Skin findings related to chronic usage of anti-epileptic drugs

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ABSTRACT

Objective: Chronic type skin reactions are defined as unwanted effects of drugs. As there are more benign conditions, skin findings related to chronic usage of anti-epileptic drugs (AEDs) have not been studied previously. In this study, we investigate the skin findings associated with the chronic usage of AEDs.

Methods: The study was conducted in the Post, Telephone and Telegraph Training and Research Hospital between May 2002 and January 2003 during a 6-month work period. Skin lesions were first assessed individually, and then their correlations with AEDs were examined. Skin findings were then divided into skin disease groups to evaluate statistical significance. The prevalence of skin findings occurring in 62 epileptics was compared with that of an age-matched group of 33 non-epileptics.

Results: The rate of skin findings defined in the workgroup was 85.5%, while it was 84.8% in the control group. The most common skin findings were acneiform eruptions for both groups. There was no significant differences between the work and study group as for skin findings ($p>0.05$). Alopecia was the only skin condition related to AED usage and it was seen in 4 patients (6.5%) using valproate ($p<0.05$). None of the 11 patients with infectious skin findings were using valproate, and that was the only significant relationship between antiepileptic drugs and skin diseases ($p=0.015$).

Conclusion: The inflammatory skin diseases were the most commonly seen problem in both patients and controls. The alopecia ratio with valproate usage in our patient group was similar to literature reports.

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Anti-epileptic drugs (AEDs), which are being widely used for non-epileptic diseases with an increasing frequency, may result in dermatological and cosmetic problems in addition to their acute reactions.[1,2] Acute skin reactions, or those observed within the first month, have always been seen as more important, and more frequently reported due to their severity. However, skin findings related to chronic usage of AEDs in the same age group have not been taken into as much consideration and reported, most likely as there are more benign skin lesions. In this study, we aimed to investigate the skin findings associated with the chronic usage of AEDs.

Methods. The study was conducted between May 2002 and January 2003 during a 6-month work period in the Neurology Clinic of Post, Telephone and Telegraph Training and Research Hospital, establishment in Turkey and Dr. Lutfi Kirdar Kartal Training and Research Hospital, the hospitals that present primary and secondary health care services to people in Istanbul, which harbors 1/10 of the Turkish population. Subjects, who had been under observation for at least one year due to epilepsy diagnosis, and who were using AEDs formed the workgroup. Those with structural or metabolic epilepsies, those with skin lesions related to antibiotic, steroid or any drug usage, and those with

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anoxic birth history were excluded. Subjects of the control group were selected in accordance with the work group and included patients without a systemic disease, and who have not been using drugs during the past one year. All subjects were assessed with a full dermatological examination during the day. Skin lesions were first assessed individually, and then their correlations with AEDs were examined. Our study group included younger individuals with acneiform lesions. Acne and acneiform eruptions which do not contain comedo are mostly found together, so it was difficult to classify them separately. We named these lesions as acneiform eruptions. The skin findings were then divided into the following groups to evaluate statistical significance: 1. Inflammatory skin disorders (acneiform eruptions, dyshidrotic eczema, seborrheic eczema, intertrigo, psoriasis, rosacea, stasis dermatitis). 2. Atopic diseases (atopy, xerosis, pruritus, atopic hand dermatitis, hyperkeratosis), 3. Infectious skin disorders (mycosis, pyoderma, herpes simplex, warts). 4. Diseases characterized by pigmentary changes (lentigo, post-inflammatory hypo-hyper pigmentation). 5. Skin tumors (actinic keratosis, skin tags). 6. Hair and bristle diseases (alopecia, hirsutism). 7. Urticaria. Obtained results were evaluated with frequency analysis. Differences between groups were studied using chi-square, student-T, and Fisher's exact tests.

