Darier’s Disease and Schizophrenia

Darier氏病与精神分裂症的关系

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Abstract

Darier’s disease, also known as Darier-White disease or keratosis follicularis, is a rare autosomal dominant genodermatosis. Clinical experience has long suggested an association between neuropsychiatric abnormalities and Darier’s disease. Although there are no formal epidemiological studies confirming this association, there have been a number of reports of patients with neuropsychiatric manifestations and Darier’s disease in the literature. However, most reports have come from Caucasian populations, with limited reports of Darier’s disease and its neuropsychiatric associations among Asian populations. This report describes 2 Asian patients presenting with associated schizophrenia and Darier’s disease.

Key words: Asian continental ancestry group; Darier disease; Schizophrenia

摘要

Darier氏病，亦稱Darier-White氏病／毛囊角化症，是一種罕見的自體顯性遺傳性皮肤病，臨床經驗一般認為這跟神經精神異常相關。尽管這種說法目前還未經流行病學研究证实，但不少醫學文獻曾記載有關神經精神異常和Darier氏病患者的病例報告。然而，大部分病例均來自白種人口，亞洲人口的只占少数。本文報告2宗精神分裂症和Darier氏病的亞裔患者病例。

關鍵詞：亞洲大陸血統群、Darier氏病、精神分裂症

Introduction

Darier’s disease is a rare autosomal dominant genodermatosis characterised by warty papules and plaques in the seborrhoeic regions, palmoplantar pits, and distinctive nail dystrophy. Darier1 and White2 first described the disease independently in 1889, and White2 initially suggested the genetic nature of the disease when he reported the simultaneous affliction of a mother and her child.

Darier’s disease occurs worldwide, with an estimated incidence of 4 per million per decade3 and an estimated prevalence ranging from 1 in 30,0004 to 1 in 100,000.5 In a retrospective study from Singapore, the incidence rate was found to be comparable to the global rate of 3.1 per million per decade.6 Men and women are affected equally; and the age of onset is typically in the second decade of life.7

During the past decade, significant advances have been made in elucidating the molecular basis of Darier’s disease. In 1993, a single locus for Darier’s disease was mapped to chromosome 12q23-q24.1.8 In 1999, mutations in the ATP2A2 gene were found to cause the disease. The ATP2A2 gene encodes the sarcoplasmic / endoplasmic reticulum calcium–adenosine triphosphatase isoform 2 protein (SERCA2),9 a calcium pump with a central role in intracellular calcium signalling. However, attempts at genotype-phenotype correlation have not been successful. Family members with confirmed identical ATP2A2 mutations can exhibit differences in the clinical severity of disease, suggesting that other genes or environmental factors affect its expression.10 Although expressivity is variable, penetrance is high at 95%.11

There have been descriptions of neuropsychiatric manifestations such as mental retardation,5,12-14 epilepsy,7 mood disorders,7,14-18 suicide,5,19 psychosis13,20 and schizophrenia21 in patients with Darier’s disease. In a local study of new patients with Darier’s disease seen at the National Skin Centre from 1982 to 2002, 3 of 24 unrelated patients had associated neuropsychiatric disorders.6 Reports of the association between Darier’s disease and neuropsychiatric disorders have mostly come from Caucasian populations. This report describes 2 unrelated Chinese patients with Darier’s disease who developed schizophrenia.
Case Reports

Patient 1
A 47-year-old Chinese woman with no prior history of psychiatric illness presented in November 2009. She was brought to the Institute of Mental Health, Singapore, after the police had found her walking into an open sea. She was initially agitated and restless, and was uncooperative during the interview. A corroborative history obtained from her daughter revealed that the patient had been unwell in the week prior to admission. According to her daughter, she had become increasingly irritable and was seen talking to herself. She had complained of children’s voices speaking to her, and believed that somebody had brainwashed her mind and wanted to take her life away. She did not abuse alcohol or other substances, and did not have any medical problems except for skin lesions since adolescence, for which she had not sought dermatological treatment. Premorbidly, she was sociable and was able to take care of her grandchildren and manage the household chores. Her mental state at admission revealed an unkempt and restless woman who was blunted in affect, and occasionally mumbled to herself. She also appeared preoccupied and was unable to engage in conversation. In the first few days after admission to hospital, she developed features of catatonia. She refused to talk, eat, or open her eyes, and required assistance with her activities of daily living (ADL). Extensive biochemical, haematological, and microbiological investigations performed on blood, urine, and cerebrospinal fluid did not reveal any abnormalities. Radiological investigations including magnetic resonance imaging of the brain and electroencephalography did not yield any significant findings.

A dermatological consultation was sought for assessment of her skin condition. Her mother and 3 other siblings had similar skin lesions. One of these siblings had schizophrenia and committed suicide in 1985. Another sister, who did not have the skin condition, had schizophrenia. Taking into consideration the characteristic clinical features and positive family history (Fig), a provisional diagnosis of Darier’s disease was made. The diagnosis was later confirmed by the histological findings from a skin biopsy. She was diagnosed with psychosis and given risperidone 2 mg/day orally. An antidepressant, fluvoxamine 50 mg/day orally, was later added when she was noted to be tearful and depressed in the ward. Her condition stabilised gradually and, in the third week of admission, she started to eat and could attend to her ADL independently. After 3 weeks, her condition improved further, and she was able to provide an account of hearing voices for at least the past year. Her diagnosis was revised to schizophrenia, and she was discharged with outpatient follow-up appointments for her psychiatric and dermatological conditions.

