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Investigation of neuraminidase 1 gene association in Henoch-Schönlein Purpura (HSP) with renal involvement

Henoch Schönlein purpura vaskülitinde nöraminidaz-1 geni ile böbrek tutulumunun ilişkisi

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Abstract

Purpose: HSP is a common small vessel vasculitis. It is the most common cause of non-thrombocytopenic purpura in childhood. The role of genes in etiopathogenesis of the disease, which has not yet been clearly elucidated, is being emphasized. Many genes called sialidases are being studied and is thought that the NEU1 gene may be particularly important in the etiopathogenesis of HSP. The aim of this study is to investigate the role of the NEU1 gene in the etiopathogenesis of HSP and its relation to renal involvement.

Materials and methods: Fifty patients followed in the Celal Bayar University Hafsa Sultan Hospital Pediatric Nephrology Department, with the diagnosis of HSP renal involvement were included into the study. For the control group, age and gender matched 50 cases were accepted among the outpatients admitted to Pediatric Department without any chronic diseases. NEU1 gene mutation analysis was performed in blood samples of both patient and control groups by using the Sanger DNA sequencing method.

Results: NEU1 genetic mutation was not detected in any HSP patient with renal involvement and control group.

Conclusion: In our study, the NEU 1 gene was not found to be associated with HSP nephritis. No changes were detected in the investigated regions of the NEU1 gene.

Key words: HSP vasculitis, Nephritis, NEU1 gen, Immunoglobulin A1 (IgA1), nonthrombocytopenic purpura.

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Öz

Amaç: Henoch-Schönlein Purpura (HSP) yaygın bir küçük damar vaskülitidir. Çocukluk çağında trombositopenik olmayan purpuraların en sık nedenidir. Hastalığın etyopatogenezi henüz net olarak aydınlatılmamış olmakla beraber genlerin rolü üzerinde durulmaktadır. Sialidazlar adı verilen birçok gen üzerinde çalışılmakta ve nöraminidaz 1 (NEU1) geninin HSP etyopatogenezinde özellikle önemli olabileceği düşünülmektedir. Bu çalışmanın amacı, NEU1 geninin HSP etyopatogenezindeki rolünü ve böbrek tutulumu ile ilişkisini araştırmaktır.

Gereç ve yöntem: Celal Bayar Üniversitesi Hafsa Sultan Hastanesi Çocuk Nefroloji Kliniği'nde HSP böbrek tutulumu tanısı ile takip edilen 50 hasta çalışmaya dahil edildi. Kontrol grubu olarak, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı polikliniğine herhangi bir kronik hastalığı olmayan hasta grubu ile yaş ve cinsiyet uyumlu 50 olgu kabul edildi. Hasta ve kontrol gruplarının kan örneklerinde NEU1 gen mutasyon analizi yapıldı.

Bulgular: Böbrek tutulumu olan HSP hastalarında ve kontrol grubunda NEU1 genetik mutasyonu saptanmadı.

Sonuç: Çalışmamızda NEU1 geninin HSP nefriti ile ilişkisi bulunmamıştır. NEU1 geninin araştırılan bölgelerinde herhangi bir değişiklik tespit edilmemiştir. Daha geniş hasta sayısıyla çalışılmasına ihtiyaç vardır.

Anahtar kelimeler: HSP vasküliti, Nefrit, NEU1 geni, Immunglobulin A1 (IgA1), trombositopenik olmayan purpura.

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Introduction

HSP is a common small vessel vasculitis. It is the most common cause of non-thrombocytopenic purpura in childhood [1]. The incidence is 14-18/100.000 children per year. It is often characterized by palpable purpura accompanied by abdominal pain and arthritis. About 50% of HSP patients have kidney involvement varies from asymptomatic microscopic haematuria to severe progressive glomerulonephritis [1, 2]. The role of genes in etiopathogenesis of the disease, which has not yet been clearly elucidated, is being emphasized. Many genes called sialidases are being studied and is thought that the *NEU1* gene may be particularly important in the etiopathogenesis of HSP. Neuraminidase 1 (lysosomal sialidase) is the enzyme responsible for the catalysis of the hydrolysis of terminal sialic acid residues of sialylated glycoconjugates. Loss of this enzyme causes intracellular progressive accumulation of sialylated glycopeptides and oligosaccharides [3-10].

