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Association of Interleukin-6 −174 (G/C) Gene Polymorphism and IL-6 Expression in Children with Cerebral Palsy: A Case–Control Study

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Abstract

Background: Understanding the molecular and genetic mechanisms underlying cerebral palsy (CP) may facilitate improvements in its diagnosis and management. Investigation of genetic susceptibility factors, particularly cytokine gene polymorphisms, offers a targeted approach to elucidate the role of inflammation in the pathogenesis of CP.

Methods: This case–control study included 65 children diagnosed with cerebral palsy and 65 age-, sex-, and ethnicity-matched healthy controls. Healthy controls had no history of neurological disorders or known inflammatory conditions. Genotyping of the interleukin-6 (IL-6) −174 (G/C) polymorphism was performed using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis. Serum IL-6 levels were quantified by enzyme-linked immunosorbent assay (ELISA). The expression pattern of the IL-6 gene in cerebral palsy patients was assessed using real-time polymerase chain reaction (RT-PCR).

Results: The distribution of the IL-6 −174 (G/C) polymorphism did not differ significantly between cerebral palsy patients and controls. The C allele was more frequent than the G allele in both groups, indicating a higher prevalence of the G>C variant in the study population. Serum IL-6 levels were higher in cerebral palsy patients compared to controls, although this difference was not statistically significant. The CC genotype was associated with altered IL-6 synthesis, demonstrating a significant effect on IL-6 expression ($p < 0.05$).

Conclusion: The lack of a significant genetic association between the IL-6 −174 (G/C) polymorphism and cerebral palsy may be attributed to the limited sample size. Larger, well-powered studies incorporating environmental and perinatal risk factors are required to further elucidate the role of IL-6 gene polymorphisms in the etiopathogenesis of cerebral palsy.

Keywords: Cerebral Palsy; Interleukin - 6; −174 (G/C) Polymorphism; PCR-RFLP

1 Introduction

Cerebral palsy (CP) is a group of non-progressive motor impairment syndromes caused by lesions of the brain arising early in development. The motor disorders are often accompanied by disturbances of sensation, perception, cognition,

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communication, and behavior; by epilepsy; and by secondary musculoskeletal problems [1, 2]. Globally published literature has reported that the range of CP from 1.5 to 4 per 1000 live births but the prevalence range reported for India is higher ranging from 2.08 to 3.88 per 1000 live births [3]. In an analysis of 1000 cases of CP, it was found that spastic quadriplegia constituted 61% of cases followed by diplegia 22% [4]. The inflammatory reaction is an important part of the immune response and is closely associated with CP [5, 6]. The inflammatory reaction involves factors associated with adhesion, metastasis, invasion, and activation of inflammatory cells, as well as the release of inflammatory cytokines. Various inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), participate in the inflammatory reaction [7, 8, 9]. Interleukin -6 (IL-6) gene and IL-6 protein levels have been linked with increased risk of CP [10, 11]. Within the IL-6 gene, the C allele at rs1800795 has been associated with increased risk of neurological disorder in large population studies. The objectives of the study were to determine the presence of the IL- 6 rs1800795 polymorphism in children with CP, to evaluate IL-6 mRNA expression levels in the study group, and to quantify serum IL-6 concentrations using ELISA. Additionally, the study aimed to assess the correlation of these molecular and biochemical parameters with relevant clinical and demographic characteristics.

In humans, attempts to find important interactions between polymorphism in specific alleles, such as IL- 6-174 G/C promoter allele and genotype frequency are not conclusive. Moreover, elevated cerebrospinal fluid IL-6 levels have been associated with worse neurologic outcomes. These studies have not been conducted in Indian population. Preliminary data could suggest the possibility of ethnic group specific disease related polymorphism.

2 Material and method

2.1 Study subjects

The study was a case-control pilot study conducted in the Multi-disciplinary Research Unit and Department of Pediatrics of University College of Medical Sciences (UCMS) and GTB hospital, Delhi. The study was approved by Institutional Ethics Committee-Human Research (IEC-HR) of UCMS. The study included 65 children with CP and 65 age- and sex-matched healthy controls. Cases and controls were recruited from the same hospital and geographic region to minimize population stratification. Participants were enrolled after obtaining informed consent from their guardian/parent. Cerebral palsy was diagnosed based on the clinical definition proposed by Rosenbaum et al. [12].

