**Possible Piracetam-induced Raynaud’s Phenomenon in a Male Patient**

Raynaud’s phenomenon (RP) is characterized by episodic sharply demarcated color changes of the skin of the distal extremities. These changes are caused by recurrent vasoconstriction of the digital arteries and small arterioles in reaction to a stimulus, such as environmental cold or distress [1]. Secondary RP is usually caused by various connective tissue disorders (e.g., Sjögren’s syndrome, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis), occlusive arterial disease, systemic sclerosis, thoracic outlet syndrome, pulmonary hypertension, myxedema, trauma, or some drugs (including clonidine, ergot alkaloids, beta-adrenoceptor blockers, selective serotonin reuptake inhibitors, dopaminergic agonists, and stimulants) [1, 2]. But piracetam has never been included in this list. Furthermore, piracetam has never been included in several sequential and complementary studies [3]. Here, we report a case of an elderly male patient with RP possibly induced by piracetam.

**Case Report**

A 60-year-old unmarried male patient has a history of only a four-year education level as it was cut short due to a childhood learning disability. Mild mental retardation was diagnosed. His mother and three brothers also have a history of mental retardation or psychosis. He could do part-time cleaning work and did personal daily activities independently before the onset of psychosis. At the age of 22 years, he started to have psychotic symptoms with aggression, agitation, compulsive talking, insomnia, and bizarre behaviors. He had also several episodes of recurrent mania-related symptoms, and he was admitted to a hospital two times. Bipolar I disorder, recurrent mania with psychotic features, was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Because he had a poor support system, he was sent to a long-term care center where has been living for decades.

The patient developed a tongue protrusion, acute onset of bilateral finger twisting postures, psychomotor slowing, and worsened personal care about two years ago. Antipsychotic agent-induced dystonia could not be ruled out. A brain computed tomography (CT) showed a right anterior internal capsule lacunar infarct. After his medicines were changed to quetiapine 400 mg per day and some benzodiazepines as adjuvant therapies, his slow psychomotor was improved, but he still needed another’s partial help for daily personal care. His tongue protrusion was also improved, and he could use a spoon with his fingers. He took quetiapine 400 mg/day regularly for at least one year. During those days, he took daily flunitrazepam 4 mg, lorazepam 1 mg, and bethanechol 50 mg. Nevertheless, he had psychomotor retardation, increasing sexual need, declined cognitive function with misidentification to place, and urination on the floor of the nursing home for one month. He then received piracetam and the dose was titrated to 2,400 mg/day at our outpatient clinic. The above-described symptoms were not improved. But on the week following having regularly taking piracetam for a few days, the nurse found that all ten of his fingers were cold, as well as mixed pale and cyanotic colors (Figure 1a), while his bilateral metacarpals were warm. He did not have wound or other new physical or neurological symptom. The cyanosis persisted even with warming and postural changes of the hands. He did not have any history of trauma, strenuous exercise, superficial thrombophlebitis, or contact with a cold environment. The symptoms persisted for a few days. According to te Physician Global Assessment, the score of the severity for RP was 3. He then was brought back to our hospital for further study and treatment. Laboratory results (such as hematocrit, white blood cell and platelet counts, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and thyroid function) all were normal. His piracetam was discontinued; cold and cyanosis features of all fingers were rapidly improved and completely disappeared, one week after his piracetam was stopped (Figure 1b). Piracetam-induced RP was diagnosed.

The patient has been following up for six months at our outpatient clinic. So far, his mental and physical conditions have been stable without further symptoms of Raynaud.
syndrome. Based on a review of his recent changes of environment for possible causative factors of his physical condition, we identified that the piracetam was the one obvious variable after the piracetam was stopped.

**Comment**

RP symptoms commonly first occur in the winter as they did in this case. Because of mental disability, our patient could not actively express the color changes on his fingers, and it went unremarked until a worker noticed his RP. He did not complain of cold, numbness, or painful, even cyanosis affected all of his fingers. Fortunately, he did not have any gangrene. In addition to RP, we should also consider some other diseases, such as vascular occlusive syndromes, allergic dermatitis, cellulitis, and carpal tunnel syndrome. Our patient had the finding of a normal erythrocyte sedimentation rate, negative testing result for antinuclear antibodies, and the absence of structural micro- or macro-vascular damage or other diseases. We suggest that all older patients with new onset of RP should be carefully evaluated for any underlying cause because of a great likelihood of RP being secondary rather than primary. Although both primary and secondary RP most often affect the hands, the involvement of the thumb in particular is one of a number of clinical indicators that should alert a clinician to the possibility of a secondary cause of RP. Besides, a patient presenting with sharply demarcated color changes of the digits has primary RP due to reversible small- vessel vasospasm rather than secondary RP involving vasospasm plus structural disease in the microcirculation. Nailfold capillaroscopy is most commonly used to help distinguish primary RP from secondary RP. This patient did not receive nailfold capillaroscopy since his RP was remitted after discontinuing piracetam. Many conditions, such as systemic sclerosis, systemic lupus erythematosus, vasculitis, atherosclerosis, and hypothyroidism, can result in secondary RP. In this patient, we could rule out most systemic disease because he presented only symptoms on both hands. Besides, the symptoms were improved completely after discontinuing piracetam.

RP is thought to be the abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses [4]. In secondary RP, both endothelial damage and inhibition of vasodilation play a larger rôle [5]. Drugs reported to induce RP include sympathomimetics, bleomycin, interferons, ergotamine, nicotine, and polyvinyl chloride [5]. Components in drug development, and drug-related cause that are correlated with RP, include nitric oxide (NO), endothelin-1, alpha adrenergic receptor activation, abnormal signal transduction in vascular smooth muscle, oxidative stress, and platelet activation [6]. The acetylcholine is an endothelium-dependent and -independent vasodilator and stimulator of NO synthase [7, 8]. Resistance arteries from RP patients display an attenuated response to the endothelium-dependent dilator, acetylcholine, compared with normal vessels [8].

Piracetam is a cyclic derivative of the neurotransmitter \(\gamma\)-aminobutyric acid and is clinically being used as a nootropi
drug, but so far, the details of its neuroprotective mechanisms are not well-studied [9]. Although it has been studied in the treatment of primary and secondary RP in the past, it is not in a recent list of suggested medical treatments [6]. One study has shown that repeated piracetam administration resulted in regionally reduced levels of acetylcholine [10]. We suggest that the reduction of acetylcholine induces RP under repeated piracetam administration. But the investigators of that study focused on several regions of brain, such as hippocampus change, but not peripheral vessels [10]. It needs further study if the reduction of acetylcholine also presents in the peripheral vessels and induces RP under repeated piracetam administration.

The case report is limited due to a single case rather a series of patients. We did not re-challenge the patient with piracetam to reproduce the RP symptoms for strengthening the finding in this case. Furthermore, we did not assess our patient with Naranjo scale for estimating the probability of adverse drug reaction of piracetam [11].

So far, many controversial opinions exist about the effects of piracetam on cognition. For example, in some countries in Europe, it is used as a drug to improve memory and brain function. But the United States Food and Drug Administration does not consider piracetam to be a legal dietary supplement. Thus, it needs more studies to clarify the association between piracetam and RP. (This case report was approved by the institutional review board of National Cheng Kung University Hospital for publication [protocol number = B-ER-106-276 and date of approval = January 5, 2018]. Written informed consent from the patient was also obtained for the purpose of publication).

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**Conflicts of Interest**

The authors declare no conflicts of interest in writing this letter.

**References**


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