Results. Of the 62 patients in the work group using AEDs, 31 were males and 31 were females, while, of the 33 individuals in the control group, 18 were males and 15 were females. The mean age of the workgroup was 27.37±12 years, and it was 28.88±11.21 years for the control group. There were no statistically significant differences between the groups for age and sex (p>0.05). Sex-specific diagonal tables were studied while patient and control groups were assessed separately (as groups). None of the males in the hair-bristle diseases group had problems. Six of the females (9.4%) had diseases, however, no significant results were noted when evaluating the skin diseases groups and sex groups (Fisher's exact test; p=0.012). When studying individually, rather than in groups, none of the skin findings displayed significant differences between the sexes. The most common type of seizure was generalized-tonic-clonic seizure (n=43, 69%), and the most commonly used AED was carbamazepine (n=35, 56%). Other AEDs, according to the frequency of use were valproate, phenytoin, phenobarbital, lamotrigine, and clonazepam. Of the subjects, 50 were cured with monotherapy, and 16 with polytherapy. The rate of skin findings defined in the workgroup was 85.5% (n=53), while it was 84.8% (n=28) in the control group. When the workgroup and control group were assessed for skin problems, the most common

Table 1 - Dermatological findings of our workgroup.

Findings	Patient (N=62) n	(%)	Control (N=33) n	(%)	*P*-value
Stasis dermatitis	1	(1.6)	-	-	
Xerosis	1	(1.6)	-	-	
Senile pruritus	1	(1.6)	-	-	0.731
Actinic keratosis	2	(3.2)	-	-	0.160
Acneiform eruptions	19	(30.6)	9	(27.3)	0.547
Mycosis	8	(12.9)	8	(24.2)	0.949
Dyshidrotic eczema	3	(4.8)	1	(3.0)	0.926
Urticaria	4	(6.5)	2	(6.1)	0.600
Seborrheic dermatitis	6	(9.7)	3	(9.1)	
Post-inflammatory hyperpigmentation	10	(16.1)	4	(12.4)	
Intertrigo	1	(1.6)	-	-	
Hirsutism	3	(4.8)	-	-	
Rosacea	1	(1.6)	-	-	
Pyoderma	1	(1.6)	-	-	
Alopecia	4	(6.5)	1	(3.0)	
Herpes simplex	1	(1.6)	-	-	
Keratoderma	5	(8.1)	2	(6.1)	
Pruritus	1	(1.6)	1	(3.0)	
Ecchymosis	1	(1.6)	-	-	
Post-inflammatory hypopigmentation	5	(8.1)	2	(6.1)	
Café au lait	2	(3.2)	-	-	
Atopy	2	(3.2)	1	(3.0)	
Lentigo	1	(1.6)	-	-	
Skin tags	-	-	2	(6.1)	
Psoriasis	-	-	2	(6.1)	
Hyperhidrosis	1	(1.6)	-	-	
Warts	1	(1.6)	1	(3.0)	

finding was found to be acneiform eruptions for both groups. Of the subjects in the work group, acneiform eruptions were observed for 31%, while this rate was 27% in the control group (**Table 1**). The rates of acne having comedo differing from acneiform eruptions in the present study for the patient group was 17.9% (n=11) and control group was 18% (n=6). Other skin problems observed in the work group, and their rates were, post-inflammatory hyperpigmentation (30.6%), mycosis (12.9%), and seborrhea dermatitis (9.7%). The most prevalent skin problems defined in the control group, after acneiform eruptions, were mycosis (24.2%), post-inflammatory hyperpigmentation (12.4%), and seborrhea dermatitis (9.1%). As demonstrated in **Table 1**, there was no significant difference between the work and study group for skin problems ($p>0.05$). Psoriasis (n=2) and skin tags (n=2) were observed only in the control group. When the defined skin problems were assessed as groups, inflammatory skin disorders were the most common in the work group, followed by pigmentary skin diseases, with rates of 50% and 22.6%. In the work group, inflammatory skin disorders were again the most frequently seen disease group (45.4%), whereas it was followed by infectious skin diseases with a rate of 24.2%. However, there were no significant differences between the work and the control group for skin disease groups ($p>0.05$). Therefore, it would not be right to merely study the relationship between the used drugs. Nevertheless, we examined them individually to provide an insight. Only the relationship between valproate and infectious skin diseases were found significant ($p=0.015$), which was that none of the 11 patients with infectious skin findings were using valproate. A study of relationships between used AEDs and skin problems revealed a statistically significant level of alopecia observed in 4 subjects using valproate ($p=0.005$). Pyoderma was defined in a subject using clonazepam. The correlations between other AEDs and skin findings were not statistically significant ($p>0.05$). When the subjects were compared for single drug use and polypharmacy, no skin findings were noted in 5 of the 16 subjects with polytherapy. The most prevalent skin finding was acneiform eruptions (n=5, 31%). This percentage for subjects using a single drug was 39% (n=14).

