A Diagnostic Algorithm for Eosinophilic Granulomatosis with Polyangiitis Initially Diagnosed as Lumbar Disc Hernia or Lumbar Spinal Stenosis: Personal Experience and Review of the Literature

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Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is a rare systemic vasculitis and is difficult to diagnose. EGPA has a number of symptoms including peripheral dysesthesia caused by mononeuropathy multiplex, which is similar to radiculopathy due to lumbar disc hernia or lumbar spinal stenosis. Therefore, EGPA patients with mononeuropathy multiplex often visit orthopedic clinics, but orthopedic doctors and spine neurosurgeons have limited experience in diagnosing EGPA because of its rarity. We report a consecutive series of patients who were initially diagnosed as having lumbar disc hernia or lumbar spinal stenosis by at least 2 medical institutions from March 2006 to April 2013 but whose final diagnosis was EGPA. All patients had past histories of asthma or eosinophilic pneumonia, and four out of five had peripheral edema. Laboratory data showed abnormally increased eosinophil counts, and nerve conduction studies of all patients revealed axonal damage patterns. All patients recovered from paralysis to a functional level after high-dose steroid treatment. We shortened the duration of diagnosis from 49 days to one day by adopting a diagnostic algorithm after experiencing the first case.

Key words: eosinophilic granulomatosis with polyangiitis, mononeuropathy multiplex, lumbar disc hernia, lumbar spinal stenosis, nerve conduction study

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA) is a systemic necrotizing vasculitis that invades small to medium vessels [1, 2], and it is difficult to diagnose because of its rarity [3]. The primary symptoms often arise from asthma or eosinophilic pneumonia, and mononeuropathy multiplex occurs in 50–78% of all EGPA patients [1, 4, 5]. Mononeuropathy multiplex in the lower extremities causes muscle weakness and dysesthesia, and these symptoms are similar to radiculopathy due to lumbar disc hernia (LDH) or lumbar spinal stenosis (LSS) [6]. Therefore, some patients visit orthopedic clinics [7]. However, orthopedic doctors and spine neurosurgeons as well as physicians have few opportunities to diagnose or treat EGPA patients because of its rarity. Because mononeuropathy multiplex of EGPA requires early diagnosis and high-dose steroid treatment [4, 5], delays in diagnosing EGPA should be avoided [7].

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From March 2006 to April 2013, we experienced consecutive series of 5 patients who were introduced to our department by other clinics as LDH or LSS patients but who fulfilled the American College of Rheumatology (ACR) diagnosis criteria for EGPA (Table 1) [8]. All patients had visited more than 2 institutions prior to coming to our department. Four were initially diagnosed as having LDH and one as having LSS. Lumbar lesion was ruled out with magnetic resonance imaging (MRI) or physical examination by at least 2 spine surgeons. Similarly, diabetic radiculopathy was ruled out (fasting blood glucose was found to be less than 110mg/dl before breakfast two or more times).

Here, we report a case series of EGPA initially diagnosed as LDH or LSS by at least two medical institutions. To the best of our knowledge, no previous report detailing the clinical prognosis of peripheral neuropathy in the lower extremities associated with EGPA has been documented.

Case Reports

Case 1. A 58-year-old female patient suffered from pain in both legs for 3 months and diarrhea with abdominal pain for 1 month. She was introduced to our institute as a having radiculopathy of LSS. She had been diagnosed with asthma 9 years previously. In a physical examination, she showed pitting edema and muscle weakness in both lower limbs (Table 2) and dysesthesia in both feet. She did not have low back pain. Straight leg raising (SLR) and femoral nerve stretch test (FNST) were negative. An X-ray showed degenerative scoliosis, but an MRI did not display narrowing of the lumbar spinal canal (Fig. 1A). Blood tests revealed a white blood cell (WBC) count was 20,800/µl and eosinophil percentage was 48.7. Chest imaging did not show enlarged lymph nodes but displayed peribronchial thickness and minor pulmonary infiltrates. A nerve conduction study (NCS) showed an axonal neuropathy pattern. A biopsy of her left sural nerve was compatible with small vessel vasculitis and eosinophilic granulomatosis with polyangiitis (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>American College of Rheumatology diagnosis criteria for eosophilic granulomatosis with polyangiitis [8]</th>
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<tbody>
<tr>
<td>Asthma (wheezing, expiratory rhonchi)</td>
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<td>Eosinophilia of more than 10% in peripheral blood</td>
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<td>Paranasal sinusitis</td>
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<td>Pulmonary infiltrates (may be transient)</td>
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<td>Histological proof of vasculitis with extravascular eosinophilis</td>
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<td>Mononeuritis multiplex or polyneuropathy</td>
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The presence of four or more criteria yields a sensitivity of 85% and a specificity of 99.7%.

