# Hypereosinophilic Syndrome with Recurrent Strokes: A Case Report

Wei-Lun Chang[1], Huey-Juan Lin[2], and He-Hsiung Cheng[3]

**Abstract-**

***Purpose:*** Hypereosinophilic syndrome is a rare disorder which can cause ischemic stroke. Although cardioembolism is acknowledged as the most common etiology for stroke, the underlying pathogenesis of hypereosinophilic syndrome could be heterogeneous. Herein we describe a patient with persistent hypereosnophillia with recurrent strokes focusing on the pathogenetic mechanism of stroke.

***Case report:*** A 43-year-old male patient with persistent primary eosinophilia presented with ischemic stroke which persisted for three weeks. Magnetic resonance imaging showed bilateral multiple cerebral infarctions over both anterior and posterior vascular territories. Segmental stenosis of the right posterior cerebral artery was revealed with magnetic resonance angiography and computed tomography angiography. Extensive laboratory workup ruled out other etiologies for the strokes except eosinophilia, which responded well to corticosteroid therapy.

***Conclusions:*** Cerebrovascular wall damage inflicted by eosinophilia may be the pathogenesis of the thromboembolic strokes in this case.

**Key Words:** Cerebrovascular diseases, Hypereosinophilic syndrome, Ischemic stroke

*Acta Neurol Taiwan 2008;17:184-188*

## INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare disorder characterized by marked and persistent eosinophilia with organ system dysfunction. HES has substantial clinical heterogeneity and a highly variable prognosis. We report a case of HES presenting with recurrent ischemic strokes over a period of three weeks and discuss the possible underlying pathogenesis.

## CASE REPORT

A 43-year-old man presented at the emergency room of our hospital with acute onset of unsteady gait and diplopia after waking up on the day of admission. On examination, he had mild limitation in vertical gazes, mild weakness in the right arm, and cerebellar ataxia in the right limbs. There were two enlarged lymph nodes in the left inguinal area. Chronic eczematous changes over

From the Departments of Neurology, [1]Chi Mei Medical Center, Liouying, Taiwan; [2]Chi Mei Medical Center, Tainan, Taiwan; [3]Division of Rheumatology in Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan.
Received January 30, 2008. Revised March 14, 2008.
Accepted April 18, 2008.

Reprint requests and correspondence to: Huey-Juan Lin, MD. Department of Neurology, Chi-Mei Medical Center, No. 901, Chung-Hwa Road, Yong-Kang, Tainan, Taiwan.
E-mail: huikuanlin@gmail.com

the dorsum of bilateral hands were noted. The past medical history elicited a significant two-decade nephrotic syndrome, which had remitted for 3 years. In addition, he had suffered from intermittent itchy erythematous eczema over the bilateral hands, forearms, and legs for 2 years. Brain magnetic resonance imaging (MRI) study showed multiple acute small infarcts over the left thalamus and centrum semiovale (Fig. 1). Etiology workup for stroke, including lipid profile, electrocardiogram, carotid duplex ultrasound, transcranial Doppler ultrasound, transthoracic echocardiogram (TTE), and tests for disseminated intravascular coagulation, was non-revealing. Mild leukocytosis (12,700 /mm$^3$) and elevated eosinophil count (1,134 /μL, normal range: < 600 /μL) were noted but obtained no special attention. Abdominal computed tomography (CT) scan revealed left parailiac and bilateral inguinal lymphadenopathy. Biopsy on one of the enlarged inguinal lymph nodes showed reactive lymphoid hyperplasia of follicular patterns. The patient was given oral aspirin 100 mg per day and recovered gradually from the neurologic deficits over the following weeks.

Three weeks after the first stroke, he was readmitted due to acute onset of right oculomotor nerve palsy. However, followed by progressive psychomotor slowing, decrease of spontaneous speech, dysphagia, and left hemiparesis were found in the first week after this admission despite adequate anticoagulation therapy. Brain MRI revealed new acute multiple infarcts in the right midbrain, occipital cortex, thalamus, and bilateral subcortical white matter. Intracranial magnetic resonance angiography (MRA) showed marked segmental stenosis in the right posterior cerebral artery (PCA) (Fig. 2).

