Cytokine Gene Polymorphisms and the Realtionship with: Congenital Cytomegalovirus Infections and Mother-to-foetus CMV Transmission

THE CHILDREN'S MEMORIAL HEALTH INSTITUTE

B. Kasztelewicz [1], J. Czech-Kowalska [2], M. Kornacka [3], K. Dzierżanowska-Fangrat [1]

[1]Dept. of Clinical Microbiology & Immunology, The Children's Memorial Health Institute, Warsaw, Poland
[2]Dept. of Neonatology and Neonatal Intensive Care; The Children's Memorial Health Institute, Warsaw, Poland
[3]Dept. of Neonatology and Neonatal Intensive Care, Warsaw Medical University, Warsaw, Poland.

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INTRODUCTION AND PURPOSE

Cytomegalovirus (CMV) is the most common congenital viral infections and a leading non-genetic cause of sensorineural hearing loss (SNHL). Primary infected women have high risk for viral transmission to their fetus. There is evidence that host genetics have an impact on various infectious diseases. Genetic risk factors for congenital CMV infection are currently poorly understood. Important role in establishing and maintaining pregnancy have cytokines. Genetic polymorphism within cytokine genes, by influencing the overall host-viral interactions, might have an impact on susceptibility to infection, clinical outcome and the risk of mother to child transmission of CMV.

The aim of the study was to analyze the cytokine gene polymorphism that may be involved in pathogenesis of CMV infection in newborns and their mothers.

MATERIAL AND METHODS

The study population consisted of 251 infants and 295 pairs of newborns and their mothers, enrolled prospectively during March 2009 – July 2013. All children were white Caucasian. Congenital CMV was diagnosed in 96 infants (a case group), 75/96 children were identified by CMV DNA detection in urine, blood and/or CSF collected within the first 2-3 weeks of life, remaining 21 were tested after 3rd week of life and diagnosed based on clinical grounds (after excluding of other congenital infections). A group of 452 infants CMV- negative at the initial screening in the neonatal period, were assigned as controls. Two hundred and fifty-five out of 295 mothers, experienced CMV infection before or during pregnancy (and 26 of them transmitted CMV to their child), remained 40 mothers were CMV naïve. Demographic and clinical data were collected from newborns hospital records. Genomic DNA was isolated from blood samples in all subjects included in the study and preserved for genotyping assays. Eleven candidate single nucleotide polymorphisms (SNPs) were genotyped: TNFA -1031T/C (rs1799964), TNFA -308G/A (rs1800629), TNFRI -201C/A (rs4149570), CCL2 +1543C/T (rs13900), IL-10 -1082A/G (rs1800896), IL-10RA +5964C/T (rs4252270), IL-1B -511C/T (rs16944), IL-1B +3954C/T (rs1143634), IL12B 3'UTR A/C (rs3212227), CCL2 -2518A/G (rs1024611), (CCR5Δ32, rs333) using PCR, RFLP-PCR or real-time PCR TaqMan SNP allelic discrimination. The Hardly-Weinberg equilibrium (HWE) test and association of the genotypes with CMV infection status in children and mothers were performed using SNPStats software (Solé X. Bioinformatics 2006;22:1928-9).

Table 1. Characteristics of infants with congenital CMV infection and controls

	Congenital CMV (n = 96)	CMV uninfected (n = 452)	P-value
Male, %	52.08	56.19	0.462
Maternal age at delivery, mean ± SD,y	27.47 ± 4.94	29.68 ± 5.28	**0.0002**
Maternal parity – primigravida, %	54.7	56.50	0.780
Mode of delivery - vaginal, %	51.14	63.64	0.051
Preamturity (<37 wks)	26,04	20.67	0.245
Small for gestational age, %	35.42	8.98	**$< 10^{-6}$**
Gestational age, mean ± SD, wk	37.55 ± 3.13	38.56 ± 10.34	0.384
Birth weight, mean ± SD, g	2735.31 ± 794.34	3045.50 ± 834.57	**0.00012**
APGAR at 5 min, mean ± SD (range)	8.99 ± 1.63 (2-10)	9.24 ± 1.43 (3-10)	0.097

