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The effect of apoprotein E gene polymorphism on neurocognitive functions of children with CHD

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Abstract

Studies have demonstrated an association between CHD and neurodevelopmental delay. This delay is associated with many factors like reduced blood flow and oxygen, cardiac catheterisations, and genetic factors. Apo E gene polymorphism is one of these genetic factors. This study aims to show the effect of Apo E gene polymorphism on neurodevelopmental process in children having CHD. A total of 188 children having CHD were admitted to the study. Apo E gene polymorphism of these patients was determined, and psychometric evaluation was performed. The relationship between psychometric test results and gene polymorphism was evaluated. This study shows that, similar to the literature, patients having cyanotic CHD have worse scores than acyanotic patients, and the children with CHD are under risk in terms of neuropsychiatric disorders. Other novel and important findings of this study were the lower verbal scores of ε2 allele carriers than ε4 carriers in Wechsler Intelligence Scale for Children-Revised group and the worse test score of patients having VSD than other acyanotic patients. Besides, some special disorders may be seen in this patient group.

CHDs are the most common congenital anomalies occurring in approximately 1%–3% of live births.[1] Mortality can be as high as 20%, especially for patients having complex defects.[2] Children who survive are at risk of neurodevelopmental delay and deficits in cognition, behaviour, and attention.[3] This delay is because of the neuronal damage associated with some factors, such as reduced blood flow and oxygen level during the foetal period, which may impede brain maturation.[4] Brain injury may also occur with cardiac operations and catheterisations in these children.[5] Besides, genetic factors including chromosomal abnormalities (like Down syndrome, trisomy 18, trisomy 13, Turner syndrome) or single-gene disorders that accompany CHDs may increase the risk of brain abnormalities in this population. Apoprotein E polymorphism is one of the single-gene disorders.[6]

Apoprotein is the protein content of plasma lipoprotein. It is synthesised in astrocytes in the central nervous system and is responsible for the distribution and conveyance of cholesterol and phospholipids.[7] This conveyance is essential in the reconstruction of neuron membranes. When the brain suffers injury, apoprotein E production increases. The encoded protein is involved in neuronal repair and plasticity.[8]

The apoprotein E gene consists of three alleles (ε2, ε3, ε4) with six gene combinations.[8] Carrying one of these isotypes (regardless of being homozygous or heterozygous) has different functional properties, and the isotype plays different roles according to age and underlying disease.[6] For instance, a report indicated that neuronal recovery was not as good in patients with apoprotein E 2 gene as those having apoprotein E 3 gene.[9] It has been proposed that the apoprotein E ϵ2 allele renders patients less resistant to neuroinjury that may occur in utero- or perioperatively in these patients. Similarly, the effects of APOE ϵ4 have been shown to be associated with poor outcomes after brain injury, Alzheimer disease and cognitive decline in adult studies.[10] Also in different paediatric studies, it was shown that the apoprotein E ϵ4 and ϵ2 genotypes might negatively affect brain development.[10,11] The negative effects of these genes in children with CHD are also shown in paediatric literature.[12,13]

This study aims to show the effect of apoprotein E gene polymorphism on the neurodevelopmental process of children with CHDs. Since the data on this subject are limited, this study will contribute to the paediatric literature on this subject and may lead to future studies.

Material and methods

Patient demographics

A total of 188 children with CHDs between 1 and 15 years of age were included in the study. The children who applied for outpatient follow-up visit to Gazi University Faculty of Medicine, Pediatric Cardiology department between January 2009 and December 2013, were included. There was no hospitalised or perioperative patient in the study. Patients with underlying neurologic disease, intellectual disability, genetic syndrome or a history of prematurity-less than 32 weeks of gestational age were excluded from the study.

The patients' parents were asked to take a questionnaire that evaluated their socio-demographic background following the physical examination. This questionnaire also included questions on the patient's age and gender, way of delivery, birth age, birth weight, whether there was complication in delivery or not, parents' education status, household income.