Children with associated chronic liver or kidney disease, congenital malformations, syndromic diagnoses, or known inborn errors of metabolism were excluded from the study. Clinical and demographic data of all participants were recorded. Clinical data included a detailed medical history, thorough physical examination, and relevant investigations to determine the possible etiology of CP.

2.2 Sample collection

Taking full aseptic precautions blood samples (3ml) were collected by venipuncture from each participant. Blood was centrifuged at 1000 g for 15 min for plasma and serum separation. Plasma and serum samples were frozen at −80 °C until assayed. All parameters were determined within a month after sample collection. Clinical and demographic data of the patients were recorded using a predefined proforma. Control samples were collected and analyzed in the same manner.

2.3 IL-6 genotyping

Genomic DNA was extracted from peripheral blood lymphocytes by using commercially available Quick- gDNA Mini Prep kit (Irvine, California, USA). The genotyping was performed using PCR-RFLP technique. IL-6 -174 G/C gene polymorphism was detected by PCR on the Thermon Cycler instrument (Bio-Rad Inc. Hercules, CA, USA) with subsequent restriction analysis of PCR products (RFLP). Briefly, a PCR fragment containing the base pair change was generated using the following forward and reverse primers: IL6 5'-GGAGTCACACACTCCACCT-3' and IL6 5'-GTGGGGCTGATTGGAAACC-3. The

PCR reactions were carried out in 15 ML aliquots containing approximately 50 ng genomic DNA, 0.5 PMOLE of each primer, 1X reaction buffer, 200 MM deoxynucleotide triphosphates, and one unit of Taq polymerase. The PCR products were digested with SfaN1 (New England Biolabs, USA). The digested fragments were visualized on 1.5% -2% agarose gel with ethidium bromide staining to identify the base pair change. The G > C change at position 174 created a restriction site for this enzyme and as a consequence G-allele produced an un-cleaved 532 bp product while the C-allele yielded two products of 474 and 58 bp respectively upon digestion of the PCR products with SfaN1.The identified genotypes have been named according to the presence or absence of the enzyme restriction sites i.e., (C/C), (G/C) and (G/G). The representative gel picture for IL6–174 (G/C) genotypes was shown in Figure 1

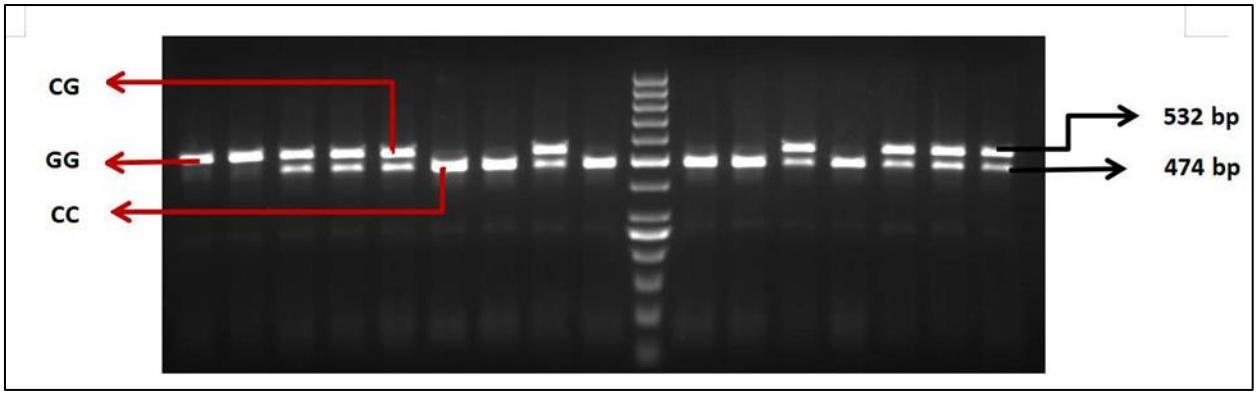

Figure 1 Representative gel picture for IL6–174 (G/C) Genotypes

2.4 IL-6 m-RNA expression

Total RNA was extracted from whole blood using TRI ZOL reagent (Invitrogen, Carlsbad, CA, USA). The purity of the extracted RNA was assessed by spectrophotometry, and samples with an OD260/280 ratio between 1.9 and 2.0 were used for further analysis. Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using a High-Capacity cDNA Archive Kit (Applied Biosystems, Foster City, CA, USA). Quantitative real-time polymerase chain reaction (QRT-PCR) was performed using a CFX96 Real-