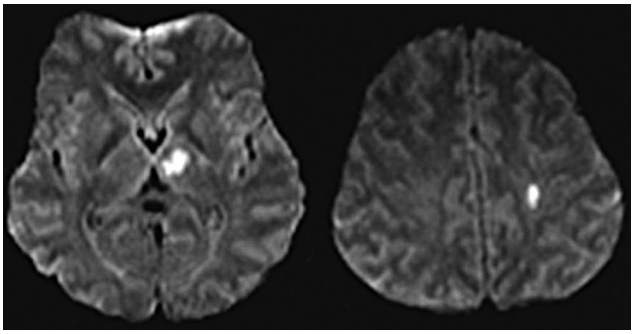

**Figure 1.** Axial MRI diffusion weighted imaging on the first stroke shows acute infarcts over the left thalamus and left centrum semiovale.

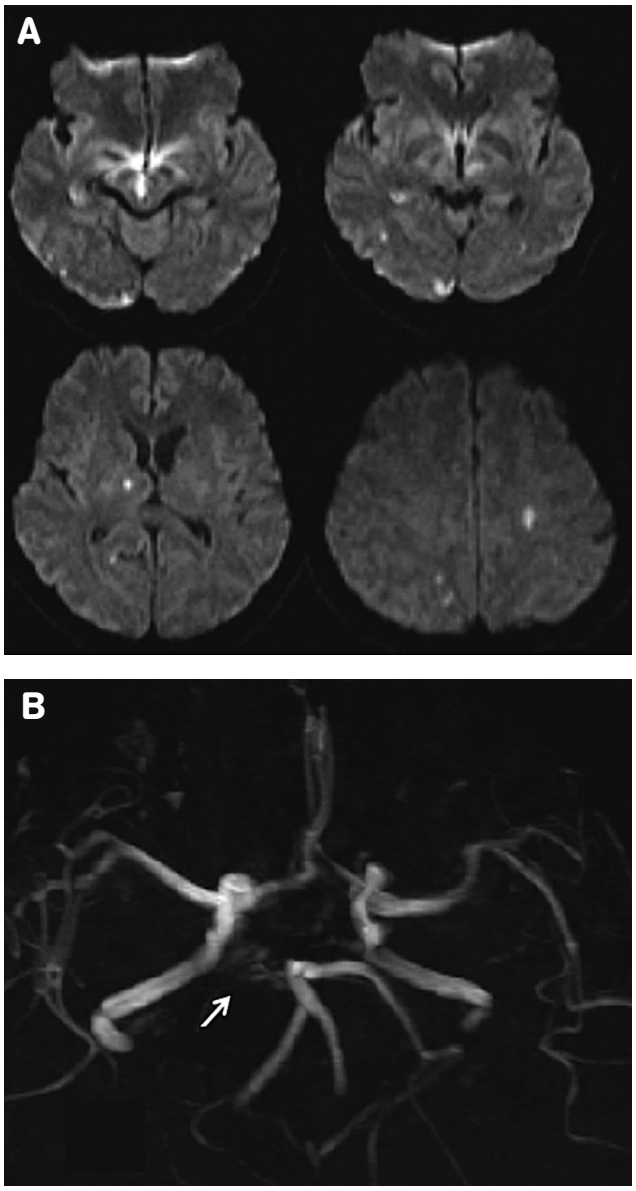


**Figure 2.** (A) MRI diffusion weighted imaging on the second stroke shows new small infarcts over the right central midbrain, occipital cortex, thalamus, and bilateral subcortical white matter. (B) MR angiography reveals decreased flow in the right posterior cerebral artery (arrow).

More laboratory tests to search for the cause of stroke, including transesosphageal echocardiogram (TEE), proteins C and S, antithrombin III, antinuclear antibody, anti-phospholipid antibody, anti-human immunodeficiency virus antibody, rapid plasma reagin for syphilis, erythrocyte sediment rate, anti-Sjogren's syndrome A and B antibodies, perinucear anti-neutrophilic cytoplasmic antibody, cytoplasmic anti-neutrophilic cytoplasmic antibody, and cerebrospinal fluid studies, were all negative or inconclusive. Mild vitamin B12 level elevation was detected (1132 pg/ml, normal range: 180-914 pg/ml), but there were no anemia, thrombocytopenia, hepatomegaly or splenomegaly. The reports of a bone marrow biopsy and the leukocyte alkaline phosphatase score were normal, ruling out the possibility of chronic myeloproliferative disease. In 5 serial examinations during the acute stage of both stroke events before initiation of steroid therapy, the blood eosinophil counts were fluctuating between the levels of 936-2,256 /μL. A high serum immunoglobulin E (IgE) level (6,450 IU) was also noted. No parasites or ova were found on stool examination, and the serum anti-amoeba antibody was within normal limits.

