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Learning Objectives:

Introduction: Cisplatin (CDDP) is a widely used chemotherapeutic drug with important side-effects, such as ototoxicity. CDDP ototoxicity affects individuals variably, which is mostly due to individual genetic factors. Aim of this study is to analyse the genetic background of the patients in which severe ototoxicity occurred.

Methods: 72 children who received CDDP chemotherapy between January 2013 and March 2015 were included in the study. Audiological evaluations were performed before and minimum three months after the therapy. Ototoxicity was evaluated using Muenster, Brock classifications. During routine controls, 5cc of peripheral blood samples were taken into EDTA-coated tubes. Peripheral blood mononuclear cell and subsequent DNA isolations were performed. In order to analyze the genetic background of patients, we performed comparative genomic hybridization (CGH) arrays for 5 patients with the most severe ototoxicity (Grade 3 and 4), among the studied 72 patients. Results were evaluated statistically by using "Agilent CytoGenomics Software".

Results: CGH analysis showed some common genetic differences among evaluated patients. Chr8.p23.1 (Defensin-family genes) deletion was seen in 3 patients. Chr11.q13.2 (NDUFV1) gain was observed among 4 patients. Chr14.q32.33 (ADAM6) amplification, Chr2.p21 (SIX3) amplification and Chr11.p15.5 (H19) gain were common in all patients. Chr20.q13.32 (GNAS) gain was also seen in 3 patients and this chromosomal region was deleted in one patient. Further assessments may be important to understand the roles of these genes in CDDP induced ototoxicity.

Conclusion: In order to minimize the risk for CDDP ototoxicity, identification of genetic differences is of great importance. Further studies on new candidate genes such as Defensin-family genes, ADAM6, SIX3, GNAS, NDUFV1, and H19 should be performed to better understand their effect on CDDP ototoxicity.

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Network analysis of Innate Immune Interaction in Cholesteatoma

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Learning Objectives: Innate Immunity, Cholesteatoma, Network Analysis, Regulatory Network.

Introduction: The etiopathogenesis of Cholesteatoma is controversial, but it is associated with recurrent, persistent ear infections and bacteria. Thereby the interaction between pathogen susceptibility and innate immunity is relevant. Toll-like (TLRs) and Nod-like receptors (Nods) are known to be important participants in the innate immune response to pathogens at other sites, via elaboration of inflammatory cytokines. We explored the network of Innate Immune Receptor-signalling and cytokine production in cholesteatoma.

Methods: Cholesteatoma and control tissue of the external auditory canal skin (EAS) from patients undergoing surgery were evaluated for innate immune pattern and molecules. Cholesteatoma thickness and cellular infiltration were evaluated histologically. mRNA expression of receptors and downstream molecules were evaluated by microarray, real-time PCR, while protein levels were determined by Immunohistochemistry and bioinformatical network analysis.

Results: A subset of receptors involved and downstream molecules in Innate Immunity such as TLRs, Nods and TNF are expressed in cholesteatoma. NOD2 mRNA and protein, but not TLRs or Nod-receptors were significantly induced compared to control samples of the external auditory canal skin (EAS). Moreover, regulation of genes in an interaction network of the RIPK2 was detected. In addition to NOD2, NLRC4, PYCARD, the downstream molecules IRAK1 and anti-apoptotic regulator CFLAR, showed significant upregulation, whereas SMAD3, a pro-apoptotic inducer, was significantly downregulated.

Conclusions: The network interaction of innate immune regulation is important in the etiopathogenesis and growth of cholesteatoma.

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