The prognostic factor in HSP is renal involvement. It is thought that the accumulation of IgA in the vascular wall plays a role in the pathogenesis of HSP renal involvement [3-10]. It is known that the cellular lysosomal sialidase *NEU1* gene is responsible for the sialiation of the IgA molecule and that the defect in the sialiation steps causes IgA accumulation in the vessel wall. Therefore, the role of the *NEU1* gene in HSP disease can be elucidated by investigating the nucleotide substitution of NEU1 gene by the Sanger DNA sequencing method in patients with HSP. Identification of the role of the *NEU1* gene in the etiopathogenesis of HSP and its renal involvement, may light on new approaches, especially in the aspect of early diagnosis and treatment. The aim of this study is to investigate the role of the *NEU1* gene in the etiopathogenesis of HSP and its relation to renal involvement.

Materials and methods

Among the 80 patients followed in the Celal Bayar University Hafsa Sultan Hospital Paediatric Nephrology Department with the diagnosis of HSP, 50 of them which had renal involvement were included into the study. That was carried out in January 2017 and June 2017. For the control group, age and gender matched 50 cases were accepted among the outpatients admitted to Paediatric Department without any chronic diseases. *NEU1* gene mutation analysis was performed by the Sanger DNA sequencing method in blood samples of both patient and control groups. The study was approved by the local ethics committee.

Demographic data of patients were evaluated retrospectively. Age, gender, age at diagnosis, clinical findings, family history, recent family history of connective tissue disorders, presence of hypertension, other organ involvements were recorded.

Genetic studies

The genomic DNA was obtained from 200 µL sample of 1 mL peripheral blood in EDTA anticoagulated tube. DNA was extracted by using an automatic DNA isolation method with magnetic beads (Invitrogen Co. Paisley UK). PCR amplification was performed with primers designed to exons 1-6 of NEU1 gene and the primers used were listed in Table 1 [11].

PCR amplification was performed in the gradient program on Invitrogen Co. MyGene Gradient Thermal Cycler. The PCR products were purified by enzymatic methods using Exo SAP. Big Dye chemistry sequencing was done after purification of the PCR samples. Purified samples were placed on the ABI 3130XL Genetic Analyzer automatic DNA sequencing device and the nucleotide sequences were read according to the peaks. Nucleotide changes after DNA sequencing were compared with the gene bank (NM_000434.4) and protein database (NP_000425.1) reference sequences in the web pages of the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/).

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 software. The normal distribution of variables was examined visually (histogram and probability graphics) and by analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). Descriptive statistical methods were used to present demographic and clinical data. Mean, median, standard deviation, and interquartile range (IQR) was calculated for numeric variables. 2x2 tables were compared with Pearson Chi Square and Fisher's Exact Tests. *P*-values below 0.05 were considered statistically significant.

Table 1. PCR oligoprimers for 6 exons of genomic sequence of the *NEU1 gene* (Ncbi Refseq.gene NG_008201.1)

EXON1F-5'-GCTTAAGGGTGACATCTGCGCTTT-3'
EXON1R-5'-TGGGAGAAAGAAAAGGGTCCTGTC-3'
EXON2F-5'-AACTCCCCTTCGTGTTCCTCTTTC-3'
EXON2R-5'-CAACCAACCCTCTAAGTTCCCCTATC-3'
EXON3F-5'-CTAGCAGAAGGTGGGAAATTAACGG-3'
EXON3R-5'-GAAAGGAGTCCATTTTGGGGGTATC-3'
EXON4F-5'-ATTTGGGAAGTGGTGGGTTCTCTG-3'
EXON4R-5'-AGTGGTAGTTGTTCTGGTTTCGGG-3'
EXON5F-5'-AGATGTTCCCTACCCATTTGACCC-3'
EXON5R-5'-CATGAGGTACCATTGCTGAAGCTC-3'
EXON6F-5'-CATTGTCTTCTTCTTCTCCAACCCAGC-3'
EXON6R-5'-GATTTCCCTGGTAAAGGGAAGGTG-3'

Results

Of the 50 children with HSP renal involvement, 24 male and 26 female patients were included to the study. The mean age of patients was 10.21±3.95. Among the control group, 30 were male and 20 were female. The control group's mean age was 11.24±4.16. The demographic characteristics of children in our study are listed in Table 2. There was no significant difference between the HSP patients and the control group in terms of age and gender (p=0.232 and p=0.201, respectively).

