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NÖROKÜTANÖZ SENDROMLAR: KLİNİK VE NÖRORADYOLOJİK BULGULARIN DEĞERLENDİRİLMESİ

NEUROCUTANEOUS SYNDROMES: EVALUATION OF CLINICAL AND NEURORADIOLOGICAL FINDINGS

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ÖZ

AMAÇ: Nörofibromatoz tip I (NF1), Tuberoskleroz kompleksi (TSC) ve Sturge-Weber sendromu (SWS) en sık görülen nörokütanöz sendromlar arasında yer almaktadır. Bu çalışma ile NF1, TSC ve SWS tanısı alan hastaların klinik ve nöroradyolojik bulgularını değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Kliniğimizde Aralık 2017 ile Mayıs 2019 arasında NF1, TSC ve SWS tanılı 15 hastanın kayıtları retrospektif olarak incelendi. Hastaların klinik ve nöroradyolojik bulguları ayrıntılı olarak değerlendirildi.

BULGULAR: Dokuz gün ile 13,83 yaş arasında (5 kız ve 10 erkek) değişen 9 NF1, 5 TSC ve 1 SWS tanısı alan 15 hasta belirlendi. Tüm NF1 hastalarında café au lait lekeleri vardı. Bir olguda (% 11.1) Lisch nodülü, bir olguda (% 11.1) optik gliom, bir olguda (% 11.1) epilepsi, iki olguda(% 22.2) makrosefali, iki olguda (% 22.2) hidrosefali ve yedi olguda aile öyküsü (% 77,7) saptandı. Tüm TSC hastalarında hipomelanotik maküller ve epilepsi vardı. Üç hastada (% 60) kardiyak rabdomiyom, bir hastada (% 20) anjiyomiyolipom ve bir hastada (% 20) polikistik böbrek mevcuttu. SWS tanılı olguda fasiyal anjiyom, glokom ve epilepsi saptandı. NF1 tanılı hastalarda 6 olguda (% 66.6) UBO (bilinmeyen parlak cisim), 2 olguda(% 22.2) hidrosefali, bir olguda (% 11.1) subependimal nodül ve bir olguda (% 11.1) optik gliom gösterildi. Tüm TSC hastalarının beyin manyetik rezonans görüntülemesinde kortikal / subkortikal tüberler ve iki hastada subependymal nodül saptandı. SWS tanılı hastanın kraniyal bilgisayarlı tomografisinde kortikal ve parankimal atrofi ve kalsifikasyon gösterildi.

SONUÇ: Nörokütanöz sendromların klinik ve nöroradyolojik bulguları tanı açısından yol gösterici olup, ayrıntılı inceleme ve nöroradyolojik bakış açısı tanı ve takipte kolaylık sağlayacaktır.

ANAHTAR KELİMELER: Nörokütanöz sendrom, Nörofibromatoz tip I, Tuberoskleroz kompleksi, Sturge-Weber sendromu, Nöroradyolojik bulgular

OBJECTIVE: Neurofibromatosis type I (NF1), Tuberous sclerosis complex (TSC) and Sturge-Weber syndrome (SWS) are the most common neurocutaneous syndromes. The purpose of this study is to evaluate the clinical and neuroradiological manifestations of patients diagnosed with NF1, TSC, and SWS.

MATERIAL AND METHODS: In our clinic, records of 15 patients with NF1, TSC, and SWS were retrospectively reviewed between December 2017 and May 2019. Clinical and neuroradiological manifestations of patients were detailed.

RESULTS: 15 patients consisting of 9 NF1, 5 TSC, and 1 SWS were determined between the ages of 9 days and 13,83 years (5 females and 10 males). All NF1 patients had café-au-lait spots. One (11.1%) with lisch nodules, one (11.1%) with optic glioma, one (11.1%) with epilepsy, two (22.2%) with macrocephaly, two (22.2%) with hydrocephalus, one (11.1%) with optic glioma and seven (77.7%) with family history were established. All TSC patients had hypomelanotic macules and epilepsy. It was indicated cardiac rhabdomyoma in 3 (60%) patients, angiomyolipoma in one (20%) patient and polycystic kidney in one (20%) patient. The patient with SWS was showed available of facial angioma, glaucoma, and epilepsy. It was pointed UBOs (unknown bright objects) with 6 (66.6%) patients, 2 (22.2%) patients with hydrocephalus, one (11.1%) patient with subependymal nodule and one (11.1%) patient with optic glioma in NF1 patients. Brain magnetic resonance imaging of all TSC patients showed cortical/subcortical tubers and two patients with subependymal nodules. Cortical and parenchymal atrophy and calcification were presented in cranial computed tomography of the patient with SWS.