Under the diagnosis of HES, the patient received intravenous hydrocortisone 100 mg per 6 hours for one day, and the blood eosinophil count became zero on the next day. He continued oral prednisolone 60 mg per day for two weeks, and the eosinophil counts remained within the normal range. Tapering of steroid was successful, with no recurrence of eosinophilia on daily 10 mg prednisolone. The neurological deficits improved with limited magnitude, but his skin lesions in the hands and legs completely subsided. Three months later, he was left with moderate disability. Cerebral computed angiography (CTA) at this time demonstrated the persistent stenosis in the right PCA (Fig. 3). He continued the low-dose daily prednisolone (10 mg qd) treatment, which successfully controlled the eosinophilia. Two attempts to lower prednisolone dosage to 7.5 mg per day were unsuccessful because eosinophilia recurred (1,590 /μL and 1,610 /μL). The patient remained free of further stroke recurrence and skin lesions during the two-year follow-up period.

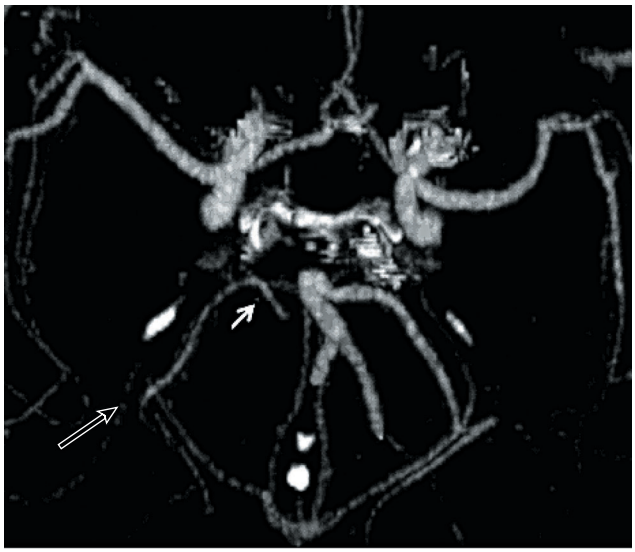

**Figure 3.** CT angiography 3 months after the second stroke demonstrates the persistent stenosis in the right posterior cerebral artery (arrow).

## DISCUSSION

Acquired eosinophilia can be divided into primary and secondary. Common causes of secondary eosinophilia include parasite infection, allergic disorders, medications, toxins, autoimmune diseases, endocrine disorders, and malignancies in which eosinophils are not considered part of the neoplastic clone. Primary eosinophilia includes clonal and idiopathic eosinophilia. Clonal eosinophilia encompasses acute leukemia and chronic myeloid disorder. If after a thorough examination, no cause of clonal or secondary eosinophilia can be identified, a diagnosis of idiopathic eosinophilia must be considered[1]. HES is a subcategory of idiopathic eosinophilia. The diagnostic criteria of HES include (1) blood eosinophilia >1,500 /μL for more than 6 months, (2) absence of an underlying cause of eosinophilia despite extensive diagnostic evaluation, and (3) evidence of organ system involvement[2]. Basically, a diagnosis of HES is one of exclusion[3]. In our patient, blood eosinophil count was never checked before the vascular events. Although during tapering of steroid therapy, the eosinophil count did flare up to > 1500 /μL, it was not

possible to keep observing the laboratory tests without interventions. Even though the patient did not completely fit the first diagnostic criterion of eosinophilia duration due to practical reasons, after excluding other possibilities, HES was the most likely diagnosis attributed to the clinical manifestations of the skin and the cerebrovascular system.