Table 2. Distribution of groups according to gender and age

	Patients (n=50)	Control (n=50)	*p* value
Gender (M/F)	24/26	30/20	0.232
Age (mean ± SD)	10.21(±3.95)	11.24(±4.16)	0.201

SD, standard deviation; M, Male; F, Famale

The seasonal distribution of disease in our study is listed as the most common in fall, the second frequent in winter, then summer and spring. 11 (22%) patients were found to have upper respiratory tract infection (URTI). Three (6%) of the patients have familial Mediterranean fever (FMF) in their first-degree relatives. Drug intake history before diagnosis was found 5 (10%) patients. Two of these five patients had antibiotics and three of them had nonsteroidal anti-inflammatory drugs before HSP symptoms (Table 3). 21 (42%) of the patients admitted to our hospital with abdominal pain, 47 (94%) with purpuric rash, 2 (%4) with edema, 16 (32%) with arthralgia and arthritis. In total there were 20 (40%) cases with gastrointestinal involvement and 16 (32%) cases with joint involvement. Hypertension was conducted in 17 (34%) patients.

Three (6%) patients and 33 (66%) patients were admitted with macroscopic and microscopic haematuria and presented with microscopic haematuria, respectively. There were only two patients (4%) represented as nephrotic syndrome clinic while 33 (66%) had proteinuria. 8 of the patients with nephrotic proteinuria and haematuria had renal biopsy proven Ig A nephritis. 5 of the 20 patients presented with FMF-like symptoms had positive FMF genetics.

After the genetic analysis, *NEU1* genetic mutation was not detected in any of our HSP patient with renal involvement and control group. Direct nucleotide sequencing of the PCR-amplified *NEU1* gene DNA of the control and the patient have been shown in Figures 1, 2.

Table 3. Patients' demographic data

	Patients (n=50)	%
Season at Diagnosis:		
Spring	10	20
Summer	11	22
Fall	15	30
Winter	14	28
Findings:		
URTI	11	22
Family history of connective tissue disease	3	6
History of medications	5	10
Abdominal pain	21	42
Purpuric rash	47	94
Edema	2	4
Arthralgia/Arthralgia	16	32
Hypertension	17	34
GIS involvement	20	40
Joint involvement	16	32
Hematuria	36	72
Proteinuria	33	66
FMF Mutation	5	10

URTI: Upper respiratory tract infection, GIS: gastrointestinal system, FMF: familial Mediterranean fever

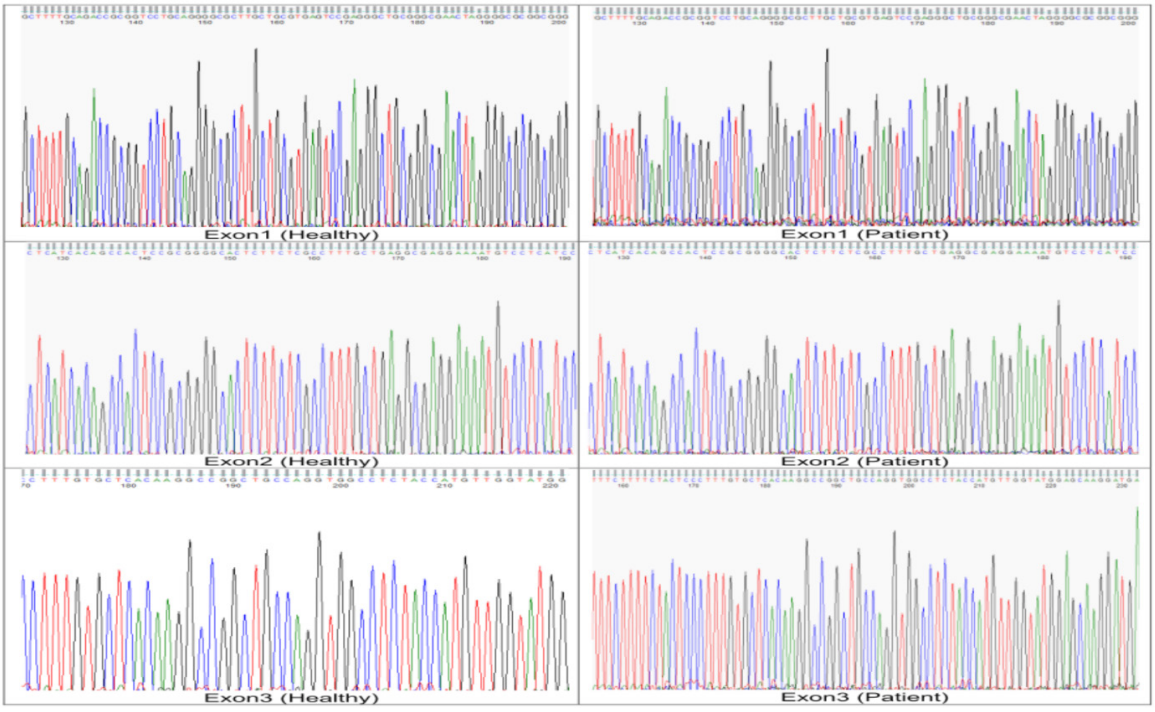

Figure 1. Sanger Sequencing Results of NEU1 gene all 1-3 exons in healthy (left) and HSP patients (right)

