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Paediatric incidence of acute rejection and obliterative bronchiolitis: a comparison with adults

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Abstract Obliterative bronchiolitis (OB) continues to be a major cause of morbidity and mortality following heart-lung transplantation. We compared the incidence of death from obliterative bronchiolitis in 19 children and 72 adults following heart-lung transplantation at our institutes. The incidence of death from OB at 2 years was 38% for children compared with 17% for adults, this difference was significant (Cox-Mantel Z value = 2.243, $P < 0.05$). The frequency of acute lung rejection and persistent lung rejection, previously described as risk factors for OB in adults, were significantly more common in children, $P = 0.004$ and $P = 0.001$, respectively. Average forced expiratory volume in 1 s was lower in children than in adults for each 3-month period after transplantation ($P < 0.001$). In conclusion, identified risk factors for the development of OB were more common, and the risk of death from OB was greater in children than in adults following heart-lung transplantation.

Key words Children · Lung transplantation · Obliterative bronchiolitis · Rejection · Infection

Introduction

Heart-lung transplantation (HLT) for the relief of terminal cardiopulmonary disease in children has been successfully undertaken in several centres [1–3]. For these children as well as for adult patients, obliterative bronchiolitis remains the major obstacle to long-term well-being and survival following heart-lung transplantation [4, 5]. In adults, the development of OB is closely related to the incidence of persistent and severe acute rejection confirmed by transbronchial biopsy (TBB) [6]. In children as young as 3 years, transbronchial lung biopsies can be used successfully to monitor pulmonary rejection and infection [7]. Age has been described as influencing the frequency of rejection, which in adults may be higher in younger patients than in older patients [8]. In adults, the number of TBB demonstrating rejection is clearly related to the grade of rejection [9]. However, it seems that the diagnosis of rejection in children requires far fewer TBBs than in adults, suggesting that in children the rejection is more diffuse, and potentially more severe [7, 9]. Decline in lung function, particularly forced expiratory volume in 1 s (FEV_1), is closely related to both the rate of acute rejection and the persistence of acute rejection on subsequent biopsies [8].

We, therefore, reviewed the rates of biopsy-confirmed acute and persistent rejection, together with lung function and the culmulative incidence of death from OB in both adults and children receiving HLT at our two hospitals.

Methods

Nineteen children, mean age 11.3 years (range 3–15 years) transplanted since June 1987 at Papworth Hospital and Great Ormond Street Hospital for Sick Children, were compared with 72 adults, mean age 32.4 (range 16–53 years), transplanted over the same time period. All patients were ABO matched, none were HLA matched and 71 adults and 18 children were cytomegalovirus (CMV) matched.

For the purposes of this study, rejection was defined as an episode fulfilling the clinical criteria for rejection, without intercurrent infection as previously described [6], in which characteristic histological features of acute rejection [6, 7] were found. Background and enhanced immunosuppression were as previously reported [1, 6] and were the same for both groups of patients. Obliterative bronchiolitis (OB) was defined as extensive occlusion of terminal airways by fibrous tissue resulting in death and was taken as the endpoint for diagnosis and cumulative survival curves. Tissue and lavage culture, serological screening and treatment of pulmonary infections were as previously reported [6]. All acute respiratory illness was investigated with a chest radiograph and routine lung function measurements were performed in all patients after 2 weeks, then monthly, decreasing to 3 monthly after 4–6 months. Biopsy numbers varied from 4–22 in adults [9]. However, only five are required for 99% likelihood of detecting rejection in children [7].

Analysis

Acute lung rejection is defined as a histologically confirmed episode of lung dysfunction requiring treatment with enhanced immunosuppression. Persistent rejection is defined as histological evidence of lung rejection following a treated episode of lung rejection at least 2 weeks before with no intervening biopsies that are free of rejection. Rejection episodes are reported as the mean number of episodes and the standard deviation for each 3-month period post-transplantation. Since rejection episodes are in the form of counts we assumed they follow a Poisson distribution. Logrank testing was applied to compare adult and child survival to OB-related death curves. Linear rejection rates were compared for each 3-month interval from transplantation, using a poisson distribution and chi-square analysis. Two-way analysis of variance was used to assess the average forced expiratory volume in 1 s (FEV_1) for each 3-month interval from transplantation.

Results

The cumulative survival curves were significantly different with a 2-year mortality from OB of 38% in children and 16% in adults (Cox-Mantel Z value = 2.2, $P < 0.05$). Pre-transplant diagnoses were unrelated to the development of OB. Comparison of linear rejection rates given as events/100 patient days was significantly higher in children than in adults; chi-square = 8.5, with one degree of freedom, $P = 0.004$. Comparison of persistent rejection rates for children and adults indicated significantly higher rates for children than for adults; chi-square = 13.7, with one degree of freedom, $P < 0.001$. Finally, average FEV_1 over each 3-month period demonstrated lower values for the paediatric group. By two-way analysis of variance, by group F1, 194; $P < 0.01$ and by time F2, 194 = 11.58; $P < 0.001$.

Discussion

Comparison between adults and children indicated a higher rate of acute rejection, lower FEV_1 values and a higher rate of death from OB in children than in adults. Obviously, these results were influenced by the small numbers involved and also by the time that we chose to perform the analysis. However, they appeared to clearly identify children as having the major risk factors for OB that are seen in adults [8] and, therefore, as being a risk group for OB. Our incidence of OB was somewhat lower than the 71% incidence of OB in children reported by the Stanford group [9]. In contrast, the infants receiving single lung transplants at Stanford may have a reduced incidence of OB [10], although in infancy compensatory growth of the transplanted lung has yet to be studied. Infection does not appear important in adults as a risk factor for OB in our programme [5, 8], although two of the children with OB had significant pulmonary infections with *Staphylococcus aureus* and *Mycoplasma pneumoniae*. The early decline to death with terminal infection in children with OB may, therefore, be related, at least in part, to poor lung function, as well as to mucosal oedema from both rejection and infection [8] in inherently small airways, with or without palsies of phrenic or recurrent laryngeal nerves in such small patients, or tracheal stenosis or tracheomalacia [11]. Two children with OB deaths had tracheal stenosis, suggesting that this might be related to bronchiolar rejection.

Conclusion

These results are similar to early results in adult patients following heart-lung transplantation [4]. Further improvements in monitoring intrapulmonary fibrosis, immunosuppression and the detection of acute pulmonary rejection are essential if the problem of OB is no longer to haunt these patients. The risk of rejection in children is higher than in adults, the level of FEV_1 as a percentage of predicted values is lower and the cumulative survival until death from OB is lower in children than in adults.

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