Time PCR Detection System (Bio-Rad, USA) to measure IL-6 mRNA expression employing TaqMan probe chemistry. Primers and probes for the target gene (IL-6) and the internal control gene (β-actin) were designed by Sigma-Aldrich (India). The average threshold cycle (Ct) values were calculated for both the target gene and the housekeeping gene. β-actin was used for internal normalization. Gene expression levels were determined using the ΔCT method, where ΔCT was calculated as the Ct value of the target gene minus the Ct value of the housekeeping gene; lower ΔCT values indicated higher gene expression. Relative gene expression (fold change) was calculated using the 2^{-}ΔΔCt method.

2.5 Measurement of serum IL-6 levels

Serum IL-6 protein levels were measured by commercially available ELISA kit (Cayman Chemical, USA) according to the manufacturer's instructions, using a standard curve for quantification.

2.6 Statistical analysis

Statistical analysis was carried out using standard statistical methods (SPSS software version 20.0). Data were expressed as mean ± standard deviation. In case of high inter-individual variability and non-normal distribution data were expressed as median. Multiple linear regression analysis was done with IL-6 level as dependent variable. For all statistical tests, $p < 0.05$ was considered as the level of significance.

3 Results

3.1 Demographic data and Clinical characteristics of study subjects

There were 65 patients with CP in the study. The ages of these patients ranged from 8 to 144 months. The median age of the patients was 54 months. There were 44 male patients, which represents 67.7% of the total and 21 female patients, which represents 32.3% of the total. Additionally, there were 65 healthy control subjects and were matched in terms of age and gender to the children with CP. Considering socio- demographic characteristics of the family of children with CP, 93.8% of families had a monthly total income of less than Rs.20,000, 46.1% had the even less than Rs.10,000 monthly income.

Quadri paretic with Seizure (58.4%) was the most common CP type, followed by spastic hemiplegic (16.9%), spastic quadriplegic CP (12.3%), spastic diplegic (10.7%), and 1.5% Dystonic CP. Global developmental delay was seen in 64 (98.4%) CP cases. 45 (69.2%) cases showed developmental delay whereas 20 (30.7%) cases showed seizure as chief complain. The age of onset of seizure varied between at birth, days to months (0 days to 84 months). Generalized tonic clinic seizure was the most common type (10, 50%), followed by complex partial seizures (5, 25%) and Myocloni (5, 25%). Data showed that of 65 children referred with a diagnosis of CP, 47 (72.3%) children had microcephaly. One case

showed simple partial seizure with developmental delay as chief complain. Out of 65, 15 male and 5 female patients showed family history of seizure.

We observed 89.2% were full term deliveries, 78.4% of the children were born normal and 66.1% were born at the hospital. Few children had suffered from some kind of antenatal complications like exposure to drug radiation (1, 1.5%), fever with rash during pregnancy (3, 4.6%), toxemia of pregnancy (2, 3%) and Jaundice (1,1.5%). The children had mean birth weight 1.6 kg, 67.6% of children were advised NICU admission with neonatal seizure (26.1%), neonatal jaundice (15.3%) and neonatal sepsis (36.9%). Besides, other clinical features like poor feeding (67.6%), umbilical sepsis (3%), first 3-month scissoring (49.2%), tonic posturing (66.1%), diaper changing difficulty (49.2%), feeding difficulty (49.2%) and consanguineous (3.07%) were observed. Of the 65 cases, 37(56.9%) had squint on clinical examination. Hearing loss was present in 21 (32.3%) patients.