<table>
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<tr>
<th>Table 2</th>
<th>The characteristics and recovery process of our case series</th>
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<tr>
<td></td>
<td>patient 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58</td>
</tr>
<tr>
<td>sex</td>
<td>female</td>
</tr>
<tr>
<td>Past history asthma</td>
<td>asthma</td>
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<tr>
<td>Duration</td>
<td>49 days</td>
</tr>
<tr>
<td>Quad</td>
<td>5/5</td>
</tr>
<tr>
<td>TA</td>
<td>2/2</td>
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<td>EHL</td>
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<td>FHL</td>
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<td>GS</td>
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Duration means the number of days from first visit to the start of treatment. The figure showed the strength of the right muscle/left muscle on a scale of 0–5 based on the Medical Research Council scale. Quad, quadriceps muscle; TA, tibialis anterior muscle; EHL, extensor hallucis longus muscle; FHL, flexor hallucis longus muscle; GS, gastrocnemius muscle.
axonal damage. She was treated with prednisolone and later with intravenous cyclophosphamide. Her muscle weakness improved, but minor dysesthesia remained.

Case 2. A 59-year-old female patient presented a severe pitting edema and drop-foot and severe dysesthesia in her right leg over four weeks. Her past medical history included eosinophilic pneumonia within the previous three years. A physical examination revealed severe muscle weakness of her tibialis anterior and extensor hallucis longus. She had minor chronic low back pain, but SLR and FNST were negative. An MRI did not reveal LDH (Fig. 1B). Blood tests showed marked eosinophilia (WBC 29,600/µl and eosinophil percentage 48.5%), and NCS showed a mononeuropathy multiplex pattern. A sural nerve biopsy was performed, and it showed eosinophilic infiltration and fibrosis of her sural nerve. Successive treatment with high-dose oral prednisolone led to a gradual response. Moderate improvement of her anterior tibial muscle was observed, but the dysesthesia remained.

Case 3. A 49-year-old female suffered from dysesthesia in her left foot for one week, and the dysesthesia spread to her lateral leg. She visited an orthopedic clinic, and LDH was suspected after a physical examination. After edema emerged in her left leg, she was admitted to our hospital. She did not have low back pain. SLR and FNST were negative. An MRI was not performed because her muscle weakness was moderate, so no emergency MRI was needed before consulting the Department of Rheumatology. Her past medical history included asthma for 13 years. Physical examinations showed muscle weakness, hyporeflexia, hypoaesthesia and pitting edema in the left lower leg. Blood tests revealed eosinophilia (WBC 25,500/µl and eosinophil percentage 70.5%) and a lung CT and chest X ray showed enlarged lymph nodules and pulmonary infiltration. NCS revealed a slightly decreased amplitude of the peroneal nerves. Treatment with prednisolone caused rapid improvement of all symptoms.

Case 4. A 53-year-old female patient was admitted due to suspicion of LDH with right L5 or S1 root radiculopathy. She had complained of severe dysesthesia in the lateral side of her right thigh for 2 weeks and had dropped foot and minor edema. However, an MRI did not show compression of the nerve roots (Fig. 1C). Her past medical history was significant in that she was diagnosed with asthma at the age of 30. She sometimes used oral prednisolone at a maximum dose of 20mg. Physical examinations were compatible with both radiculopathy and peripheral

Fig. 1  A, Lumbar spine MRI T2/WI of patient 1. She had a severe loss of muscle strength in the tibialis anterior (TA), extensor hallucis longus (EHL), flexor hallucis longus (FHL), and gastrocsoleus (GS). Patient 1 was introduced as an LSS patient; in the sagittal image, the alignment showed normal lordosis with a narrow disc height, and there was no redundancy. There was no nerve root compression in the axial images in L4/5 and L5/S; B, Lumbar spine MRI T2/WI of patient 2. She was introduced as an LDH patient with drop-foot. In the sagittal image, the alignment showed normal lordosis, and we did not observe narrowing of the spinal canal. There was no nerve root compression on the axial images in L4/5 and L5/S; C, Lumbar spine MRI T2/WI of patient 4. She was not able to move her right TA or EHL, and she lost muscle strength in her right FHL and GS. Patient 4 was introduced as an LDH patient with suspected right L5 or S1 compression. Minor disk density changes were observed in L4/5 and L5/S in the sagittal image. There was no nerve root compression in the axial images in L4/5 and L5/S.
neuropathy, but SLR and FNST were negative. She did not have low back pain. Blood tests revealed significant eosinophilia (WBC 16,000/µl and eosinophil percentage 74.5%). Her chest X ray showed pulmonary infiltration. NCS showed axonal damage patterns of her right peroneal, tibial, and sural nerves (Fig. 2). A rapid and significant improvement was observed after high-dose prednisolone and intravenous immunoglobulin treatment. Sixteen months later, the patient continued to suffer from minor dysesthesia, but her right leg weakness had improved.

