DERMATOLOGICA SINICA 32 (2014) 133–136

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

ORIGINAL ARTICLE

Dermatological conditions in patients with brain damage

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ARTICLE INFO

Article history:
Received: Jan 18, 2013
Revised: Nov 25, 2013
Accepted: Dec 2, 2013

Keywords:
brain damage
coma
inpatient consultations
skin disorders

ABSTRACT

Background: As a result of the focus on vital functions in patients with brain damage, dermatological symptoms are often overlooked during their period of admission to hospital. However, patients with brain damage are more likely to have dermatological diseases than the general population and other inpatients for various reasons, including immobilization, treatment with multiple drugs, long-term hospitalization, and their immunocompromised status.

Objectives: The purposes of this study were: (1) to analyze the frequency and characteristics of dermatological consultations among patients who were admitted to hospital as a result of brain damage; and (2) to compare these findings with other reports about inpatient dermatological consultations.

Methods: We analyzed data for 240 patients with brain damage who attended our department of dermatology between January 1, 2007 and December 31, 2011. The total numbers of male and female patients were 132 (55%) and 108 (45%), respectively (male to female ratio 1.22:1). We retrospectively reviewed medical records, demographic information, reason for dermatological consultation, and the diagnosis of the dermatoses.

Results: The age group most frequently seen was patients in the 7th decade of life and the most common underlying brain injury was traumatic intracranial hemorrhage. The mean ± standard deviation score on the Glasgow Coma Scale (GCS) was 6.8 ± 3.0. When the levels of brain damage of the patients were classified using the GCS, 68.3% of the patients were in the severe (GCS ≤ 8) category. The most common skin disorders were seborrheic dermatitis (17.9%), followed by mycoses (15.5%), and drug-induced skin eruption (13.2%).

Conclusion: The characteristics of dermatological consultations in patients with brain damage may be different from those of other inpatients attending dermatological clinics. The analysis of dermatological disorders in patients with brain damage can assist in understanding the "brain–skin connection".

Introduction

Although the practice of dermatology has recently become a predominantly outpatient-based specialty, there continues to be a need for dermatological expertise within hospitals, where patients have a wider spectrum of severe and serious dermatological disorders associated with significant morbidity.[1,2] Many patients who are admitted to hospital for various nondermatological diseases often have underlying skin disease, whereas others develop acute dermatological problems during their stay in hospital. These general illnesses contribute to developing and worsening the primary dermatological diseases; the management of an underlying disease can also cause dermatological disease.

Patients with brain damage due to various causes, such as intracranial hemorrhage, hypoxia, metabolic disease, infection, or tumor, may have many dermatological problems, but these are often overlooked during their stay in hospital because of many other complicated medical problems. However, it is still important for doctors to have a consultation with patients with brain damage regarding their skin problems. Such patients are especially vulnerable to drug-induced skin eruptions or infections due to the administration of many different drugs and exposure to immunocompromised conditions including underlying disease and long term steroid use.

Several recent studies have independently shown that our skin is an unexpectedly prominent target organ for numerous neuroendocrine, neurotrophic, neurotransmitter, and neuropeptide signals, which have a profound effect on skin biology in health and disease.[3] The aim of this study was to characterize the profiles of patients with brain damage and the scope and referral pattern of

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.dsi.2013.11.003

dermatology consultations in a tertiary hospital, which has not previously been well studied.

Patients and methods

All consultations with patients in hospital were referred to the Department of Dermatology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, between 1 January, 2007 and 31 December, 2011. The data were collected retrospectively from the admission and daily progression notes provided by the attending doctor and the consultation notes made by the dermatological consultant. Final diagnoses were classified according to the English version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[4] Only the dermatological disorder responsible for the consultation was recorded. During weekdays, each request was allocated to one of three different dermatology consultants, assisted by a 3rd-year dermatology resident. A potassium hydroxide smear test from skin scrapings, swabs for bacterial culture, and biopsy samples were taken as appropriate by the dermatologist to reach a definitive diagnosis. The severity of brain damage was classified into three groups (severe, moderate, and mild) based on the Glasgow Coma Scale (GCS) and these scores were evaluated by the attending doctors.

All statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Absolute and relative frequencies were analyzed for all data. Continuous variables, such as age, were expressed as mean values with standard deviations. The difference in the prevalence of skin disease according to the GCS score was evaluated by the Chi-square test. In all instances, $p < 0.05$ was considered significant.

Results

During the 5-year study period, 240 patients who presented with altered consciousness due to brain damage were referred to the dermatologists. We diagnosed 341 dermatological diseases, performed 45 skin biopsies, 11 bacterial cultures, 67 potassium hydroxide smear tests, and 13 dermatological procedures of various kinds (cryotherapy, intralesional injection, and wet dressing). Ninety-five patients (39.6%) were seen twice by a dermatologist for different dermatological symptoms. The most frequent age group was the patient's 7th decade of life (25.3%) and the next most frequent was the 6th decade (19.5%) (Table 1).

The most frequent cause of brain damage was traumatic intracranial hemorrhage (50.4%), followed by spontaneous intracranial hemorrhage (28.7%), hypoxia (10.4%), metabolic disease (4.6%), infectious disease (2.9%), and brain tumors (2.6%) (Table 2). The most frequent diagnosis was seborrheic dermatitis (ICD-10:L21; 17.9%), mycoses (ICD-10:B35～37; 15.5%), drug-induced skin eruption (ICD-10:L27.0, 27.1; 13.2%), xerosis cutis (ICD-10:L85.3; 9.1%), irritant contact dermatitis (ICD-10:L24; 5.3%), and pruritus (ICD-10:L29; 4.4%) (Table 3). It took a mean of 39.4 days for seborrheic dermatitis to become symptomatic and for the patient to be seen by a dermatologist after initial brain damage, 31.4 days for mycoses, 15.0 days for drug-induced skin eruption, and 47.1 days for xerosis cutis.

Table 1 Demographic data of 240 patients (age, sex).

Age (y)	Men ($n = 132$)	Women ($n = 108$)	Total, n (%) ($n = 240$)
<30	4	5	9 (3.7)
30–39	10	10	20 (8.3)
40–49	18	18	36 (15)
50–59	29	18	47 (19.5)
60–69	36	25	61 (25.3)
70–79	25	21	46 (19.2)
≥80	10	11	21 (9)

Table 2 Causes of brain damage in patients referred to a dermatologist.

Cause of brain damage	Patients, n (%)	Mean GCS score
Intracranial hemorrhage		
Traumatic intracranial hemorrhage	121 (50.4)	5.0
Spontaneous intracranial hemorrhage	69 (28.7)	7.7
Hypoxia	25 (10.4)	9.3
Metabolic disease	11 (4.6)	9.8
Brain tumor	6 (2.5)	10.6
Infectious disease	7 (2.9)	8.6
Total	240	6.8[a]

GCS = Glasgow Coma Scale.
[a] Average score of all patients.

Based on the level of brain damage using the GCS, 68.3% of patients were at the severe ($GCS \leq 8$) level (Table 4). The most common dermatological diseases in the severe group were mycoses (24.9%), seborrheic dermatitis (20.6%), and drug-induced skin eruption (18%). For the 25.5% of patients in the moderate ($9 \leq GCS \leq 12$) group, the common diseases were seborrheic dermatitis (20.6%), pruritus (13.8%), and drug-induced skin eruption (12.6%). For the 6.2% of patients in the mild ($GCS \geq 13$) group, the common diseases were seborrheic dermatitis (28.6%), pruritus (14.3%), and herpes simplex (14.3%). The incidence of mycoses is statistically significantly higher in the severe group ($p < 0.01$).

Discussion

The dermatological diseases of patients with brain damage are often overlooked during their period of admission to hospital because of many other complicated medical problems. Patients with brain damage have difficulty in describing their symptoms because of an alteration in consciousness, and this tends to delay diagnosis. However, we should also consider the fact that the opportunity to develop dermatological problems is relatively high in patients with brain damage. Decreased movement, altered immunity, and long-term stays in hospital provide suitable conditions for the growth of microorganisms, and treatment with antibiotics or aromatic anticonvulsant drugs (e.g. carbamazepine, phenytoin, phenobarbital, primidone, and oxcarbazepine) can cause severe adverse drug reactions. In particular, a recent study has shown that the central nervous system and the skin are connected by various mechanisms.[3] The fact that the skin and nervous system develop from the same embryological origin, share common molecular syntax, and communally utilize the immune system to provide signals and regulation, is generally acknowledged.[3,5] The central nervous system is directly or indirectly connected to the functioning of skin.[5] The direct connection is via efferent nerves or mediators derived from the central nervous system, and the indirect connection is via the adrenal glands or immune cells.[5] We thus speculate that damage of the central nervous system can contribute to the development of dermatological diseases.