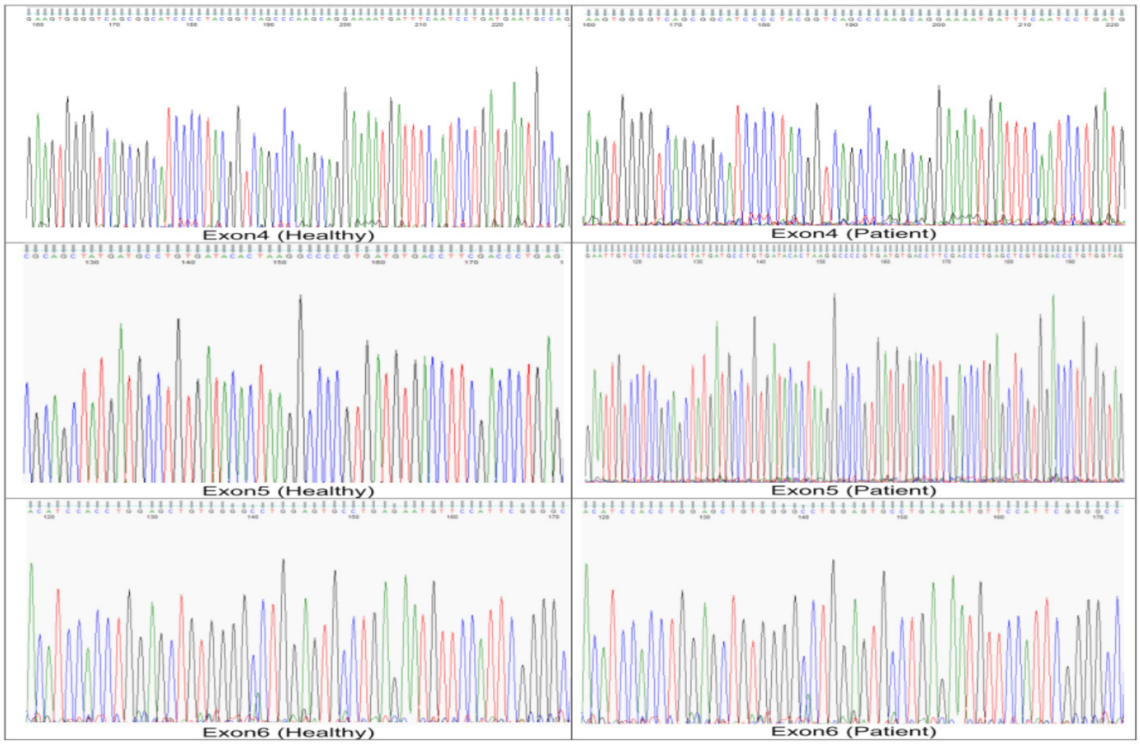

Figure 2. Sanger Sequencing Results of NEU1 gene all 4-6 exons in healthy (left) and HSP patients (right)

Discussion

HSP is the most common vasculitis in children, usually presents with the symptoms of purpuric rash, arthralgia, abdominal pain, and renal involvement.

Gender in HSP has not been identified as a risk factor in many studies made in different parts of the world and mentioned in the literature. The rates determined in our study are similar to the literature [12-15].

In HSP studies, the disease was seen most often in the spring, but least frequent in summer [12, 15]. The seasonal distribution of disease in our study is listed as the most common in fall, the second frequent in winter, then summer and spring. Differences in outcomes with respect to literature are attributed to regional and climatic differences. The more frequent occurrence of the disease in the spring and winter may be related to the presence of more URTI in these months and because it is shown that infections in the aetiology of HSP are triggering factors.

Studies done regarding HSP in Turkey show that URTI plays role as triggering factors of up to 70% [16], Chen et al. [12] found 47.4% URTI in history of the patients. In this study, 78% of the patients were found to have no URTI, this finding can be explained with infection story limitation time up to 15 days and that the region we were is in the temperate climate zone.

In a study with 131 patients, FMF was detected in only one affected sibling [17]. HSP nephritis was detected in just one brother of patients in a serial of 88 HSP patients diagnosed with nephritis [18, 19]. However, there is also one study in which three brothers affected in the same family are presented [19]. In these publications, the family story is negative in terms of other connective tissue diseases.