CONCLUSIONS: Clinical and neuroradiological manifestations of neurocutaneous syndrome are guidance for diagnosis so that detailed examination and neuroradiological perspective on neurocutaneous diseases will provide convenience in diagnosis and follow-up.

KEYWORDS: Neurocutaneous syndrome, Neurofibromatosis type I, Tuberous sclerosis complex, Sturge-Weber syndrome, Neuroradiological findings

ABSTRACT

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INTRODUCTION

The neurocutaneous syndromes are a group of disorders that involve abnormalities of the central nervous system, in addition to characteristic skin lesions. Neurofibromatosis type I (NF1), Tuberous sclerosis complex (TSC) and Sturge-Weber syndrome (SWS) are among the most common neurocutaneous syndromes (1). Neurofibromatosis type 1(NF1) is the most common autosomal dominant neurocutaneous syndrome. The disease is caused by mutations in the NF1 gene and the incidence at birth is reported to be approximately 1: 3000 (2).

Tuberous sclerosis complex (TSC) is an autosomal-dominant genetic disorder that involved multisystem hamartomas. TSC1 and TSC2 genes have been identified that are mutated or deleted in children with TSC (1). Sturge-Weber syndrome (SWS) is a sporadic developmental disorder with variable intracranial involvement by facial cutaneous capillary malformation (port wine stain), leptomeningeal angiomatosis, and glaucoma (1, 3).

In this study, it was aimed to discuss the clinical and neuroradiological findings of NF1, TSC, and SWS in our cohort.

MATERIAL AND METHODS

In this study, 15 patients who were followed up regularly in the Pediatric Neurology Outpatient Clinic of Afyonkarahisar Health Sciences University Hospital between December 2017 and May 2019 with the diagnosis of NF1, TSC, and SWS were included. NF-1 was diagnosed according to the criteria defined by National Institute of Health (4). TSC was diagnosed according to the diagnostic criteria determined by the International Tuberculosis Complex Consensus Group (5) **(Figure 1)**.

The study was approved by demographic data, clinical manifestations, neuroimaging features (brain MRI, cranial CT), electroencephalography (EEG) findings, and treatment were evaluated retrospectively.

Figure 1: Diagnostic criteria of NF1 and TSC.

ETHICS COMMITTEE

Afyonkarahisar University of Health Sciences (02.08.2019, 2011-KAEK-2).

STATISTICAL ANALYSIS

SPSS for Windows version 21.0 statistical package program was used to evaluate the data. In descriptive statistics, variability criterion was given as mean ± standard error.

RESULTS

A total of 15 children with NF1, TSC, and SWS were identified between the ages of 9 days and 13.83 years (median=7.58 standard deviation (SD)=4.49), including 5 females and 10 males. The diagnosis of the patients consisted of 9 NF1, 5 TSC, and 1 SWS. The follow-up period of patients varies between 3-17 months.

All the NF1 patients had café-au-lait spots. Lisch nodules in one (11.1%) case, optic glioma in one (11.1%) case, epilepsy in one (11.1%) case, macrocephaly in two (22.2%) cases, hydrocephalus in two (22.2%) cases, and family history in seven (77.7%) cases were observed. There was one patient, who had optic glioma, which was diagnosed with abnormal visual evoked poten-

tial (VEP) and findings of MRI. She was treated with chemotherapy (cisplatin/etoposide) **(Table 1)**.