In our study, 68.3% of the patients who were seen by a dermatologist had a severe alteration of consciousness. We believe that dermatological disease is likely to occur when a patient's brain damage is severe. The severe brain damage can cause immobilization. In addition, the patients with more severe brain damage tend to be treated with a larger number of drugs, such as anticonvulsant drugs, antibiotics, and diuretics.

The most frequent diagnosis was seborrheic dermatitis in 17.9% of the patients. Previous reports for a diagnosis of seborrheic dermatitis ranged from 3.1% to 5.2% of patients referred to a dermatologist.[2,6] It has long been recognized that patients with Parkinson's disease and mood disorder who have been treated with neuroleptic drugs often develop seborrheic dermatitis.[7] The

Table 3 Diagnoses (ICD-10 code).[4]

Disease	Patients, *n* (%)	GCS score	Duration (d)
Infections of the skin and subcutaneous tissue			
Cellulitis (L03.X)	3 (0.9)	5.3	
Cutaneous abscess, furuncle and carbuncle (L02.X)	1 (0.1)	7.0	
Viral infections characterized by skin and mucous membrane lesions	12 (3.5)		18.1
Herpes simplex (B00.1)	9	7.2	
Zoster (B02)	3	4.0	
Mycoses	53 (15.5)	4.9	31.4
Dermatophytosis (B35)	21	5.6	
Other superficial mycoses (B36)	3	9.3	
Candidiasis (B37)	29	4.0	
Scabies (B86)	1 (0.3)	5.0	
Neoplasms	12 (3.5)		
Melanoma and other malignant neoplasms of skin (C43-C44)	3	4.7	
Kaposi's sarcoma (C46)	1	6.0	
Benign neoplasms	3	11.7	
Carcinoma *in situ* of skin (D04)	2	11.5	
Secondary malignant neoplasm of skin (L79.2)	3	4.7	
Endocrine, nutritional and metabolic diseases			
Metabolic disorders (E70–E90)	1 (0.3)	3.0	
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism			
Allergic purpura (D69.0)	3 (0.9)	7.7	
Diseases of the circulatory system			
Phlebitis and thrombophlebitis (I80)	4 (1.2)	7.8	
Venous insufficiency (chronic) (peripheral) (I87.2)	2 (0.6)	11.0	
Diseases of the digestive system			
Other diseases of lip and oral mucosa (K13)	2 (0.6)	3.5	
Pregnancy, childbirth and the puerperium			
Other maternal disorders predominantly related to pregnancy (O20–O29)	2 (0.6)	8.0	
Diseases of the skin and subcutaneous tissue			
Bullous disorders (L10–L14)	1 (0.3)	12.0	
Dermatitis and eczema			
Seborrheic dermatitis (L21)	61 (17.9)	6.9	39.4
Diaper (nappy) dermatitis (L22)	7 (2.1)	4.5	
Allergic contact dermatitis (L23)	11 (3.2)	6.9	
Irritant contact dermatitis (L24)	18 (5.3)	8.0	
Dermatitis due to substances taken internally (drug eruption)	45 (13.2)		15.0
Generalized skin eruption due to drugs and medications (L27.0)	32 (9.4)	5.6	
Localized skin eruption due to drugs and medications (L27.1)	13 (3.8)	7.4	
Lichen simplex chronicus and prurigo (L28)	3 (0.9)	10.7	
Pruritus (L29)	15 (4.4)	10.0	
Papulosquamous disorders			
Psoriasis (L40)	2 (0.6)	9.5	
Urticaria and erythema			
Urticaria (L50)	10 (2.9)	7.8	
Erythema multiforme (L51)	6 (1.8)	5.8	
Erythema nodosum (L52)	2 (0.6)	6.0	
Other erythematous conditions (L53)	3 (0.9)	8.7	
Disorders of skin appendages			
Nail disorders (L60)	2 (0.6)	8.5	
Acne (L70)	4 (1.2)	8.3	
Other follicular disorders (L73)	4 (1.2)	7.5	
Other disorders of the skin and subcutaneous tissue			
Corns and callosities (L84)	2 (0.6)	12.5	
Xerosis cutis (L85.3)	31 (9.1)	6.9	47.1
Lupus erythematosus (L93)	1 (0.3)	10.0	
Vasculitis limited to skin, not elsewhere classified (L95)	5 (1.5)	6.2	
Chronic ulcer of skin, not elsewhere classified (L98.4)	3 (0.9)	8.7	
Amyloidosis of skin (L99)	1 (0.3)	9.0	
Medical devices associated with adverse incidents in diagnostic and therapeutic use (Y70–Y82)	8 (2.3)	8.9	
Total	341	6.8	