One of the factors known to be involved in the pathogenesis of the disease is the drug intake ratio. It was found as 10% in our patients before diagnosis and was lower than the literature [12, 15, 16]. No other etiologic factor was detected when evaluating other patients with no history of infection or drug intake.

Renal involvement tends to be more frequent and carries a worse prognosis. We included cases with renal involvement into our study. Among the whole our cases renal involvement ratio was 62.5%. Calvo Rio et al. [15] found 41.2% of patients, Chen et al. [12] found 54.2% of patients, Tabel et al. [13] found

21.6% of patients Donmez et al. [16] found 32.8% of patients, and De Almeida et al. [20] found that there was kidney involvement in 49% of patients. The rate of kidney involvement in our study is at the upper limit according to the literature. This may be related to the fact that our hospital is a district hospital with tertiary health care institution and that the patient group is selected from patients who are being followed in the paediatric nephrology clinic.

HSP nephritis is a polygenic and multifactorial disorder [21]. Since HSP nephritis is the result of glycosylation disorder that occurs in the IgA1 molecule, changes in genes that control glycosylation of this molecule may affect susceptibility to these diseases [22, 23]. Previous studies have identified several candidate genes that may cause HSP nephritis susceptibility. Within these genes, HLA gene family, T-cell receptors, genes involved in the renin-angiotensin system, and several inflammatory factor genes have been identified as candidate genes that may cause immunglobulin A nephropathy (IgAN) susceptibility [24, 25]. In a study by López Mejías et al. [26], no association was found between *PTPN22* and *CSK* genes with HSP. Yu et al. [27] have shown that chemokines play an important role in the pathogenesis of HSP. *MCP1 / CCL2* gene polymorphism may be associated with HSP. It is observed that *RANTES / CCL5* gene polymorphism may be related to the severity of HSP disease and renal involvement [27]. In a study by Xu et al. [28], no association was found between *IFN gamma* gene polymorphism +874 (A / T) and HSP [28]. Wang et al. [29] found that the TNF-α-308GA genotype could be associated with increased renal involvement in children with HSP. Zeng et al. [25] have shown that *VEGF-634G/C* gene polymorphism may be associated with HSP renal involvement [28]. In a study conducted by Nalbantoglu et al. [30], *ACE I / D* polymorphism was found to be significantly associated with HSP in Turkey.

Evidence suggests that abnormal glycosylation of the IgA1 molecule hinge region plays an important role in the pathogenesis of HSP nephritis [21]. Many studies have shown that lysosomal sialidase plays a role in sialic acid destruction [18, 19, 22, 23, 31]. It is known that a wide variety of mutations in the sialidase-gene *NEU1* is caused by sialidosis, an autosomal recessive disease group [22].

Studies conducted by Li et al. [32, 33] in 2007 showed that polymorphisms in the *ST6GALNAC2* and *NEU1* genes, which play a role in IgA1 sialiation, may cause IgAN susceptibility and SNP detection was performed in the nucleotide sequences of *ST6GALNAC2* and *NEU1* genes. It has been shown that the etiopathogenesis of HSP and IgAN diseases is similar, and that the susceptibility to both diseases may be caused by O-glycosylation disorder of the IgA1 molecules in organism [34]. In some studies, investigating the relationship between glycosylation impairment in the IgA1 molecule and susceptibility to IgAN disease, it has been shown that a reduction in the rate of sialiation in IgA1 affects this susceptibility. IgA1 levels in serum of IgAN patients was found to have less sialyl coating in O-glycans than control subjects [35].

Recent studies have shown that sialidases are expressed at different levels in healthy tissues and are rearranged in tumors and focused on the relationship between sialidases and cancers. Although the function of the sialidases on the immune system is not fully understood yet, it is about new investigations of the sialiation reactions in autoimmune diseases, cancer cells, virus-infected cells and healthy cells and its clinical results [36-41].

In our study, the *NEU1* gene was not found to be associated with HSP nephritis. No changes were detected in the investigated regions of the *NEU1* gene.

The limitations of the study can be listed as; the relatively small number of diagnosed patients with the incidence of HSP renal involvement as well as low histopathological evidences. The higher number of related cases may help to drive more conclusive results.

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of the authors to the article

The authors N.B.Y., P.E., S.Y., G.D.H contributed equally to researching data for the article, discussion of its content, writing and reviewing and/or editing of the manuscript before submission. The author N.N. examined the specimens. The author A.H.B. performed the genetic analysis.