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Early childhood thymectomy - Impact on immune function

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, den 2. juni 2017, klockan 13:00

av

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Fakultetsopponent:

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Germany

Avhandlingen baseras på följande delarbeten:

I. **Judith Gudmundsdottir**, Sólveig Óskarsdóttir, Gabriel Skogberg, Susanne Lindgren, Vanja Lundberg, Martin Berglund, Anna-Carin Lundell, Håkan Berggren, Anders Fasth, Esbjörn Telemo, and Olov Ekwall. Early thymectomy leads to premature immunological ageing; an 18-year follow-up. J Allergy Clin Immunol. 2016 Nov;138(5):1439-1443.e10. doi: 10.1016/j.jaci.2016.05.014.

II. **Judith Gudmundsdottir**, Christina Lundqvist, Hanna IJspeert, Eva van der Slik, Sólveig Óskarsdóttir, Susanne Lindgren, Vanja Lundberg, Martin Berglund, Jenny Lingman-Framme, Esbjörn Telemo, Mirjam van der Burg and Olov Ekwall. T cell receptor sequencing reveals reduced diversity 18 years after early thymectomy. Manuscript, submitted.

III. **Judith Gudmundsdottir**, Jonas Söderling, Håkan Berggren, Sólveig Óskarsdóttir, Martin Neovius, Olof Stephanson and Olov Ekwall. Long term effects of early thymectomy: associations with autoimmune diseases, cancer, infections and atopic diseases. Manuscript, submitted.

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Abstract

Introduction: The thymus is the site of T cell maturation. Children born with a congenital heart defect often endure surgery early in life, and during surgery their thymus is routinely removed, as it blocks the surgeons access to the heart. The overall aim of this study was to investigate the long-term immunologic and clinical impact of early childhood thymectomy.

Objectives: Investigation of the immunologic impact of early childhood thymectomy at 18 months and 18 years of age with regards to the subset composition of T cells, thymic output and the T cell receptor repertoire diversity (I, II). Investigation of the association between early childhood thymectomy and risks of autoimmune diseases, cancer, infectious diseases and atopic diseases (III).

Methods: Lymphocyte subsets were characterized with flow cytometry in eleven subjects pre-operatively, at 18 months and 18-years follow-up. In addition, the T cell receptor repertoire was analyzed with TCR Vß flow cytometry, T cell receptor excision circles were quantified with PCR and telomere lengths of T and B cells were analyzed with PCR at 18-year follow-up (I). Also, the diversity of the T cell receptor ß chain genes and the immunoglobulin heavy chain genes was determined using next generation sequencing (II). A nationwide population based cohort study was conducted using Swedish patient registers to identify subjects and controls and to analyze clinical outcome measures (III).

Results: Thymectomy was associated with a reduction in the number of T cells, especially the naive subset. The naive regulatory T cells and recent thymic emigrants ($CD31^+$ T cells) were also reduced. TRECs, indicative of thymic output, were unmeasurable in all but one thymectomized individual. Telomere lengths were shorter in $CD8^+$ T cells of thymectomized individuals (I). Disturbances were found in the TCR Vß repertoire (I), and sequencing of the T cell receptor confirmed reduced diversity (II). Compared with surgery controls, thymectomized individuals were at increased risk for hypothyroidism, type 1 diabetes and both viral and bacterial infections. Compared with the general population they were at increased risk for hypothyroidism, juvenile idiopathic arthritis, rheumatic diseases, celiac disease, cancer, infections and asthma (III).

Conclusion: Early childhood thymectomy is associated with immunologic aberrations as well as with increased risks of autoimmune diseases, cancer and infections. This indicates that avoidance of total thymectomy during early cardiac surgery is advisable.

Keywords: Thymus, T lymphocyte, immunology, pediatric cardiac surgery, congenital cardiac defect

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