Patient 2
A 26-year-old Chinese woman presented with her second episode of psychosis in May 2009 after she was brought to the Emergency Department by her parents for odd and disorganised behaviour. She had first presented with a psychotic episode at the age of 21 years, and was diagnosed with Darier’s disease at the age of 17 years. She had no family history of dermatological or psychiatric conditions. During her first presentation with an episode of psychosis in 2005, she exhibited odd behaviours, such as refusal to go home, refusal to talk, increased irritability, and reduced hygiene. A trial of oral antipsychotics including risperidone 4 mg/day and trifluoperazine 15 mg/day orally was given. However, she had a poor response to the medications, and a course of electroconvulsive therapy (ECT) was administered. The patient eventually improved after 9 sessions of ECT, and was discharged 7 weeks after admission to hospital.

She was subsequently followed up by the Early Psychosis Intervention Programme, but later defaulted because she did not want to take antipsychotic medications which included olanzapine 15 mg/day and trifluoperazine 10 mg/day orally, and preferred to take traditional Chinese medicine instead. She remained well without treatment for about 1 year, and was able to attend college. However, she was readmitted to the Institute of Mental Health in 2008 for a second psychotic episode, which presented similarly to the first. During this admission, her skin condition had worsened, and a dermatological consultation was sought. The dermatologist diagnosed an acute exacerbation of Darier’s disease. She was given olanzapine 10 mg / day orally, and a gradual improvement in her mental state was noted. After discharge, she was followed up in the outpatient psychiatric clinic, and olanzapine was switched to sulpiride 200 mg/day orally due to financial concerns. She improved gradually, and became more forthcoming and reactive in affect. She was able to return to normal functioning after 6 months of sulpiride 200 mg/day orally. She was finally diagnosed with schizophrenia in view of the presence of at least 6 months of continuous signs of disturbances.

Discussion

This report of 2 patients highlights the association between Darier’s disease and schizophrenia. Darier’s disease is an autosomal dominant disease with high penetrance. In a local study, Goh et al reported that the demographic and clinical profiles of Asian patients with Darier’s disease was comparable to that of the western population in terms of incidence rate, age of onset, distribution of disease patterns, and wanted to take her life away. She did not abuse alcohol or other substances, and did not have any medical problems except for skin lesions since adolescence, for which she had not sought dermatological treatment. Premorbidly, she was sociable and was able to take care of her grandchildren and manage the household chores. Her mental state at admission revealed an unkempt and restless woman who was blunted in affect, and occasionally mumbled to herself. She also appeared preoccupied and was unable to engage in conversation. In the first few days after admission to hospital, she developed features of catatonia. She refused to talk, eat, or open her eyes, and required assistance with her activities of daily living (ADL). Extensive biochemical, haematological, and microbiological investigations performed on blood, urine, and cerebrospinal fluid did not reveal any abnormalities. Radiological investigations including magnetic resonance imaging of the brain and electroencephalography did not yield any significant findings.

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and association with neuropsychiatric disorders. However, there has only been a single case report describing the association between Darier’s disease and bipolar disorder in Taiwan.\(^\text{18}\) The present report aims to raise awareness of this rare dermatological condition and its association with psychosis among clinicians in this region where reports have been limited.

Certainly, future studies are necessary to prove that the observations made for these 2 patients were more than coincidence. However, psychiatrists and dermatologists should consider such an association in clinical practice. Heritability for schizophrenia has been estimated to be as high as 80%. Family, twin, and adoption studies provide evidence implicating genetic factors in the aetiology of schizophrenia.\(^\text{22}\) Molecular genetic approaches now provide the tools that will allow the identification of susceptibility genes. Promising findings are emerging, but no gene has been identified yet.

One of the strategies used for identifying susceptibility genes is to study their co-segregation with Mendelian disorders. The family of patient I illustrates such an opportunity as some of her members had co-occurrence of schizophrenia and Darier’s disease. There are 4 possible interpretations for this association. First, the association may be purely chance, with no true biological basis (chance hypothesis). Second, the psychiatric disorder could have been triggered by an understandable psychological reaction to the presence of a chronic disfiguring skin disease and is unrelated to biological susceptibility (reactive hypothesis). Third, the Darier mutation, through pleiotropic effect, could have increased vulnerability to neuropsychiatric illnesses (pleiotrophy hypothesis).\(^\text{23}\) Fourth, there could be a genetic linkage between the Darier gene and a separate susceptibility gene for schizophrenia (linkage hypothesis).\(^\text{24}\)

The argument for the association between Darier’s disease and neuropsychiatric disorders is strengthened by the observation that the skin and brain share a common ectodermal origin. There has been a gradual evolution towards conceptualising schizophrenia as a disorder of the brain neural circuits, of which intracellular calcium signalling in neurones plays an important role. More compellingly, the \textit{ATP2A2} gene that is mutated in Darier’s disease encodes SERCA2.

There have been 2 reports on the association of Darier’s disease and psychosis, both in Caucasian populations. Hellwig et al\(^\text{20}\) reported the simultaneous occurrence of exacerbation of Darier’s disease and the emergence of psychosis. In the only published linkage study, 4 markers in the Darier’s disease region on chromosome 12q were used to evaluate this association in 5 Canadian families.\(^\text{21}\) The study failed to provide evidence of genetic linkage, but the authors argued that since schizophrenia is a heterogeneous condition, the chromosomal region 12q might be important in other families segregating with schizophrenia.\(^\text{21}\) With the identification of the \textit{ATP2A2} gene causing Darier’s disease, perhaps examination of additional and larger families in which both disorders are segregating may help to identify susceptibility genes for schizophrenia in the future.

**References**