include various combinations of; glucocorticoids (prednisolone), calcineurin inhibitors (cyclosporine, tacrolimus), mammalian target of rapamycin (MTOR) inhibitors (sirolimus, everolimus), inhibitors of de novo nucleotide synthesis (mycophenolate mofetil - MMF), antimetabolites (azathioprine) and monoclonal antibodies (anti-CD25, basiliximab) [37]. Use of immunosuppression regimens in solid organ transplantation in children often reflects region-specific preferences, evidence based on clinical experience only and a lack of robust, well-controlled randomised controlled trials. Despite the heterogeneity in approach to immunosuppression, all solid organ recipients will receive induction, initial and then maintenance therapy to prevent graft rejection. Common induction therapy agents include, antithymocyte globulin (ATG) or basiliximab, initial therapy is often composed of the use of triple therapy with a calcineurin inhibitor in combination with a