Blood sampling and Apo E gene polymorphism detection

Peripheral venous blood samples of patients were collected with ethylenediaminetetraacetic acid and stored at 20°C. The deoxyribonucleic acid isolation process was realised via the spin column method (MN Macherey-Nagel Germany). Isolated deoxyribonucleic acid samples were measured using a spectrophotometer (NanoDrop, ND 1000, USA). Isolated deoxyribonucleic acid has been cut through polymerase chain reaction and restriction enzymes (Restriction fragment length polymorphism) methods. Polymorphism of isolated deoxyribonucleic acids (one or more of ε2 or ε3 or ε4 allele) was examined, and apoprotein E gene polymorphisms were assessed.

Neurocognitive evaluation

Following the blood sampling and gene detection, a neurological examination was conducted. Developmental outcomes were assessed using the appropriate test according to age, by a professional paediatric psychologist. According to the availability of the psychologist, the tests were completed either immediately or by appointment at the appropriate time. Bayley Scales of Infant Development-II (the psychomotor development index and mental development index) includes problem-solving, early number concepts, generalisation, vocalisation. Stanford-Binet Intelligence Scale and Wechsler Intelligence Scale for Children tests were applied to the patients and assessed by the same experienced paediatric neurophysiologist according to age groups.

The Bayley Developmental Scale for babies is a personal test performed between the ages of 2 months and 3.5 years and is used to evaluate the development of young children and infants. It is essential in assessment of the development of premature and risky babies. There is a Motor Scale that evaluates gross and fine motor skills and a Behavior Assessment Scale that qualitatively evaluates the child's behaviours such as attention, social participation, and affect. Those who score 69 and below on the test have significant developmental delay, 70–84 moderate developmental delay, 85–114 normal, 115 and above good developmental performance.[14]

The Wechsler Intelligence Scale for Children-Revised, which was used to determine the intelligence levels of the children in the study, was developed by Wechsler in 1949, and a revised form (Wechsler Intelligence Scale for Children-Revised) was created in 1974. Wechsler Intelligence Scale for Children-Revised consists of two parts: verbal and performance. Those who score 69 and below are considered mild intellectual disability, those between 70–79 are considered borderline intellectual disability, those between 80–89 are dull normal, those between 90–99 are normal, and those with a score above 100 are considered bright normal.[15]

The Stanford-Binet Individual Intelligence Scale was revised again in 1960, after 23 years of implementation. In the new revision completed in 1986, the scale was changed considerably with structural and psychometric processes. These tests make it possible to measure intelligence from age two to adulthood. However, this test is mainly used to measure child intelligence.[16]

Statistical analyses and ethical approval

Data analysis was performed with the SPSS Program, Version 20 (SPSS Inc., Chicago, IL, USA). Continuous variables that follow a normal distribution were expressed as mean and standard deviation and compared using the 2-sample Student's t-test. Continuous variables that do not follow a normal distribution are reported by medians and interquartile range and compared using Mann–Whitney U-test, Wilcoxon, and Kruskal–Wallis tests. Conover test was used for paired comparisons. A P value of 0.05 was considered significant. Categorical variables were reported by their relative frequencies and compared by the $\chi 2$ test or Fisher's exact test.

In defining the difference between groups, non-parametric tests were used. The significance level was considered as $p < 0.05$.

The Research Ethics Committee of the Gazi University Faculty of Medicine approved the study. Informed consent was taken from the legal guardians of the children.

Results

Socio-demographic features

Age, gender, and education level of patients

One hundred eighty-eight patients with CHD applied for the examination. 87 (46,3%) of them were female. Female patients had significantly higher Bayley Scales of Infant Development and total Wechsler Intelligence Scale for Children-Revised than males ($p = 0.020$, $p = 0.018$).

The median age of the study group was 3 (interquartile range:2–5) years. 17% of children were at school age (6–18 years), and 83% were not (0–6 years). 12.5% of the children who were at school age attended preschool education (6–7 years), 84.3% attended primary school (7–12 years), and 3.1% attended high school (12–18 years). The level of education did not significantly affect psychometric test results ($p = 0.23$).