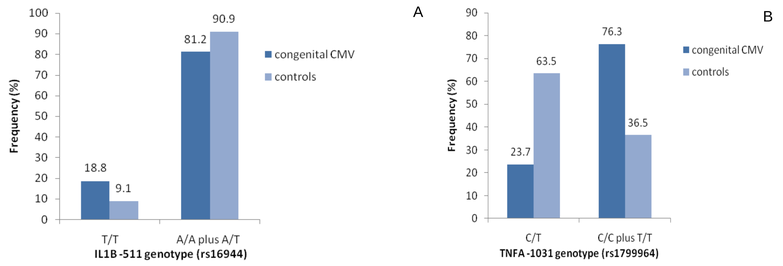

Fig. 1. Genotype frequencies of IL1B -511 **(A)** and TNFA-1031 **(B)** polimorphisms in children with congenital CMV infection (n = 96) and uninfected controls (n = 452).

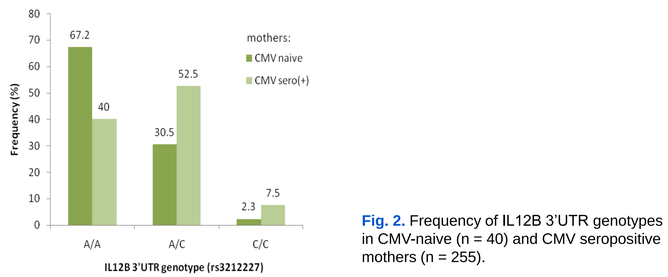

Fig. 2. Frequency of IL12B 3'UTR genotypes in CMV-naive (n = 40) and CMV seropositive mothers (n = 255).

RESULTS

Table 1 shows the characteristic of children in congenital CMV and control groups.

Association of SNPs in IL1B and TNFA genes with congenital CMV

To analyze the association of SNPs with congenital CMV, genotype frequencies were compared in cases and control groups. The IL1B-511 T/T genotype was found more frequently in children with congenital CMV compared with controls (18.8% *vs* 9.1%; OR = 2.31; 95% CI:1.26 – 4.24; p = 0.009; **Fig. 1A**). In addition, the TNFA-1031T/C genotype was overrepresented in congenital CMV group compared with uninfected children (36.5% *vs* 23.7%; OR = 1.85, 95% CI:1.16 – 2.96; p =0.012 **Fig. 1B**). Both these associations remained significant after adjusting for mother's age and birth weight (OR = 2.18; 95% CI:1.13 – 4.19; p =0.024 and OR = 1.80, 95% CI:1.08 – 3.01; p = 0.026, respectively for ILB-511 and TNFA-1031). No significant difference in genotype frequencies for the remaining cytokine polymorphisms were observed between congenital CMV and control groups.

Relation between maternal SNPs with mother-to-child CMV-transmission and mother's CMV status

When looking at mother-to-child transmission of CMV, no statistically significant associations were observed for any maternal SNPs. However, comparison of SNPs frequencies in CMV-naïve and -seropositive women, reveal that carriage of rare C allele of IL12B 3'UTR genotype, which has been associated with decreased IL12p40 production, was significantly associated with CMV-negative status in mothers (OR = 2.6; 95% CI:1.48 – 4.56; p < 0.001; **Fig. 2**).

CONCLUSION

The results of this study reveal that: (i) IL1B-511 T/T and/or TNFA-1031 T/C genotypes might predispose to congenital CMV in exposed foetus and (iii) the carriage of rare C allele of IL12B 3'UTR might be protective for CMV infection in mother and thus indirectly influence the risk for CMV primary infection during pregnancy and mother-to-child virus transimssion.

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