

Flaccid Paralysis of the Limbs After an Asthmatic Attack

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Acute exacerbations of asthma are common in children, but limb weakness after such exacerbations is very unusual. Hopkins' syndrome, a poliomyelitis-like illness associated with asthma, is seldom reported in the literature. We describe a child with weakness of the lower limbs after an asthmatic attack. The clinical profile, possible pathogenesis, and treatment of Hopkins' syndrome are discussed. © 2010 by Elsevier Inc. All rights reserved.

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Introduction

Hopkins' syndrome (poliomyelitis-like illness associated with asthma or asthmatic amyotrophy) was first described by Hopkins [1] in 1974. It is a rare disorder. The affected child manifests weakness of the limbs 4-11 days after the onset of asthmatic attack and during the recovery period from bronchospasm. Flaccid paralysis of one or more limbs occurs. The child will likely exhibit significant morbidity, with poor recovery of the paralyzed muscles. Few patients manifest pleocytosis in the cerebrospinal fluid, and no poliomyelitis virus has been isolated from the cerebrospinal fluid in documented cases. We recently encountered a child who presented with weakness of the lower limbs after an acute exacerbation of asthma. We discuss the clinical profile and possible mechanisms

for the pathogenesis of Hopkins' syndrome, and its treatment.

Case History

A 7-year-old boy of Southeast Asian descent presented at our Emergency Room with difficulty breathing, after a 2-day history of cough and wheeze. He had manifested a mild exacerbation of asthma 3 months earlier. During the present admission, he was in severe respiratory distress. He was admitted to the Intensive Care Unit, and was treated with nebulized salbutamol and intravenous hydrocortisone and ceftriaxone. His condition stabilized, and he was discharged home after 3 days. He again presented at the Emergency Room 2 days later, this time with complaints of difficulty walking.

In terms of past medical history, the boy was the product of an uncomplicated pregnancy. His birth weight was 7 pounds. No previous developmental concerns had been evident, and he was performing well at school. He was up to date with all immunizations, including polio. He had received his most recent doses of diphtheria, tetanus, and polio vaccines 1 year earlier. There was no family history of neuromuscular disorders.

On examination in the Emergency Room, he was alert and orientated, with no speech abnormalities. His cranial nerves were intact, and no abnormalities were discovered upon neurologic examination of his upper limbs. In regard to his lower limbs, he was unable to walk without assistance. He was able to bear weight on his right lower limb, but not on his left. Tone was decreased in his left lower limb, with weakness of the left hip flexor and extensor muscles. Marked weakness was evident in his left quadriceps (power, 1/5) and left hamstrings (power, 2/5). Dorsiflexion of his left foot measured 2/5, and his plantar flexion measured 3/5. He had mild weakness of dorsiflexion of the right foot (power, 3/5). The patellar tendon reflex was absent on the left. Plantar responses were normal bilaterally. He complained of slight pain in the anterior aspect of his left thigh, but sensation (including pain, touch, vibration, and proprioception) was normal in both lower limbs. He exhibited no disturbance of bladder or bowel function. He was readmitted to the hospital for further investigation of his neurologic deficits.

Laboratory Investigations

A complete blood count revealed a hemoglobin level of 14.3 g and a white cell count of 15,400/mm³, with a normal differential. His erythrocyte sedimentation rate was within normal limits (3 mm), as were his levels of creatine kinase, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, calcium, glucose, urea, and creatinine. His antinuclear factor and rheumatoid factor were both negative. Urine analysis was normal. A throat swab, blood culture, and urine culture all yielded no growth of microorganism.

A lumbar puncture was performed, and the cerebrospinal fluid demonstrated a white cell count of 53/mm³, with 30%

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polymorphonuclear cells and 70% mononuclear cells. An erythrocyte count yielded $10/\text{mm}^3$. The level of cerebrospinal fluid glucose was 78.2 mg/dL, and the level of protein was 25.8 mg/dL (both within normal limits). A Gram stain produced negative results, as did bacterial and viral cerebrospinal fluid cultures. A polymerase chain reaction for herpes simplex produced negative results. No oligoclonal bands were evident in the cerebrospinal fluid. His level of immunoglobulin G was 3.7 mg/dL, and his level of serum immunoglobulin G was 1120 mg (both within normal limits).