Discussion. The adverse effects of antiepileptic therapy are common and may affect the patient's quality of life to an even greater extent. Many skin reactions have been reported related to AED usage.[1-5] The most common is delayed type hypersensitivity reactions, which are seen in 10% of patients using AEDs within the first month following the administration of the drug.[1-5] This reaction may sometimes necessitate the termination of the drug. Dermatitis may be the first indictor of secondary allergic reactions in phenytoin treatment.[5] Lethal reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis can also be seen related to the use of AEDs.[6-8] Allergic reactions have also been reported with new generic AEDs gabapentin and vigabatrin.[3,7]

Benign reactions with most of the AEDs have been previously reported, most of which are acne, hirsutism and hair loss.[1-4] Acneiform eruptions may be seen during the use of conventional AEDs and most often take place with the use of carbamazepine, phenytoin and lamotrigine. It is associated with the initial or charging doses.[1] Acne, ephelides, nevus and leukonychia are more prevalent in subjects with epileptics and those using AEDs.[9] Phenytoin is a highly effective and widely prescribed anticonvulsant agent used in the treatment of epilepsy. During chronic administration, cosmetic changes, such as hirsutism, gingival hyperplasia, and facial coarsening, make phenytoin especially troublesome in the treatment of young women.[1,2,10] Hirsutism and hypertrichosis has been reported for the chronic use of phenytoin that ranges from 5-30%.[1,3,4] Rare cutaneous side-effects include drug-induced lupus, purple-hand syndrome, pigmentary alterations, and IgA bullous dermatosis.[10] Reports associated with drugs are mycosis fungoides triggered by phenytoin use, and bullous eruptions related to carbamazepine use.[8,11] Hair loss is another important problem that develops secondary to valproate usage.[1,4]

Skin findings associated with the presence of epilepsy are also known. Hypopigmented stain prevalence is markedly more in epileptic children than healthy children: there are studies reporting these stains to be 4.7% in normal population, while 14.3% in pediatric epilepsy patients.[9,12] These percentages were 8.1% for epileptic subjects, and 6.1% for the control group in our study, and differing from the findings of the above mentioned literature. Age and sex are 2 important factors that affect the prevalence of skin findings. That, in our study, the number of subjects in the control and the work group was well matched for age and sex, makes our findings valuable. The ratio of acneiform eruptions in our study for the patient and the control groups were 30.6% and 27.3%. We could not compare it with any reports of acne in previous studies with similar age groups, because it is not exactly known. However, the ratio of acne in the normal population varies according to age and sex, ranging from 23.1-50%.[13] Our results were just lower, namely, 17.9% for epileptics and 18% for controls, from these reports. This can be related to the difficulty in differentiating acne and acneiform eruptions. In most cases, the exact pathogenesis of acneiform eruption remains unknown. It is a nonallergic reaction that does not appear to have a