3.2 IL-6 Genotyping, m-RNA expression and association

No statistically significant association was observed between IL-6 genotype and CP patients when compared to a control group but the frequency of C allele was found higher in both cases and controls compared to G allele representing frequent mutation of G>C allele in the study population (Table 1). A statistically significant difference was detected in the frequency of homozygous CC genotype between CP patients with and without poor feeding condition where the G allele is restricted to children with normal feeding condition (p=0.05, chi square 6.4, using 5 by 2 exact test). Similarly, near to statistical significance can be observed in CP children admitted to Neonatal ICU (p=0.07, chi square 5.0). Rest of the parameters didn't show any significance with respect to genotypes (Table 2).

Table 1 Distribution of IL-6 genotypes in patients with Cerebral Palsy (CP) and the control group

Genotype/allele	Case (n=65) (%)	Control (n=65)
CC	45 (69%)	40 (62%)
CG	18 (28%)	23 (35%)
GG	2 (3%)	2 (3%)
C allele	83%	79%
G allele	17%	21%

Table 2 Distribution of IL-6 genotypes among CP patients with clinical presentations

Genotype/allele	GG	CG	CC	P value (chi square)
NICU admission				0.07 (5.05)
No	0	14	29	
Yes	2	4	16	
Poor feeding				0.04 (6.42)
No	0	15	29	
Yes	2	3	16	

We observed higher serum levels of IL-6 in patients with CP compared to the control group, but this difference was not statistically significant (138 PG/ml vs. 121 PG/ml). We observed relation between genotypes and serum level could not be established. The CC genotype of the 174C/G variation is related to higher levels of IL-6 compared to the GG genotype (Table 3). In this study, log linear regression model have been utilized to study the association of independent variables on IL-6 levels of the patients (Table 4). The findings suggest that age of child, IL-6 mRNA level, poor feeding and pre-term delivery significantly contributes to the variation in the IL-6 levels. The log linear regression model shows that one-year increase in age of children is associated with 2% decrease in IL-6 levels However, pre-term delivery is positively associated with IL6 levels among patients. This means that patients that were born preterm have 5% higher IL-6 levels as compared to those who were normally delivered. On the other hand, an interesting finding from the analysis is that the patients who were poorly fed were negatively associated with IL-6 levels. The finding shows that

patients who were poorly fed have 69% lower IL-6 levels as compared to patients who were normally fed. Negative correlation was observed between delta CT mRNA level and IL-6 protein level among the patients.

Table 3 Association of serum IL-6 levels with IL-6–174 (G/C) genotypes among CP cases and controls

IL6–174 (G/C) Genotype	Serum IL-6 (PG/ml) cases	Serum IL-6 (PG/ml) control
CC	166.07± 21. 9*	134.44 ±153.5
CG	119.64±12.9	108.11 ± 11.4
GG	118.35 ±2.6	105.32± 4.1

Data expressed in mean ± Stev. *p<0.05

Table 4 Multiple linear regression model with IL-6 level as dependent variable

	Estimate	Exponentiated coefficient	Std. Error	t-value	PR (>|t|)
(Intercept)	7.693599	2194.26	5.267505	1.461	0.15488
Age (months)	-0.01243	0.9876	0.006018	-2.066	0.04784*
Sex	-0.26139	0.7699	0.430192	-0.608	0.54817
IL6 mRNA level (DCT)	-0.5607	0.5708	0.187805	-2.986	0.0057**
Diagnosis	0.164276	1.1785	0.196838	0.835	0.41078
Age at which development delay detected (months)	0.010592	1.0106	0.017983	0.589	0.56044
Chief complaint	0.302854	1.3537	0.520208	0.582	0.56494
Seizure	-0.03692	0.9638	0.313331	-0.118	0.90701
Motor delay	1.25227	3.4983	1.615769	0.775	0.4446
Antenatal	0.107368	1.1133	0.203296	0.528	0.60143
Term/ preterm	1.642168	5.1664	0.584216	2.811	0.00876**
Delivery	-0.19082	0.8263	0.273447	-0.698	0.49083
Birth h/o	-0.09293	0.9113	0.262385	-0.354	0.72577
Delay cry	-0.46533	0.6279	0.530672	-0.877	0.38776
Resuscitation	0.071263	1.0739	0.566323	0.126	0.90073
Nicu admission	-0.26607	0.7664	0.536373	-0.496	0.6236
Poor feeding	-1.17094	0.3101	0.488589	-2.397	0.02322*
Umbilical sepsis	0.874285	2.3972	1.541517	0.567	0.57497
1st 3-month scissoring	0.131472	1.1405	0.570864	0.23	0.81947
Tonic posturing	0.665886	1.9462	0.545026	1.222	0.23164
Diaper changing diff`	-0.02191	0.9783	0.482499	-0.045	0.9641
Feeding diff`	-0.78844	0.4546	0.62529	-1.261	0.21739
Consanguineous	-0.56075	0.5708	1.365516	-0.411	0.68435
Abortion	-0.13832	0.8708	0.827772	-0.167	0.86845