Natal and prenatal history

When we classify patients according to gestational age, 13.3% were 32–37 weeks gestation age, 86.7% of them were 37–42 weeks. Based on birth weight, 80% of the patients were average for gestational age, 17% were small for gestational age, and 2.1% were large for gestational age. Pregnancy period, delivery type, or gestational age of patients did not significantly affect psychometric test results ($p = 0.35$, $p = 0.11$, $p = 0.23$, respectively).

Family income and education level of parents

30.3% of patients had primary school graduate mothers, 22.3% had secondary school graduates, 28.7% had high school graduates, and 18.6% had university graduates. The education level of patients' mothers significantly affected the Stanford-Binet Intelligence Scale results ($p = 0.02$). Conover test showed that patients whose mothers graduated from university compared to those who

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graduated from high school and whose mothers graduated from high school compared to those who graduated from primary school were more successful in psychometric tests ($p = 0.036$). No significant effect was found on test results in terms of the education level of fathers ($p = 0.12$).

A similar positive correlation was found between the household's income level and the patient's test results. The test scores were higher as the household income level increased ($p = 0.009$).

Apoprotein E genotypes

78.7% of patients had apoprotein E ε3ε3 genotype, 12.2% had apoprotein E ε3ε4 genotype, 6.4% had apoprotein E ε2ε3 genotype, 1.1% had apoprotein E ε2ε4, and 1.6% had APO ε2ε2 genotype. 9% of the patients were carrying ε2 allele, and 13.3% of the patients were carrying ε4 allele.

When psychometric test results were assessed according to genotype groups, no significant difference was found with Bayley Scales of Infant Development-II and Stanford-Binet Intelligence Scale results. However, in Wechsler Intelligence Scale for Children-Revised group, verbal scores of ε2 allele carriers were significantly lower than ε4 carrier group ($p = 0.01$). In the remaining test results, carrying ε2 or ε4 allele had no significant effect ($p = 0.65$).

CHD

89.9% of the patients had acyanotic, whereas 10.1% had cyanotic CHDs. The leading CHDs were secundum atrial septal defect in 45.7%, ventricular septal defect in 11.2%, patent ductus arteriosus in 6.4%, coarctation of the aorta in 3.2%, tetralogy of Fallot in 4.3%, atrioventricular septal defect in 1.6%, and more than one defect in 27.6% of the patients. Wechsler Intelligence Scale for Children-Revised, full-scale IQ results of patients with ventricular septal defect among acyanotic patients have been found significantly lower than patients with other acyanotic CHDs ($p = 0.002$).

12.2% of the patients had a history of heart operation, whereas 87.8% of them did not. The status of being operated did not significantly affect test results in the study group ($p = 0.54$).

Psychometric test results of patients were specified in Table 1 according to oxygenation status. Accordingly, Bayley Scales of Infant Development motor and mental scores of children with cyanotic CHD were significantly lower than children with acyanotic CHDs ($p = 0.004$) (Table 1).

Specific disorders

There were no specific neurologic deficits or disorders in 78.1% of the patients, whereas 21.9% had one or more specific disorders. 8.6% of the patients had speech disorders (articulation problems, speech delay, stuttering), 2.1% had motor deficiencies (fine motor skills, gross motor deficit), 6.4% had a learning disability, 2.1% had primary enuresis, and 2.7% had attention deficiency and hyperactivity disorder.

92.7% of the patients with specific motor or behavioural disorders were acyanotic, and 82.9% of them had apoprotein E ε2ε3 genotype. These disorders did not differ between cyanotic or acyanotic patients or between apoprotein E groups ($p = 0.14$).

Discussion

To the best of our knowledge, this is one of the most significant paediatric data investigating neurocognitive functions of patients with CHDs and the effect of apoprotein E gene polymorphism on the test results. This study is superior because all types of psychometric tests were performed according to age.

This study firstly aimed to assess neurocognitive functions and neuropsychiatric comorbidities of patients with cyanotic and acyanotic CHDs and secondly searched for their relation with apoprotein E isoforms.

