

Interferon activity in newborns exposed to Ro/SSA autoantibodies in utero and the risk of autoimmune congenital heart block

*Thorlacius G.E. (1), Hedlund M. (1), Ivanchenko M. (1), Ottosson V. (1), Ossoinak A. (1), Lagnefeldt L. (1), Rönnblom L. (2), Sonesson S.E. (1), Eloranta M.L. (2), Wahren-Herlenius M. (1)
Karolinska Institutet, Stockholm, Sweden (1); Uppsala University, Uppsala, Sweden (2)*

Introduction: Autoimmune congenital heart block (CHB) is a rare cardiovascular manifestation of neonatal lupus syndrome. CHB develops in utero in fetuses of women with anti-Ro/SSA autoantibodies. Women carrying Ro/SSA autoantibodies are commonly diagnosed with Sjögren's syndrome or SLE. The maternal Ro/SSA autoantibodies are transferred over the placenta and initiate inflammatory processes, resulting in fibrosis and calcification of the atrioventricular (AV) node and a third degree AVB. Sjögren's syndrome and autoantibody positivity is often concurrent with increased systemic interferon (IFN) activity and expression of IFN regulated genes, with unknown impact on CHB development. Treatment that alters type I IFN activity has been suggested to reduce the risk of CHB. The pattern and magnitude of IFN pathway activation in Ro/SSA autoantibody exposed newborns has not been investigated.

Methods: Thirteen Ro/SSA autoantibody positive mothers either receiving no medication (Ro/SSA+) or treated with hydroxychloroquine (HCQ) and/or azathioprine (Ro/SSA+T), and their newborn babies were included in the study, together with 8 healthy mother-baby pairs (HC). Blood was drawn from the mother and baby (cord) at birth, with immediate separation into plasma and cells. Cellular mRNA expression levels were measured using microarrays and used for calculating IFN scores. Cell surface expression of molecules was investigated by flow cytometry, and IFN- α in plasma and supernatants was analyzed by immunoassays. The ability of immune cells from newborns to produce IFN- α in response to autoantibody exposure was tested by in vitro stimulation assays.

Results: Mothers with Ro/SSA autoantibodies had an increased IFN activity compared to controls, with a higher IFN score and plasma IFN- α levels, which were similarly high in mothers receiving immunomodulatory treatment. Autoantibody-exposed newborns also had significantly increased IFN activation in terms of IFN score and plasma IFN- α levels. The IFN score in newborns correlated positively with the maternal IFN scores in untreated mothers. However, maternal treatment reduced the IFN activation in the babies. Immune cells from newborns responded to autoantibodies by producing IFN- α in culture.

Conclusions: There is an activation of the type I IFN system in Ro/SSA autoantibody exposed newborns which may contribute to the risk of CHB. Immunomodulatory treatment might reduce that risk.