Magnetic resonance imaging of the brain produced normal results. Magnetic resonance imaging of the spine indicated a mild enlargement of the conus medullaris, with a subtle increase in T_2 signal (fluid) within the conus (Fig 1). Axial scans demonstrated an increased T_2 signal in the anterior horns of the central grey matter (Fig 2). An increased T_2 signal was also evident in the adjacent white matter anteriorly and posteriorly (including the pyramidal tracts). After contrast administration, no abnormal contrast enhancement was evident in the areas of the increased T_2 signal or elsewhere (Fig 3). These findings suggested edema in the grey and white matter, raising the possibility of an inflammatory condition, e.g., transverse myelitis.

Because the child's significant neurologic deficit affected mainly his left lower limb with minimal involvement of the right foot, he began to receive pulse therapy with methylprednisolone at a dose of 20 mg/kg per day for 5 days. No change occurred in the physical signs of his left lower limb, although the power of his right foot improved after pulse therapy with methylprednisolone. Intravenous immunoglobulin was given at 2 g/kg over 3 consecutive days. A nerve-conduction test and electromyogram studies were offered but were declined by the parents. He received physiotherapy in addition to his medications, and was discharged from the hospital after a stay of 12 days. At that time, he was using a wheelchair.

Three weeks after treatment, he was able to walk independently without need of a walker, although some wasting of his left quadriceps was still evident. The muscle power had improved in his left hamstring and both dorsiflexors and plantar flexors of his left foot. The muscle power in his right lower limb was normal.

Discussion

We report on a child with a severe asthmatic attack who responded well to treatment with bronchodilators. Within 1 week after the onset of his attack, progressive weakness of his extremities occurred during the recovery period from the asthmatic attack. We frequently treat children with asthmatic attacks, but we seldom encounter limb weakness after an asthmatic attack. Our patient exhibited a major involvement of the left lower limb and minimal involvement of the right foot. The main findings included motor involvement with muscle weakness, a decrease in muscle tone, and an absent deep tendon reflex without sensory involvement. This picture is suggestive of a lesion in the anterior horn



Figure 1. Sagittal turbo spin echo T_2 -weighted scan (TR/TE = 3500/86 ms) of distal end of spinal cord reveals mild enlargement of conus medullaris (arrows). A subtle increase in signal is also evident within the conus.

cells of the spinal cord, similar to infection by poliomyelitis. Our patient had received the required polio vaccines, and no virus was isolated in his cerebrospinal fluid. Pleocytosis was evident in our patient, with no elevation of cerebrospinal fluid protein. The differential diagnosis involved either transverse myelitis or Guillain-Barré Syndrome. A magnetic resonance scan of his spine revealed subtle changes

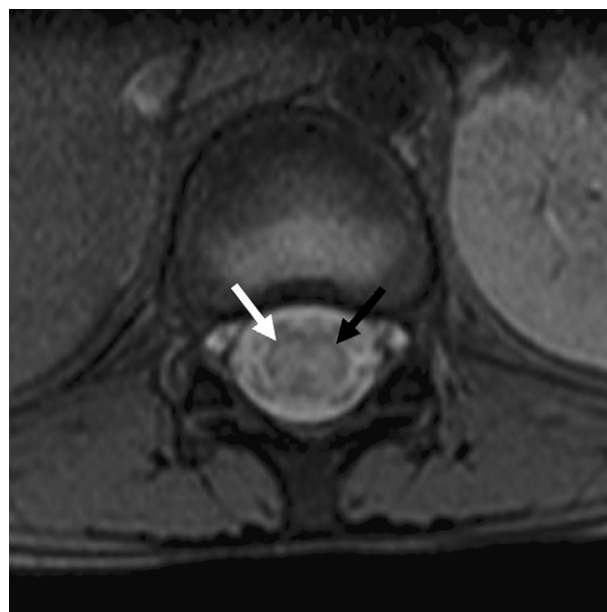


Figure 2. Axial turbo spin echo T_2 -weighted scan (TR/TE = 1500/148 ms) of spinal cord at T_{11} - T_{12} level indicates mild enlargement of conus medullaris. The signal is increased in the anterior horns of the central grey matter (black and white arrows). The signal is also increased in the adjacent white matter anteriorly and posteriorly (including the pyramidal tract).