The socio-demographic features of the patients may have an influence on neurocognitive functions in patients with CHDs apart from the type of CHD. According to a report by Forbes et al., which researched neurodevelopmental situations of children with CHDs, the patients whose parents' socioeconomic level and IQs are higher had better test results.[17] Wernovsky et al. also showed that the high socioeconomic level of parents correlated with positive results in neurodevelopmental surveillance of children post-operation of Fontan surgery.[18] Similarly, the test results of the children of families with high income were found to be higher than those of low-income families in our study. Besides, as the mother's education level increased, the Stanford-Binet Intelligence scale results of her child increased. These results may support that higher socioeconomic and education level of parents increase the stimuli affecting the neurologic development of children positively in their social environment.

As mentioned before, the apoprotein E gene plays an essential role in the recovery of post-neuronal damage. This role gains more importance in diseases in which neurons are affected negatively, such as CHDs.[19,20] Marino et al. stated that the apoprotein E gene is considered responsible for the genetic predisposition of neurodevelopment.[19] Gaynor et al. found that carrying the apoprotein E ε2 allele was related to unsuccessful results in their psychometric evaluation of 247 infants operated for CHDs. This research also showed that carrying apoprotein E ε4 allele did not affect test results.[20] In another study on patients who had cardiac surgery, it was found that the possibility of incidence of behavioural disorders among patients with apoprotein E ε2 is more than those with apoprotein E ε3 and apoprotein E ε4.[20] This means that apoprotein E ε2 allele might have adverse effects on neurological development in patients with CHDs. In our study, 9% of the patients were found to have apoprotein E ε2, 97.4% to have apoprotein E ε3, and 13.3% to have ε4 allele.

According to our study, only in Wechsler Intelligence Scale for Children-Revised group, verbal scores of ε2 allele carriers were significantly lower than ε4 carrier group. The apoprotein E ε2 allele is already known to have more adverse affects than ε4, and the effect on specifically verbal scores is a new finding for the current literature. Future studies are warranted to support this finding.

Long-term observation of infants with CHDs includes the procurement of diagnosis, treatment of brain damage that occurs during follow-up, and neurodevelopmental disabilities that may arise correspondingly.[21] Even though several studies claim that this disability depends on the perioperative care conditions and surgical process, preoperative brain damage and neurodevelopmental disability are also reported.[22,23] Furthermore, according to the current literature, it is well known that cyanotic patients have more neurodevelopmental problems than acyanotic patients. Similarly, in our study, cyanotic patients – independent from the history of operation, had worse Bayley motor scores of psychometric test results than acyanotic patients.

In addition to these, due to our findings, children with ventricular septal defect had lower Wechsler Intelligence Scale for Children-Revised total intelligence scores than those who did not have ventricular septal defect ($p < 0.05$). This is also a very new finding that asks if the patients who have ventricular septal

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Table 1. Psychometric test results of children with congenital heart diseases.