Table 1: Demographic and clinical manifestations of the patients

Patient No	Diagnosis	Age (year)/ gender	Family history	Clinical manifastations	MRI/CT	EEG	Treatment	Other findings
1	NF-1	13/F		CALM	UBO			
2	NF-1	3.08/F		CALM	UBO			
3	NF-1	11/M	+	CALM + MC	Hydrocephalus+SEN			
4	NF-1	4.5/M	+	CALM + MC	UBO			
5	NF-1	13.33/F		CALM+Lish nodules	TV Hydrocephalus+			Abnormal VEP
6	NF-1	5.41/F		CALM+optic glioma+E	UBO	N	OCZ+Cisp+epo	
7	NF-1	4.5/M	+	CALM	N			
8	NF-1	9.58/M	+	CALM	UBO			
9	NF-1	8.16/F	+	CALM	UBO			
10	TSC	1/M		HMM+ cRM+E	CoT	N	PB	
11	TSC	13.8/M		HMM+E	CoT+SCoT+SEN	N	CBZ	
12	TSC	7.58/M		HMM+cRM+E	CoT+SEN	N	VALP	
13	TSC	8.25/M		HMM+E	CoT+SCoT	N	CBZ	AML
14	TSC	0.027/M	+	HMM+cRM+E	CoT+SCoT	Modified hypsarrhythmia	Prednisolone	Polycystic kidney
15	SWS	2.66/M		Fasial angioma+E	Cortical and parenchymal atrophy + calcification	Disorganized background activity	CBZ+LEV	

MRI: Magnetic resonance imaging, CT: Computed tomography, EEG: electroencephalogram, NF-1: Neurofibromatosis type I, TSC: tuberous sclerosis complex, SWS: Sturge Weber syndrome, M: Male, F.Female, CALM: café-au-lait macules, MC: Macrocephaly, HMM: Hypomelanotic macules, cRM: Cardiac rhabdomyoma, E: Epilepsy, UBO: unknown bright object, SEN: Subependymal nodule,TV: triventricular, N: Normal, CoT : cortical tuber, SCoT: subcortical tuber, OCZ: Oxcarbazepine, Cisp+epo: Cisplatin+ Etoposide, PB: Phenobarbital, CBZ: Carbamazepine, VALP: Valproate, LEV: levetiracetam, VEP: Visual Evoked Potentials, AML: Angiomyolipoma.

All 5 TSC patients had hypomelanotic macules and epilepsy with monotherapy (phenobarbital, valproate, carbamazepine, prednisolone).

Cardiac rhabdomyoma in 3 (60%) patients, angiomyolipoma in one (20%) patient and polycystic kidney in one (20%) patient were detected.

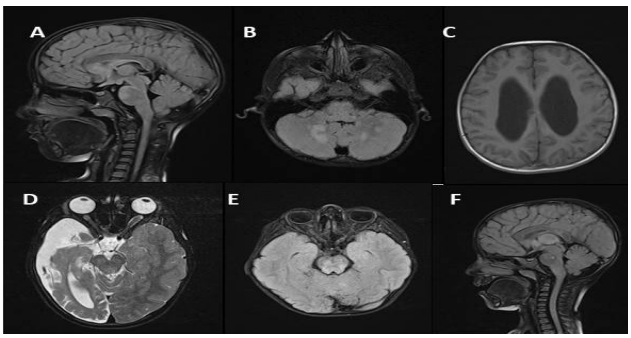
Angiomyolipoma in the bilateral renal region was detected in the size of 12 * 14 mm (patient 13, Table 1). Only one patient had family history.

Moreover, only one patient had pathological EEG as modified hypsarrhythmia.

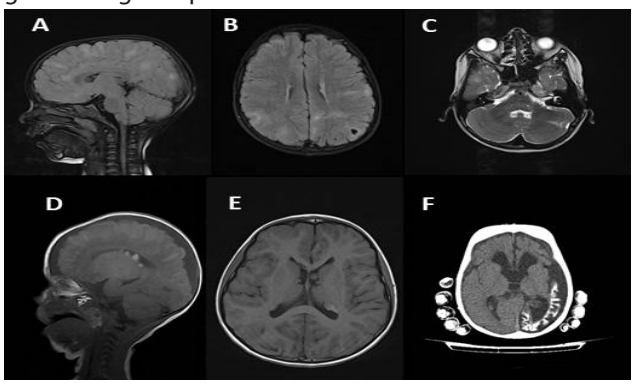
The last patient with SWS had facial angioma, glaucoma, and epilepsy. His EEG indicated disorganized background activity. Additionally, the epilepsy treatment consisted of carbamazepine and levetiracetam.

All brain MRI was abnormal except one (11.1%) in patient with NF1. Six of them (66.6%) had UBOs (unknown bright objects), two (22.2%) had hydrocephalus, one (11.1%) had subependymal nodules and one (11.1%) had optic glioma **(Figure 2)**.