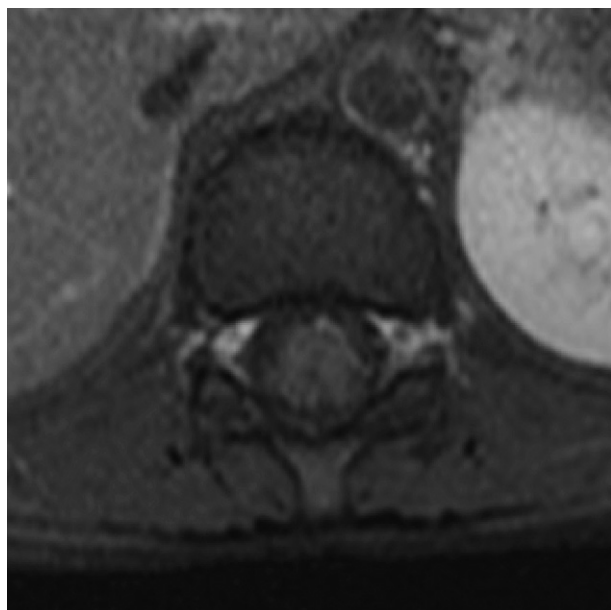


Figure 3. Axial turbo spin echo T_1 -weighted scan ($TR/TE = 426/8$ ms) of spinal cord, at same level as in Fig 2, with no evidence of contrast in areas of increased T_2 signal or elsewhere.

with an increased signal in the spinal cord, which along with the loss of grey-white matter differentiation would favor a diagnosis of transverse myelitis. However, the lack of sensory changes and bladder and bowel signs militated against transverse myelitis, and suggested lower motor neuron involvement. On the other hand, the asymmetrical presentation and lack of sensory changes and the normal level of cerebrospinal fluid protein count against a diagnosis of Guillain-Barré syndrome. In fact, the level of cerebrospinal fluid protein may rise in the later course of illness of Guillain-Barré syndrome. West Nile fever was described as a cause of anterior myelitis or polio-like illness, but we have received no reports of its occurrence in our locale. Electrodiagnostic studies with a nerve-conduction test and an electromyogram would be helpful, particularly if anterior horn cells disease is suspected. Unfortunately, these tests were declined by the parents. Because of the lack of electrophysiologic studies and the lack of clinical fasciculations, it is difficult to establish that the basic lesion occurred in the lower motor neurons. Segmental myelitis remains a possibility. However, with the lack of increase in tone, the absence of extensor plantar responses, and the absence of findings at the sensory level, a diagnosis of segmental myelitis becomes unlikely. Table 1 illustrates the differential diagnosis of flaccid paralysis of the limbs.

Poliomyelitis-like illnesses associated with asthma, asthmatic amyotrophy, and Hopkins' syndrome have been used to describe the same condition. Although poliomyelitis virus was not isolated from the cerebrospinal fluid of documented cases, other microorganisms were associated with the illness, i.e., echovirus, adenovirus, Cocksackie virus, *Mycoplasma*, and herpes simplex. In our patient, no virus was cultured in the cerebrospinal fluid, and a polymerase chain reaction for herpes simplex also produced negative results.

Hopkins' syndrome is reported mainly in children, although a postpubertal subject has been described [3]. The muscle weakness can affect the upper or lower limbs or both, and can present as monoplegia, diplegia, or hemiparesis.

The site of involvement is mainly in the anterior horn cells similar to poliomyelitis as there is no sensory disturbance. Previous electromyogram studies indicated fasciculation discharges, denervation potentials, and giant potentials, suggestive of anterior horn cell disease. A muscle biopsy of a patient with Hopkins' syndrome [2] revealed scattered atrophic fibers, indicating that lesions occur in the anterior horn cells of the spinal cord.

In our patient, magnetic resonance imaging indicated a loss of grey-white matter differentiation, suggestive of a myelitic lesion. In adults, similar cases were described of acute myelitis after an asthmatic attack [3], affecting the sensory and pyramidal tracts. Evoked potential studies confirmed the involvement of the pyramidal tracts. In adults, the illnesses seem to demonstrate a more widespread involvement. A spectrum of disorders seems to involve a similar pathology, affecting the anterior horn cells and surrounding white matter in the spinal cord.

