CONGENITAL CYTOEGALOVIRUS INFECTION: CAN THE DIFFERENCE BETWEEN THE VIRUS' RELATIONSHIP WITH THE HOST'S IMMUNE SYSTEM EXPLAIN THE DIFFERENCE IN CLINICAL PHENOTYPES?

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BACKGROUND: Human cytomegalovirus (HCMV) is a double-stranded DNA virus with ubiquitous distribution around the world. In immunocompromised hosts, HCMV has the ability to determine severe infections, with high morbidity and mortality. A paradigmatic example of what HCMV is capable of is the infection acquired during pregnancy, which leads to the congenital HCMV infection of newborns. In terms of congenital infection, the severity of the clinical situation is determined by the time of maternal infection during pregnancy: newborns infected during the first phases of pregnancy usually presents with greater morbidity and long-term sequelae during infancy. Despite the great amount of cases of congenital HCMV infection, the mechanisms underlying the ability of HCMV to determine infections with great differences in terms of severity are only partially understood.
OBJECTIVE: In this study, we aimed to identify a correlation between the phenotypical characteristics and immunomodulatory ability of different strains of HCMV, clinically isolated from organic samples (urine) of newborns with HCMV congenital infection, and the clinical phenotype presented by the patients. In particular, we aimed to identify which virological features determine not only a more severe congenital HCMV infection *in utero* and in the neonatal period, but also a greater number of long-term sequelae.
MATERIALS AND METHODS: In this study, we considered a population of 21 newborns diagnosed with congenital HCMV infection at the Neonatal Care Unit of Neonatology at the Sant'Anna Hospital of Turin, during the period of April 2015 and September 2017. The growth properties of the HCMV isolates were analyzed in different colture models. Genetic polymorphism was assessed by genetic analysis of viral genes involved in drug resistance (UL54 and UL97). Moreover, we sought to determine whether inter-host phenotipic variability of HCMV influences its ability to modulate NK cell responses to infection and consequently the its ability to determine a more severe congenital infection. For this purpose, we selected five HCMV clinical isolates from the considered cohort of patients and analyzed the expression of several ligands for specific NK cell-activating receptors. We also studied the IFN-ɣ production by NK cells co-cultured with HCMV-infected fibroblasts, in order to correlate the expression of the ligands with the functionality of the immunitary system cells.
RESULTS: Our results indicate that exist a great variability of replicative behaviour and genetic polymorphisms between the HCMV strains studied. While the genetic polymorphisms didn't show influence on the severity of the infection, we observed that that the replicative behavour's

variability influeces the immunomodulatory ability of HCMV, leading to more severe congenital infections and long-term sequelae.
CONCLUSIONS: HCMV clinical isolates with a non aggressive replicative behaviour are capable to determine a severe clinical phenotype due to an increased capability of molecular mimicry of the virus. Infections from isolates with an aggressive replicative behaviour in vitro result in asymptomatic pheontypes, due to a lower molecular mimicry.