-statistic: 1.475, 23 DF	p-value: 0.1601		
Multiple R-squared: 0.5391	Adjusted R-squared: 0.1736		
Residual standard error: 1.104 on 29 degrees of freedom			

Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

4 Discussion

Cerebral palsy is a lifelong disorder which has no effective cure till now. In the present study, the median age of the patients with CP was 54 months. The signs of a mild case of CP often go unnoticed until the child reaches 3 to 5 years of age. It is diagnosed between 12 and 24 months in high-income countries and later in low- and middle-income countries [13], for example, 5 years in Bangladesh [14]. Patients suffering from CP were mostly males (67%). The published data confirmed a higher incidence of CP in males than in females. CP, with males representing up to 70% of all affected children [15,16,17,18,19]. Several populations based and meta-analysis studies have reported an association between high prevalence of CP and low socioeconomic status [19] Many published reports have indicated an association between low family income and higher CP prevalence. A socio-economic gradient was observed in preterm birth, low birth weight and post-natal injury which might lead to CP. Epilepsy is commonly observed in children with spastic hemiplegia, followed by quadriplegia and diplegia [20]. The frequency of epilepsy was greater in the group of subjects suffering from spastic quadriplegia, and with higher motor dysfunction, as reported in the literature [21, 22]. In the study, we observed that the patients who were poorly fed have lower IL-6 levels as compared to patients who were normally fed. One possible explanation is that higher IL6 levels could have a protective role for poor eating disorder by affecting the internal biological mechanism related to appetitive traits. Infants discharged from the neonatal intensive care unit (NICU) are at increased risk for poor neurodevelopmental outcomes [8, 25-28]. They are at high-risk for developmental disabilities. According to a published report, term-born children with neonatal infection were more likely to have spastic triplegia or quadriplegia [29]. In the present study majority of children (67.6%) are showing poor feeding status and 49.2% show feeding difficulty. Cerebral palsy in children may lead to poor nutritional status due to difficulty in proper feeding and swallowing. Maximum cases showed tonic posturing (66%) with squint condition (60%) and hear impairment (34%). Cerebral palsy cases with ocular problems and hearing loss are already reported [30-33].

Plasma IL-6 levels were higher in CP patients than in the controls. Although significance couldn't be achieved but high level indicates its association with CP risk. The protein serum levels were higher in CC interleukin-6 genotype in comparison to GG+GC genotype but the association was found statistically insignificant may be due to sample size. Also, the findings also suggest that age of child, poor feeding and pre term delivery significantly contributes to the variation in the IL6 levels. The CC genotype of the 174C/G variation is related to higher protein levels of IL-6 compared to the GG genotype which is in accordance with the published literature [11, 12].

The patients who were born preterm have higher IL-6 mRNA level compared to those who were normally delivered. Concentrations of a number of cytokines like IL-1, IL-6, IL-8 were significantly related to neonatal ultrasound abnormalities including severe germinal matrix hemorrhage but did not distinguish those with later diagnoses of CP from control children [34].