Brain MRI of all TSC patients demonstrated cortical/subcortical tubers. Two patients with subependymal nodules were indicated in TSC patients. The patient with SWS had cortical and parenchymal atrophy and calcification in his CT **(Figure 3)**.



Figür 2 : A, B, E. UBOs are seen on Flair weighted images in pons, midbrain and genu of corpus callosum and cerebellar hemispheres C. Axial T1 image indicates hydrocephalus. D. Axial T2 demostrates left optic glioma with slightly thickened, irregular borders, showing minimal signal increase and tortiosity and also right temporooccipital prominent atrophy. F. UBOs are shown on flair weighted images in pons and bilaterale thalamus



Figür 3 : A. Sagittal and axial flair and T2 images demostrate multiple cortical and subcortical tubers in bilateral cerebral hemispheres. B. Axial flair image shows radial migration line in the left cerebral hemisphere. C. Axial T2 image indicates a hyperintense lesion in the left cerebellar hemisphere with associated mild retraction abnormality. D, E. Sagittal and axial flair and T1 images show multiple subependymal nodules. F. Computer tomography image of the SWS patient demostrates left temporooccipitale cortical and parenchymal atrophy and calcification.

DISCUSSION

Café-au-lait spots are one of the diagnostic criteria of NF-1 and were present in all patients with NF1 in our cohort (6). Lisch nodules exist from the age of 2 years and present nearly 50% throughout childhood (7). Only one patient (11.1%) with NF1 had lisch nodules in our study. Ophthalmologic examination of the patient who had lisch nodules was normal except abnormal VEP (Patient 5, Table 1). Optic pathway gliomas are discovered in 15%-21% of patients with NF1 and are characteristically benign, low-grade gliomas that mostly consist

in early childhood (8). Optic gliomas are seen in each part of the optic pathway. They cause thickening of optic nerve and chiasm. Treatment (surgery / chemotherapy / radiotherapy) is not recommended unless symptomatic (9-11). Chemotherapy has become the preferred treatment for optic gliomas in NF1 (8). In this study, we reported one patient with optic glioma. The MRI showed left optic glioma with slightly thickened, irregular borders, showing the minimal signal increase and tortuosity. Macrocephaly is a common finding in patients with NF-1 (12).

The incidence of macrocephaly is reported in 8%-40% of patients with NF1 (13). Macrocephaly in the absence of hydrocephalus occurs in 50% of patients with NF1 (14). We determined two patients (22.2 %) with macrocephaly and one of them was without hydrocephalus. Records of head circumference measurements in NF1 patients are extremely substantial for detecting macrocephaly. The incidence of seizures in patients with NF1 is reported to be 3.8-7% (11, 15).

In this study, one of NF1 patients (11.1%) had epilepsy (patient 6). It was described as focal aware of somatosensory seizures. The interictal EEG was normal. Thereby, it was classified as focal epilepsy. Moreover, the high incidence may explain due to a small number of patients with NF1.

In literature, 81-95% of patients diagnosed with TSC were found to have one of the characteristic skin lesions (16). Although all TSC patients had hypomelanotic macules, the newborn patient did not exhibit any skin lesions at admission in the current study. During follow-up, hypomelanotic macules appeared in the newborn.

Moreover, the patient presented with hypotonia in the newborn period. The diagnosis of TSC was based on cortical/subcortical tubers in MRI and cardiac rhabdomyoma in the patient. Then, he displayed polycystic kidney and infantile spasms over time (patient 14, Table 1). Cardiac rhabdomyoma typically develops in the intrauterine period and is usually asymptomatic or may present in the neonatal period and infancy.

Furthermore, all cardiac rhabdomyoma, even symptomatic, regress spontaneously. (17). We determined 3 (60%) patients with cardiac rhabdomyoma in TSC cases. Renal involvement is the most common reason for morbidity and mortality in TSC. Angiomyolipoma is found approximately 80% of patients with TSC and can be improved in childhood and adulthood (14).