**Case 5.** An 84-year-old male patient claimed that he could not maintain a standing position and had severe dysesthesia in his left leg over the previous one week. He was introduced to our department as an LDH patient. His past medical history included asthma in the previous year and sick sinus syndrome with pacemaker insertion 6 years before. A physical

![Image of nerve conduction velocity charts]

**NR** indicates not recorded.
**MCV** indicates motor nerve conductive velocity and **SCV** indicates sensory nerve conduction study.

Fig. 2 The nerve conduction velocity of patient 4 is shown in the right peroneal nerve (A1), left peroneal nerve (B1), right tibial nerve (A2), left tibial nerve (B2), right sural nerve (A3), and left sural nerve (B3). We also show the motor nerve conduction velocity or sensory nerve conduction velocity of each nerve (C1, C2, and C3). Her right tibial nerve showed a normal motor nerve conduction velocity and low amplitude, which corresponded to multiple axonal damage patterns. Moreover, her right peroneal and sural nerve conduction velocity could not be recorded. NR means non-recordable.
examination revealed severe weakness of his left quadriceps. But his FNST and SLR were negative, and he had minor chronic low back pain. Blood tests showed marked eosinophilia (WBC 25,700/µl and eosinophil percentage 63.5%), and NCS showed a multiplex mononeuropathy pattern including his left femoral nerve. His CT scan and chest X ray showed pulmonary infiltration. High-dose oral prednisolone led to a gradual response. One year after the treatment, he was able to stand and walk by himself despite minor dysesthesia around his left knee. Pregabalin relieved his dysesthesia around his left knee. 

Discussion

In 1951, Churg and Strauss [9] first described a syndrome characterized by asthma and symptoms of cardiac failure, renal damage and peripheral neuropathy resulting from vascular embarrassment in various systems of organs. This disease was known as Churg-Strauss syndrome for many years, and this entity was renamed and recognized as EGPA at the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [10, 11]. EGPA has 3 stages, each of which has distinctive clinical symptoms [2]. Stage I can last for several years. Atopic asthma and rhinitis are the predominant features of this stage, and they are usually difficult to control. Stage II is an eosinophilic stage. Eosinophil infiltration is seen in various organs, including the lungs and the gastrointestinal tract. In stage III, systemic vasculitis is observed with general symptoms including skin lesions, peripheral neuropathy, fever, weight loss, kidney disorder, or mononeuropathy multiplex. It takes nine years on average to advance from the first stage to the third stage [4]. Therefore, in most patients, the upper airway allergy is evident until the development of vasculitis, which causes radiating pain or diffuse deep pain in the affected legs [12, 13]. All our patients characteristically had past histories of asthma or eosinophilic pneumonia. And 4 out of our 5 patients had peripheral edema. Local edema on the skin of the involved region was observed in EGPA [22], but it is not specific to radiculopathy. A past history of upper airway allergies and local edema is characteristic when mononeuropathy multiplex in association with EGPA is taken into consideration, so blood tests, NCS, and biopsies should be considered as options.

Differentiating mononeuropathy multiplex due to GPA from other diseases association with peripheral neuropathy is important. The differential diagnosis for mixed motor and sensory multiple mononeuropathy includes diabetic neuropathy, vasculitides, sarcoidosis, infectious processes (e.g., leprosy, Lyme disease, syphilis, and cytomegalovirus infection), amyloidosis, and neoplastic infiltration (most commonly lymphomatous) [14]. All such diseases were ruled out by blood test or image study, including whole body CT scans, in our case series after admission.

All patients in our series had subacute paralysis of the lower extremities and severe dysesthesia. Mononeuropathy multiplex is observed in 50–78% of EGPA patients [1, 4, 5]. Hattori N et al. reported that the frequency of individual nerve involvement, as judged by sensory impairment, was highest in the common peroneal nerves, followed by the tibial, sural, ulnar, and median nerves [4]. In our series, peroneal nerve palsy could be ruled out because 4 of our patients experienced muscle weakness of both the anterior tibialis and gastrocnemius, which does not correspond to peroneal nerve palsy. Patients with EGPA are reported to have radiating pain or diffuse deep pain in the affected legs [12, 13]. These symptoms are similar to those of radiculopathy and peripheral neuropathy [6]. However, the neurological symptoms of our case series had some different features that differed from those of acute monoradiculopathy caused by LDH [12], which was reported to have 58–88% prevalence of a positive SLR result [15]. Although the diagnostic accuracy is limited by its low specificity, the lack of a tension sign or minor low back pain might be helpful to rule out radiculopathy in spine diseases because of their high sensitivity [15].