GCS = Glasgow Coma Scale.

organic change of the central nervous system due to brain injury may result in changes in various neuromediators and aggravate dermatitis. Furthermore, using various neuroleptic drugs in patients with brain damage can cause and worsen seborrheic dermatitis.

The second most frequent diagnosis in these patients was mycoses (15.5%) and the incidence was significantly higher in the group with severe brain injury ($p < 0.01$). This is most likely to be induced by a prolonged period of being confined to bed and the treatment of patients with brain damage with multiple antibiotic drugs.[8,9] A previous study reported that 9.5% of dermatology consultations were requested for mycosis.[2] The median time between admission to hospital (with consequent immobilization in bed) and the consultation for mycoses was 31.4 days (range 12–85 days). In a previous study for decubitus candidiasis, the median time was 24.8 days.[9]

In our study, 13.2% of the patients were diagnosed with skin eruption due to treatment with drugs. The prevalence of drug-induced skin eruption is higher here than in a previous study, which ranged from 4.2% to 10.5%.[2] This is because patients with

Table 4 Severity of brain damage determined by Glasgow Coma Scale score.

	Severe (≤8)	Moderate (9–12)	Mild (≥13)
Patients, *n* (%)	233 (68.3)	87 (25.5)	21 (6.2)
Three most common dermatological diseases, % of patients	1. Mycoses (24.9) 2. Seborrheic dermatitis (20.6) 3. Drug eruption (18)	1. Seborrheic dermatitis (20.6) 2. Pruritus (13.8) 3. Drug eruption (12.6)	1. Seborrheic dermatitis (28.6) 2. Pruritus (14.3) 3. Herpes simplex (14.3)

brain damage are treated simultaneously with multiple drugs, including anticonvulsant drugs, prophylactic antibiotics, antihypertensive drugs, and diuretics. A life-threatening drug reaction, such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome, can result from treatment with sulfonamide antibiotics and the aromatic anticonvulsant drugs (e.g. carbamazepine, phenytoin, phenobarbital, primidone, and oxcarbazepine), which are often administered to patients with brain damage.[10] It is widely accepted that the latent period of a drug reaction is approximately 2–6 weeks (mean 2–4 weeks).[11] The mean latency of drug-induced skin eruption was 15 days (range 3–45 days) in our study.

Another common disorder in our study was xerosis cutis, which occurred in 9.1% of patients. The incidence is higher than previous studies of consultations with inpatients (2.8%).[1,2,6] Xerosis is more common in elderly patients and the mean ± SD age of our patients with xerosis cutis was 76.5 ± 5.1 years. Elderly patients are more susceptible to xerosis due to pre-existing disease states, treatments, and prescribed drugs. Some of these pre-existing conditions include radiation, end-stage renal disease, nutritional deficiency (especially zinc and essential fatty acids), thyroid disease, and neurological disorders with decreased sweating, treatment with antiandrogen drugs, treatment with diuretics, human immunodeficiency virus, and malignancies. Multiple individual factors may contribute to xerosis cutis.