In this study, one patient (20%) showed angiomyolipoma in TSC patients. Polycystic kidney disease presents in 3%-5% of patients with TSC. Additionally, it is reported that the polycystic kidney disease gene is contiguous to the TSC2-tuberin gene on chromosome 16 (14). We reported one patient (20%) with a polycystic kidney. Unfortunately, the patient did not have any genetic tests. Epilepsy is the most common symptom in TSC and shows up to 80% to 90% of patients with TSC. Moreover, seizures mostly onset in childhood especially during the first year of life. Nearly one-third of the seizures are infantile spasms. Almost all seizure types can be observed in patients with TSC except 'pure' absence (14). The seizures of all TSC patients except the newborn case classified as unclassified seizure onset. During follow-up, the newborn patient developed infantile spasms. Other patients were seizure-free for at least two years. The treatment consisted of phenobarbital, carbamazepine, or valproate.

The location and extent of leptomeningeal angioma determine neurological findings. The frequency of seizures occurs in 75-90 % of patients with SWS. The seizures may be refractory to the medical treatment because of cortical dysgenesis and cortical irritability due to regional hypoxia, ischemia, and gliosis associated with leptomeningeal angioma (14). The seizures of our patient were under control with carbamazepine and levetiracetam.

The incidence of hydrocephalus in patients with NF1 has been predicted to be 1-13%. Roth et al reported hydrocephalus in NF1 had been caused mostly by obstructive etiologies (8). We showed hydrocephalus in two patients (22.2%) with NF1. T2 high-signal intensity abnormalities (unknown bright objects (UBOs)) typically are seen within the basal ganglia, thalamus and internal capsule, cerebellum, and brainstem in MRI (9, 10). Moreover, UBOs have been called hamartomas, heterotopias, or areas of altered myelin (10). UBOs are mostly seen in late chil-

dhood and adolescence and tend to regress in older ages. The lesions are thought to be associated with excessive myelination and gliosis.

Moreover, some authors suggest that UBOs may be diagnostic. We found UBOs (unknown bright objects) in the brainstem, corpus callosum, cerebellum and thalamus of 6 (66.6%) patients with NF1.

Neuroradiological findings of TSC involve white matter lesions, subependymal nodules, cortical tubers, and subependymal giant cell astrocytomas. Radial migration lines like linear abnormalities are the most frequent neuroimaging lesion indicated in TSC. They spread across the cerebral white matter. Additionally, radial migration lines display gliosis and heterotopic glia (18, 19). We observed radial migration lines in MRI of TSC patients. The imaging manifestations of tubers alter with the age. Tubers present hyperintense on T1 sequences and hypointense on T2 sequences in the neonatal period. They appear isointense on T1 and hyperintense on T2 in MRI with the advancement of age-associated with myelination. Moreover, fluid-attenuated inversion recovery (FLAIR) sequence is also used to assign tubers (1, 14). In the current study, we pointed on multiple cortical/subcortical tubers. Cerebellar lesions are pointed in 24–44% of patients with TSC (20). Cerebellar tubers are frequently described wedge-shaped, nodular or display folia distortion. Most of them indicate retraction abnormalities of the cerebellum (1, 20). Additionally, similar lesions were seen in children with TSC in this study. Subependymal nodules appear throughout the walls of the lateral ventricles. They are usually found along with the head of the caudate nucleus and best recognized on T1-weighted images (21). On the other hand, subependymal giant cell astrocytomas (SEGAs) are generally established adjacent to the foramen of Monro. They are separated from subependymal nodules by their size (greater than 1 cm) (22). In the current study, it was shown only subependymal nodules.

The pathology of SWS is suggested that vascular endothelial dysgenesis, cortical venous capillary hypogenesis due to dysregulation of endothelin, and likely small vessel thromboses related to vascular dysplasia (23). Although MRI demonstrates thickened cortex, decreased folds, and white matter changes, cranial CT displays more distinctive calcification. Gadolinium enhancement may show pial angioma so that early diagnosis exists at SWS before calcification (14). Moreover, we pointed on the characteristic calcification on cranial CT.

Current consensus guidelines do not recommend screening MRI unless there is a clinical requirement in NF1. On the other hand, neuroimaging screening is recommended every year until age 20 due to the development of subependymal nodules into SEGAs in TSC (1, 14).

This current study has some limitations. First, our study population was small. Second, the nature of the study was retrospective.

In conclusion, recognizing signs and symptoms of neurocutaneous diseases is extremely substantial in diagnosis. Identification of the neuroradiological findings with neurocutaneous syndromes contributes to the diagnosis and follow-up. Early diagnosis and regular follow-up can decrease the rate of morbidity/mortality in neurocutaneous diseases.

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