We ordered emergency MRIs for 3 patients in order to rule out LDH or LSS, and the results were negative. It has been reported that MRI is painless, that it does not subject the patient to radiation exposure, and that it has imaging modalities for diagnosing LDH [16]. If these results were positive, the clinical course might have been complicated because emergency operations would then have been considered. One report showed that patients with bilateral drop-foot had both LDH and EGPA [7]. In that case report, the female patient was diagnosed as LDH
initially, and surgical resection of the disc was performed. However, her toes and calcaneal areas gradually became necrotic. Afterward, she was diagnosed with EGPA, and both legs required amputation. In order to improve the prognosis of EGPA neuropathy, early high-dose steroid treatment is essential [4, 5].

A separate case report of an EGPA patient is also of interest here. Kukita and associates reported a patient who was diagnosed with both EGPA and spinal hematoma by MRI examination. This patient suffered from urinary incontinence and bilateral leg paralysis [17]. Considering the differential diagnosis and complications, an MRI may be needed for patients with paralysis of the lower extremities.

We performed NCS on all patients to differentiate radiculopathy from mononeuropathy multiplex [18]. NCS is less invasive than a nerve biopsy. We performed sural nerve biopsies only in patients 1 and 2 (Fig. 3), for whom 49 days and 10 days were needed, respectively, to make a diagnosis of EGPA. NCS of EGPA patients showed axonal degeneration patterns [5], in which the compound motor action potential and sensory nerve action potential of damaged nerves were decreased or not evoked, while no delay of conduction velocity was seen. On the other hand, sensory NCSs are normal in radiculopathy, even if the physical examination reveals significant sensory loss. Compound motor action potentials are normal if the peripheral nerve is damaged. When multiple root levels are involved, there may be some diminished amplitude in such radiculopathy cases [18, 19]. Both MRI and NCS are feasible tests for detecting the cause of paralysis and dysesthesia of the lower extremities when the laboratory data are abnormal.

Because of the rarity of EGPA, a delay of the diagnosis might occur in orthopedic departments even in university hospitals, although EGPA may not be rare in neuropathic units [20]. Therefore, we adopted a diagnostic algorithm (Fig. 4) after our experience with patient 1 in our department. Between patients 1 and 5, we were able to shorten the number of days required to make a diagnosis from 49 days to one day. The laboratory data of EGPA peripheral neuropathy tend to be impressive compared with those of radiculopathy caused by LDH. All our patients’ WBC and eosinophil counts were elevated, and their C-reactive protein level was also increased. These results correspond with those of other reports [4, 5], and we used WBC to screen whether the patients’ clinical information corresponded to EGPA. However, anti-neutrophilic cytoplasmic antibodies (ANCA), which are characteristic of EGPA, were negative in all of

![Fig. 3](image_url)  
**A.** Biopsy section of left sural nerve of patient 1 (hematoxylin and eosin stain). The sural nerve was totally replaced with fibrosis, and there was no axonal tissue. Fibroblast cells around the perineuria were observed, but Schwann cells were not observed. This image was compatible with small vessel vasculitis and axonal damage; **B.** Biopsy section of right sural nerve of patient 2 (hematoxylin and eosin stain). Eosinophils (arrow) infiltrated into her sural nerve which was totally replaced by fibrosis. Neuronal vacuolation was observed in nerve fascicles.
symptoms recovered to a functional level, including the dropped foot (Table 2). As for peripheral dysesthesia, the area was narrowed and the symptoms were relieved to some extent, but the annoying dysesthesia remained. Pregabalin relieved these symptoms. In order to decrease axonal damage, early diagnosis and steroid treatment are essential [4, 5].

In conclusion, orthopedic doctors and spine neurosurgeons should be familiar with the characteristic EGPA clinical history in order to make early diagnoses, because EGPA stage III is sometimes misdiagnosed as LDH or LSS. When we encounter patients who complain of dysesthesia of their lower extremities and who have medical histories of asthma or eosinophilic pneumonia, laboratory data and MRI are suitable for making an early diagnosis. Subsequently, NCS and biopsies are important for the accurate diagnosis of EGPA.

References