	Psychometric test results					
	Gender					
	Male	Female				p
n (%)	101 (53.7%)	87 (46.3%)				
BSID-II- mental	92.50 (50–120)	97 (83–112)				0.02
BSID-II- motor	91 (50–127)	99 (85–117)				0.004
SBIS	101 (63–119)	97 (80–114)				0.23
WISC-R- verbal	95 (67–117)	98 (90–107)				0.38
WISC-R- performance	95 (69–117)	101 (93–113)				0.22
WISC-R- total	94 (66–118)	100 (91–110)				0.018
	Mother level of education					
	Primary school	Secondary school	High school	University		
n (%)	57 (30.3%)	42 (22.3%)	54 (28.7%)	35 (18.6%)		
BSID-II- mental	92(50–115)	93 (73–120)	95 (87–120)	92 (82–114)		0.17
BSID-II- motor	90 (50–119)	90 (69–127)	96 (85–127)	94 (80–119)		0.15
SBIS	95 (63–114)	97 (77–119)	101 (84–113)	103 (77–119)		0.02
WISC-R- verbal	92 (67–107)	91 (69–97)	98 (69–117)	98 (97–107)		0.39
WISC-R- performance	94 (72–113)	95 (69–104)	99 (78–117)	105 (100–108)		0.45
WISC-R- total	92 (69–110)	92.5 (66–99)	98 (71–118)	100.5 (99–102)		0.18
	APOE gene polymorphism					
	APOE ε3ε3	APOE ε3ε4	APOE ε2ε3	APOE ε2ε4	APOE ε2ε2	
n (%)	148 (78.7%)	23 (12.2%)	12 (6.4%)	2 (1.1%)	3 (1.6%)	
BSID-II- mental	92.6 (50–120)	95.11 (83–112)	105 (100–110)	–	96 (96–96)	0.39
BSID-II- motor	92.81 (50–127)	96.67 (85–117)	107.50 (103–112)	–	94 (94–94)	0.45
SBIS	99.36 (63–119)	96.31 (80–114)	96.33 (90–99)	105.5 (105–109)	69 (69–69)	0.18
WISC-R- verbal	92.59 (67–117)	102 (98–106)	98.33 (90–107)	–	85 (85–85)	0.01
WISC-R- performance	95.45 (69–117)	107 (101–113)	101 (93–110)	–	88 (88–88)	0.16
WISC-R- total	92.86 (66–118)	105 (100–110)	99.67 (91–109)	–	85 (85–85)	0.14
	Congenital heart disease					
	Cyanotic	Acyanotic				
n (%)	19 (10.1%)	169 (89.9%)				
BSID-II- mental	90.17 (50–102)	93.94 (50–120)				0.32
BSID-II- motor	85.50 (50–127)	95.04 (50–127)				0.004
SBIS	101.20 (63–119)	98.44 (69–119)				0.15
WISC-R- verbal	89.83 (67–117)	94.14 (69–107)				0.17
WISC-R- performance	91.17 (69–116)	97.45 (72–113)				0.23
WISC-R- total	89.33 (66–118)	94.93 (69–110)				0.28

defects are the most cognitively unlucky group among acyanotic CHDs. Future studies are warranted to support this finding.

In a study conducted by Hovels Gurich et al., 60 cyanotic patients with operated transposition of great arteries in school age were evaluated, and it was shown that those patients had fine and gross motor functional disorder at the rate of >20%, decrease in perception and expression of language at the rate of about 20%, and speech disorder at the rate of 40%.[24–26] Wright and Nolan reported that the children with transposition of great arteries and tetralogy of Fallot had a higher rate of motor coordination disorder and visual-spatial difficulties than acyanotic children.[27] In our study, various neuropsychiatric and neurodevelopmental problems were observed in 21.9% of the children with CHDs in furtherance of literature. Speech disorder was found to be the most important disorder (8.6% among all). These findings are compatible with general literature and show that children with CHDs may be at risk of neurodevelopmental disorders. There are limited data about attention deficiency and hyperactivity disorder and CHDs. In their study about preschool-aged children with CHDs requiring surgery, Gaynor et al. showed that parental rating scales showed an

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increased prevalence of restricted behaviour patterns, inattention with a range of 22%–30%. In our study, attention deficiency was observed in 2.7% of the study group. There is a need for future studies to shed light on whether children with CHD are at risk of attention deficiency. This study is significant in terms of monitoring these problems closely and supporting them with the early diagnosis, improving the patients' quality of life.

The major limitations of our study are that a large and homogeneous patient group was not provided; the same sample size in each subgroup could not be obtained in terms of both CHDs and gene polymorphism, which would have enabled a more reliable analysis and evaluation. So this situation makes the generalisability of these measures harder. Prospective, future studies performed with homogenously distributed patient groups are warranted to generalise these results.

Conclusion

In conclusion, supporting the literature, it is observed that children with CHDs (especially cyanotic patients) are at risk of neuromotor developmental delay. Thus, these patients' neurological observations should be conducted to properly support according to their needs. The two new and interesting findings are lower verbal scores of ε2 allele carriers than ε4 carriers in Wechsler Intelligence Scale for Children-Revised group and the worse test score of patients having VSD than other acyanotic patients. This study is considered to be the preliminary step of larger-scale prospective future studies with larger numbers of patients and more homogeneous groups to support and prove these novel findings.

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Conflicts of interest. None

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