The findings of this study have certain limitations. The sample size was relatively small, which may have limited the statistical power to detect modest genetic associations between the IL-6 −174 (G/C) polymorphism and cerebral palsy, particularly for less frequent genotypes. Although cases and controls were matched for age, sex, and ethnicity, detailed perinatal and socioeconomic data were not uniformly available for all control participants, which restricted comprehensive baseline comparisons. In addition, IL-6 mRNA expression was measured in whole blood samples and may therefore reflect combined expression across different circulating cell populations rather than cell-specific transcriptional activity. Finally, the cross-sectional nature of the study precludes causal inference regarding the observed associations between IL-6 genetic variation, gene expression, and clinical characteristics of cerebral palsy. Future studies with larger sample sizes, longitudinal follow-up, and detailed adjustment for environmental and perinatal risk factors are needed to confirm and extend these findings.

5 Conclusion

This study did not demonstrate a statistically significant association between the IL-6 −174 (G/C) polymorphism and CP. Although the C allele was more prevalent in both patients and controls, no meaningful difference in genotype distribution was observed between the groups. Serum IL-6 levels were higher in children with CP compared with controls; however, this difference did not reach statistical significance. The CC genotype was associated with

increased IL-6 synthesis, consistent with previously published literature. Regression analysis identified age, IL-6 mRNA expression, preterm birth, and feeding status as significant contributors to variability in IL-6 levels. Collectively, these findings suggest that inflammatory mechanisms may modulate disease expression in CP, underscoring the need for larger, well-powered studies that integrate genetic susceptibility with environmental and perinatal factors.

To the best of our knowledge, this is the first study to investigate the associations between CP and IL-6 gene polymorphism along with its expression at mRNA and protein level among Indian pediatric patients. However, it is limited by its relatively small sample size. In future to verify the association between IL-6 - 174 G/C gene polymorphism and the risk of cerebral palsy among children, large case-control studies are required.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Oskoui M, Coutinho F, Dykeman J, Jetté N, Pranshi T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55(6):509–519.

[2] McGuire DO, Tian LH, Yeargin-Allsopp M, Dowling NF, Christensen DL. Prevalence of cerebral palsy, intellectual disability, hearing loss, and blindness: National Health Interview Survey, 2009– 2016. Disable Health J. 2019;12(3):443–451.

[3] Chauhan A, Singh M, Jaiswal N, Agarwal A, Sahu JK, Singh M. Prevalence of cerebral palsy in Indian children: a systematic review and meta-analysis. Indian J Pediatr. 2019;86(12):1124–1130. doi:10.1007/s12098-019-03024-0.

[4] Maenner MJ, Blumberg SJ, Kogan MD, Christensen D, Yeargin-Allsopp M, Schieve LA. Prevalence of cerebral palsy and intellectual disability among children identified in two US National Surveys, 2011–2013. Ann Epidemiol. 2016;26(3):222–226.

[5] Christensen D, Van Naarden Braun K, Denberg NS, et al. Prevalence of cerebral palsy, co- occurring autism spectrum disorders, and motor functioning—Autism and Developmental Disabilities Monitoring Network, USA, 2008. Dev Med Child Neurol. 2014;56(1):59–65.

[6] Van Naarden Braun K, Denberg N, Schieve L, Christensen D, Goodman A, Yeargin-Allsopp M. Birth prevalence of cerebral palsy: a population-based study. Pediatrics. 2016;137(1): e20152872.

[7] Singhi PD, Ray M, Suri G. Clinical spectrum of cerebral palsy in North India—an analysis of 1000 cases. J Trop Pediatr. 2002;48(3):162–166.

[8] Ramanand VH, Shukla YU. Sociodemographic and clinical profile of pediatric patients with cerebral palsy in Gujarat, India. Bull Fac Phys Ther. 2022; 27:19.

[9] Khankhanian P, Branzini SE, Johnson BA, Madireddy L, Nickles D, Creon LA, Wu YW. Sequencing of the IL6 gene in a case-control study of cerebral palsy in children. BMC Med Genet. 2013; 14:126. doi:10.1186/1471-2350-14-126.

[10] Wu YW, Croen LA, Torres AR, Van De Water J, Grether JK, Hsu NN. Interleukin-6 genotype and risk for cerebral palsy in term and near-term infants. Ann Neurol. 2009;66(5):663–670. doi:10.1002/ana.21766.