Although the exact mechanism of eosinophil-related tissue damage is not well known, eosinophil accumulation appears to have pathological consequences. Eosinophils have direct cytotoxiciy through the local release of toxic substances including cationic proteins, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid derived factors[4-5]. The degree of end-organ damage is heterogeneous, and there is often no correlation between the level or duration of eosinophilia and the severity of organ damage[6]. Three types of neurological manifestations are recognized in patients with HES[6-7]: (1) primary central nervous system dysfunction, (2) peripheral neuropathy, and (3) neurological consequences of thromboembolism. Cardiac involvement is often the source of the thromboembolism, with thrombi formation in areas of damaged endocardium[6]. Through the development of thromboemboli, patients with HES may experience embolic strokes or transient ischemic attacks, which may be multiple and recurrent[7-8]. In our patient, neuroimaging studies revealed multiple infarcts in the territories of both anterior and posterior circulations, with the major clinical neurological deficits from the vertebrobasilar system. However, no cardiac thrombus or structural anomaly was found with TTE and TEE. The possibility of cardioembolism causing the strokes seemed low. Furthermore, the focal stenosis of the right PCA evidenced in both MRA and CTA indicated a primary vascular lesion, which might have led to the recurrent thromboembolic symptoms and signs in the corresponding territories. Although the MRA could not depict smaller branches of the carotid system, we speculated that the bilateral small infarcts over the anterior circulation might be similarly due to thromboembolism of the damaged branches of the middle cerebral arteries. Direct eosinophilic toxicity to a vascular wall, either on arterial or venous vessels, were implicated in sparse reports[9-11]. Based on the results from the thorough clinical and laboratory tests, the most likely pathogenesis in our case was most likely multiple cerebrovascular damage as a result of eosinophilia causing thromboembolic infarction in multiple sites of the brain.

Currently, available therapies for HES are not adequate and there is no cure. The goals for the treatment of HES are to reduce peripheral and tissue levels of eosinophils, and prevent end-organ damage and thromboembolic events in patients at risk[12-14]. Antiplatelet agents and anticoagulants have no effect in thromboembolic prevention. Corticosteroids are considered the first-line therapy[6,13-14]. For patients refractory to steroids, the alternatives include cytotoxic agents (hydroxyurea, vincristine, cyclophosphamide), biological response modifiers (interferon-alpha, cyclosporine), or targeted therapy (imatinib mesylate, mepolizumab)[15]. High-dose prednisolone is typically initiated at a dose of 1 mg/kg/day[6,13]. Once eosinophilia is properly controlled, the drug can be tapered gradually[13]. Chronic maintenance therapy has been recommended as a more effective method to prevent the development of end-organ damage[6]. Patients who will respond to corticosteroid therapy can usually be identified early in the course of therapy, often on the first day[13], as in our case.

In conclusion, HES might cause recurrent ischemic strokes through vascular lesions other than cardioembolism. For young stroke patients without traditional vascular risk factors, an appropriate differential count of white blood cells would be indicated in order to detect this rare and treatable disease.

## REFERENCES

1. Tefferi A. Blood eosinophilia: a new paradigm in disease classification, diagnosis, and treatment. Mayo Clin Proc 2005;80:75-83.
2. Chusid MJ, Dale DC, West BC, et al. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) 1975;54:1-27.
3. Bain BJ. Hypereosinophilia. Curr Opin Hematol 2000;7:21-

5.
4. Roufosse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. Annu Rev Med 2003;54:169-84.
5. Gleich GJ. Mechanisms of eosinophil-associated inflammation. J Allergy Clin Immunol 2000;105:651-63.
6. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994;83:2759-79.
7. Moore PM, Harley JB, Fauci AS. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. Ann Intern Med 1985;102:109-14.
8. Spry CJ, Davies J, Tai PC, et al. Clinical features of fifteen patients with the hypereosinophilic syndrome. Q J Med 1983;52:1-22.
9. Kumar KA, Anjaneyulu A, Murthy JM. Idiopathic hypereosinophilic syndrome presenting as childhood hemiplegia. Postgrad Med J 1992;68:831-3.
10. Prick JJ, Gabreëls-Festen AA, Korten JJ, et al. Neurological manifestations of the hypereosinophic syndrome (HES). Clin Neurol Neurosurg 1988;90:269-73.
11. Kanno H, Ouchi N, Sato M, et al. Hypereosinophilia with systemic thrombophlebitis. Hum Pathol 2005;36:585-9.
12. Fauci AS, Harley JB, Roberts WC, et al. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 1982;97:78-92.
13. Roufosse F, Bartholomé E, Schandené L, et al. The idiopathic hypereosinophilic syndrome: clinical presentation, pathogenesis and therapeutic strategies. Drugs Today (Barc) 1998;34:361-73.
14. Yoon TY, Ahn GB, Chang SH. Complete remission of hypereosinophilic syndrome after interferon-alpha therapy: report of a case and literature review. J Dermatol 2000;27:110-5.
15. Wilkins HJ, Crane MM, Copeland K, et al. Hypereosinophilic syndrome: an update. Am J Hematol 2005;80:148-57.