Regarding the pathogenesis, various possibilities have been suggested. Asthmatic patients as a group yield reduced immunologic responses, compared with normal subjects. In some reported cases of Hopkins' syndrome, mild alterations occur in the level of immunoglobulins, but not to the point of immunodeficiency [4]. When a viral infection triggers an asthmatic attack, the virus can also invade the anterior horn cells, similar to the findings in poliomyelitis virus. Various microorganisms, including adenovirus type 3, echovirus type 18, Cocksackie virus type B5, *Mycoplasma* [5], and herpes simplex [6], were described in association with the illness. The clinical changes resemble those of acute poliomyelitis with acute lower motor neuron disorder, without sensory involvement, the presence of inflammatory changes in cerebrospinal fluid, and the residual wasting of muscles. The pathogenesis of Hopkins' syndrome was also postulated to be similar to vaccine-associated poliomyelitis paralysis, as illustrated in a patient [7] with acquired immunodeficiency syndrome associated with poliomyelitis. Poliovirus type 2 was isolated from the stool, and was subsequently characterized as vaccine related based on the findings in doing monoclonal antibody testing [7].

Manson and Thong [4] suggested that with an underlying immunologic deficiency, further immunosuppression occurs during an asthmatic attack because of stress, an intercurrent infection, or steroid therapy, rendering the patient more susceptible to invasion of the anterior horn cells by a viral agent, and resulting in the development of this syndrome. Another report suggested a pathogenesis related to atopic disorders with specific immunoglobulin E against common environmental allergens, such as mite antigen resulting in an atopic myelitic picture. Although atopic myelitis tends to involve the posterior column of the spinal cord, the anterior horn cells may be affected in some cases of atopic myelitis. This finding may suggest a link between

Table 1. Differential diagnosis of flaccid paralysis of the limbs

	Transverse Myelitis	Hopkins' Syndrome	Guillain-Barré Syndrome
Preceding event	Viral infection	Asthmatic attack	Viral infection
Onset	Abrupt	Progressive	Progressive
Sensory changes	With sensory level	None	Some changes
Bladder and bowel dysfunction	Presence	Absence	Transient
Cerebrospinal fluid	Pleocytosis and high immunoglobulin G index	Pleocytosis	Elevated protein
Nerve conduction velocity	Low CMAP	Normal	Reduced velocity
	Normal SNAP		Abnormal F-waves
Electromyogram	Positive sharp waves and fibrillation potentials	Fibrillation and giant potentials	Positive sharp waves and fibrillation potentials

Abbreviations:
 CMAP = Compound muscle action potential
 SNAP = Sensory nerve action potential

atopic myelitis and Hopkins' syndrome [8]. A viral infection can provoke an asthmatic attack, and acute flaccid paralysis of the limbs can occur in asthmatic patients because of a direct invasion by the virus into the anterior horn cells due to the disturbed immunologic defenses in the asthmatic patient, or the injury may be a result of immunologic damage, as seen in atopic myelitis.

In the management of this syndrome, various treatments have included oral prednisone [9], pulse therapy with methylprednisolone, plasmapheresis [10], and intravenous immunoglobulin [11]. Hopkins' syndrome has an unfavorable outcome, with persistent weakness, muscle wasting, and disability, similar to outcomes in poliomyelitis. In our patient, after pulse therapy, mild improvement in the right foot occurred. After treatment with intravenous immunoglobulin, the child was able to walk independently after 3 weeks, although wasting of the quadriceps persisted. Our patient demonstrated complete recovery of strength in his right foot, and he was able to walk unaided. Plasmapheresis was described as superior to intravenous immunoglobulin in adult cases of atopic myelitis [10]. Oral prednisone was effective for paralysis, with resolution of the paralysis within 2 months [9]. Cohen et al. [11] reported on a nearly complete recovery with intravenous immunoglobulin therapy in Hopkins' syndrome. Because Hopkins' syndrome is so rare, it is difficult to consider any treatment as definitive. Various immunomodulating agents (methylprednisolone, plasmapheresis, and intravenous immunoglobulin) were used, with apparently beneficial effects. This success may be attributable to the immunologic nature of the illness, with its similarity to atopic myelitis, which may explain why these agents are beneficial. Although our patient underwent a severe asthmatic attack, patients with mild attacks of asthma can also develop this syndrome, and thus the severity of an asthmatic attack is not the key issue. Relapses

of Hopkins' syndrome were also reported in the context of repeated attacks of asthma.

Because of the grave prognosis of Hopkins' syndrome, we suggest early treatment with either pulse therapy with methylprednisolone, plasmapheresis, or intravenous immunoglobulin. Moreover, because Hopkins' syndrome is rare, more collaborative studies are required to delineate the best effective treatment for this syndrome.

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