This study has a limitation in that many of the diagnoses were performed only by clinical impression without taking a skin biopsy sample or fungus culture. Also a computed tomography scan is preferable to the GCS in evaluating the severity of brain damage. Most of the patients included in our study were in the acute stage of brain damage. Over the past few years, several studies have repeatedly shown that bullous pemphigoid is associated with chronic neurological diseases, such as cerebrovascular disease, dementia, multiple sclerosis, and Parkinson's disease.[12–16] It is thought that bullous pemphigoid antigens or their isoforms in the central nervous system may be exposed after a neurological insult and may contribute to the generation of an immune response.[17] However, our study did not study long-term dermatological problems in the chronic stages of brain damage and did not analyze any molecular or immunological link between dermatological problems and neurological diseases. It was also unclear whether some patients had a past history of dermatological disease, such as seborrheic dermatitis, tinea pedis, or xerosis cutis. However, this study does provide the information that dermatological disorders in patients with brain damage may become symptomatic and require a consultation with a dermatologist.

In conclusion, we suggest that patients with brain damage are more likely to have dermatological diseases than both the general population and inpatients in general. This is due to various reasons, such as immobilization, treatment with multiple drugs, long-term stays in hospital, and their immunocompromised status. Furthermore, brain damage and its treatment can release steroid hormones and alter neuromediators, leading to an abnormal immune response and an aggravating inflammatory response in the skin. Although the exact mechanism has not been shown, the analysis of dermatological disorders in patients with brain damage can provide a better understanding of the "brain–skin connection".

References

1. Nahass GT. Inpatient dermatology consultation. *Dermatol Clin* 2000;**18**:533–42.
2. Penate Y, Guillermo N, Melwani P, Martel R, Borrego L. Dermatologists in hospital wards: an 8-year study of dermatology consultations. *Dermatology* 2009;**219**:225–31.
3. Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. *J Invest Dermatol* 2006;**126**:1697–704.
4. International Statistical Classification of Diseases and Related Health Problems 10th Revision 2010. Available at: http://apps.who.int/classifications/icd10/browse/2010/en
5. Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev* 2006;**86**:1309–79.
6. Tay LK, Lee HY, Thirumoorthy T, Pang SM. Dermatology referrals in an East Asian tertiary hospital: a need for inpatient medical dermatology. *Clin Exp Dermatol* 2011;**36**:129–34.
7. Gupta AK, Bluhm R. Seborrheic dermatitis. *J Eur Acad Dermatol Venereol* 2004;**18**:13–26.
8. Perlroth J, Choi B, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. *Med Mycol* 2007;**45**:321–46.
9. Nico MM, Rivitti EA. 'Decubital candidosis': a study of 26 cases. *J Eur Acad Dermatol Venereol* 2005;**19**:296–300.
10. Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, et al. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. *Neurology* 2011;**77**:2025–33.
11. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;**331**:1272–85.
12. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnaroska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: a case-control study. *Arch Dermatol* 2010;**146**:1251–4.
13. Stinco G, Codutti R, Scarbolo M, Valent F, Patrone P. A retrospective epidemiological study on the association of bullous pemphigoid and neurological diseases. *Acta Dermatol Venereol* 2005;**85**:136–9.
14. Kirtschig G, Walkden VM, Venning VA, Wojnarowska F. Bullous pemphigoid and multiple sclerosis: a report of three cases and review of the literature. *Clin Exp Dermatol* 1995;**20**:449–53.
15. Forschner A, Ulmer A, Rassner G, Fierlbeck G. Bullous pemphigoid in a patient with Parkinson's disease. *Eur J Dermatol* 2002;**12**:615 [Comment].
16. Cordel N, Chosidow O, Hellot MF, Delaporte E, Lok C, Vaillant L, et al., French Study Group of Bullous Diseases. Neurological disorders in patients with bullous pemphigoid. *Dermatology* 2007;**215**:187–91.
17. Taghipour K, Chi CC, Bhogal B, Groves RW, Venning V, Wojnarowska F. Immunopathological characteristics of patients with bullous pemphigoid and neurological disease. *J Eur Acad Dermatol Venereol* 2013;Mar 26. http://dx.doi.org/10.1111/jdv.12136 [epub ahead of print].