[11] Bi D, Chen M, Zhang X, et al. Association between sex-related interleukin-6 gene polymorphisms and the risk for cerebral palsy. J Neuroinflammation. 2014; 11:100.

[12] Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007; 109:8–14.

[13] te Velde A, Morgan C, Novak I, Tantsis E, Badawi N. Early diagnosis and classification of cerebral palsy: an historical perspective and barriers to early diagnosis. J Clin Med. 2019;8(10):1599. doi:10.3390/jcm8101599.

[14] Khandaker G, Muhit M, Karim T, et al. Epidemiology of cerebral palsy in Bangladesh: a population- based surveillance study. Dev Med Child Neurol. 2019; 61:601–609. doi:10.1111/dmcn.14013.

[15] Himmelmann K, McManus V, Hagberg G, Uvebrant P, Krägeloh-Mann I, Cans C; SCPE Collaboration. Dyskinetic cerebral palsy in Europe: trends in prevalence and severity. Arch Dis Child. 2009; 94:921–926.

[16] Stanley F, Blair E, Alberman E. Cerebral palsies: epidemiology and causal pathways. London: Mac Keith Press; 2000.

[17] Jarvis S, Glinianaia SV, Arnaud C, et al. Case gender and severity in cerebral palsy varies with intrauterine growth. Arch Dis Child. 2005; 90:474–479.

[18] Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol. 2007; 49:74–78.

[19] Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005; 352:9–19.

[20] Hjern A, Thorngren-Jerneck K. Perinatal complications and socio-economic differences in cerebral palsy in Sweden: a national cohort study. BMC Pediatr. 2008; 8:49. doi:10.1186/1471-2431-8-49.

[21] Dolk H, Pattenden S, Bonellie S, et al. Socio-economic inequalities in cerebral palsy prevalence in the United Kingdom: a register-based study. Paediatr Perinat Epidemiol. 2010; 24:149–155. doi:10.1111/j.1365-3016.2009.01083. x.

[22] Boulenouar Mesraoua B, Ali M, Deleu D, et al. Epilepsy and cerebral palsy. In: Asadi-Pooya AA, editor. Epilepsy. IntechOpen; 2019. doi:10.5772/intechopen.82804.

[23] Zelnik N, Konopnicki M, Bennett-Back O, Castel-Deutsch T, Tirosh E. Risk factors for epilepsy in children with cerebral palsy. Eur J Paediatr Neurol. 2010; 14:67–72.

[24] Pavone P, Gulizia C, Le Pira A, et al. Cerebral palsy and epilepsy in children: clinical perspectives on a common comorbidity. Children (Basel). 2021;8(1):16. doi:10.3390/children8010016.

[25] Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol. 2008;21(2):123– 128.

[26] Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ. 2012;345: e7961.

[27] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261–269.

[28] Hintz SR, Poole WK, Wright LL, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed. 2005;90(2): F128–F133.

[29] Smilga AS, Garfinkle J, Ng P, et al. Neonatal infection in children with cerebral palsy: a registry- based cohort study. Pediatr Neurol. 2018; 80:77–83. doi: 10.1016/j.pediatrneurol.2017.11.006.

[30] Jan JE, Freeman RD, Scott EP. Visual impairment in children and adolescents. In: The multihandicapped visually impaired child. New York: Grune and Stratton; 1977. p. 75–81

[31] Katoch S, Devi A, Kulkarni P. Ocular defects in cerebral palsy. Indian J Ophthalmol. 2007;55(2):154–156. doi:10.4103/0301-4738.30717.

[32] Barba M, Paczka J, Moreno R, et al. Effect of comprehensive visual therapy on cognitive attentiveness of patients with cerebral palsy. Invest Ophthalmol Vis Sci. 2014;55(13):190.

[33] Weir FW, Hatch JL, McRackan TR, Wallace SA, Meyer TA. Hearing loss in pediatric patients with cerebral palsy. Otol Neurotol. 2018;39(1):59–64. doi:10.1097/MAO.0000000000001610.

[34] Nelson KB, Grether JK, Dambrosia JM, et al. Neonatal cytokines and cerebral palsy in very preterm infants. Pediatr Res. 2003; 53:600–607.