single mechanism. Therefore, skin testing is not useful in diagnosing drug-induced acne. The patient's history, clinical findings, exposure to one of the known causative drugs, and disappearance of lesions after discontinuation of the offending medication should lead to the diagnosis. Steroid acne that is a prototype of acneiform eruption appears to result from a direct effect of the steroid on the follicular epithelium, causing a focal degeneration with a localized intrafollicular and perifollicular neutrophilic inflammatory reaction. It is assumed that large lesions do not occur because of the anti-inflammatory effect of the steroid itself. Also, unlike acne vulgaris, follicular hyperkeratosis is not an early event, as was once believed.[14] Although the correlation between hydantoin derivatives and phenobarbital, commonly used AEDs, and acneiform lesions are acknowledged in the literature, no relation was defined between the AEDs used in our study and acneiform lesions.[3,4,11] An important finding found to be related to AED use is alopecia, which was observed to secondarily develop with valproate usage and to be the most noted (7%) side effect in the literature.[3] We noted that alopecia findings with valproate usage in our patient group were similar to literature reports.

When the defined skin findings were assessed in groups, no difference was defined between the patient and the control groups. Therefore, it would not be accurate to study the correlation between the used drugs. Nevertheless, they were studied individually to provide an insight. The inflammatory skin diseases were the most commonly seen problem both in patients and controls. The difference was not significant. A significant relation was found only between the valproate and infectious skin diseases group (p=0.015), which was that none of the 11 patients with infectious skin findings were using valproate. A result to state an adverse relationship between valproate and inflammation could be derived from this finding.

References

1. Hansen BR, Gram L. Adverse effects of established and new antiepileptic drugs: an attempted comparison. ***Pharmac Ther*** 1995; 68: 425-434.
2. Bruni J, Guberman A. Individual antiepileptic drugs. In: Bruni J, Guberman A, editors. Essentials of Clinical Epilepsy. 2nd ed. USA: Butterworth Heinemann; 1999. p. 115-149.
3. Litt JZ. Drug eruption reference manual 2000. Millennium ed. New York: The Parthenon Publishing Group; 2000.
4. Swart E, Lochner JD. Skin conditions in epileptics. ***Clin Exp Dermatol*** 1992; 17: 169- 172.
5. Duchowny M, Pellock JM, Graf WD, Billard C, Gilman J, Casale E, et al, and for the Lamictal Pediatric Partial Seizure Study Group. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. ***Neurology*** 1999; 53: 1724-1731.
6. McCarthy LJ, Aguilar JC, Ransburg R. Fatal benign phenytoin lymphadenopathy. ***Arch Intern Med*** 1979; 139: 367-368.
7. DeToledo JC, Minagar A, Lowe MR, Ramsay RE. Skin eruption with gabapentin in a patient with repeated AED-induced Stevens-Johnson's syndrome. ***Ther Drug Monit*** 1999; 21: 137-138.
8. Godden DJ, McPhie JL. Bullous skin eruption associated with carbamazepine overdosage. ***Postgrad Med J*** 1983; 59: 336-337.
9. Vanderhooft SL, Francis JS, Pagon RA, Smith LT, Sybert VP. Prevalence of hvpopigmented macules in a healthy population. ***J Pediatr*** 1996; 129: 355-361.
10. Scheinfeld N. Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. ***Dermatol Online J*** 2003; 9: 6.
11. Wolf R, Kahane E, Sandbank M. Mycosis fungoides-like lesions associated with phenytoin therapy. ***Arch Dermatol*** 1985; 121: 1181-1182.
12. Karabiber H, Sasmaz S, Turanli G, Yakinci C. Prevalence of hypopigmented maculae and cafe-au-lait spots in idiopathic epileptic and healthy children. ***J Child Neurol*** 2002; 17: 57-59.
13. Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. ***Br J Dermatol*** 2001; 145: 274-279.
14. Jansen T, Plewig G. Clinical manifestations and variants of acne, including drugs and external agents aggravating or causing acne or acneiform eruptions [Acne: Pathogenesis and Treatment]. ***Dermatol Ther*** 1998; 6: 18-31.