Case 1: The case of the irritable nephrotic

A 22-month-old previously healthy boy presented to a tertiary care emergency department with a one-week history of periorbital and bilateral leg swelling. He had no fever, no recent illnesses and no blood in his urine or stool. He was known to have chronic constipation and had a poor diet consisting mainly of cow's milk. On physical examination, he had no hypertension, was in no apparent distress and displayed normal vital signs. He had marked periorbital edema and pitting edema of his lower limbs. His abdomen was distended and he had mild ascites. The rest of his examination was normal.

A urine dipstick showed a high protein level (20 g/L) and a large amount of blood. He had low serum albumin of 18 g/L (normal 32 g/L to 56 g/L), high serum triglycerides of 2.17 g/L (normal 0.31 g/L to 1.41 g/L) and high serum cholesterol of 8.82 mmol/L (normal 3.2 mmol/L to 4.4 mmol/L). His electrolytes and renal function were normal. A complete blood count revealed a low hemoglobin of 79 g/L (normal 110 g/L to 140 g/L) with a low mean corpuscular volume of 53 fL (normal 80 fL to 94 fL). His platelet count was elevated at 934×10^9/L (normal 150×10^9/L to 400×10^9/L). A blood film showed marked hypochromasia and microcytosis. His iron and ferritin levels were both low.

He was diagnosed with nephrotic syndrome, as well as iron deficiency anemia (secondary to his poor diet), and was admitted to the hospital. He was initially treated with intravenous methylprednisone because he could not tolerate oral prednisone. He was also started on iron supplementation for his iron deficiency. In addition, the nephrology department recommended starting him on dipyridamole, an antiplatelet agent, because his thrombocytosis and nephrotic syndrome put him at an increased risk for thrombosis. Two days after admission, he was found to be hypertensive and more edematous. He was then treated with two doses of intravenous albumin and furosemide. The next day, his edema had significantly improved. He was switched to oral prednisone and seemed to be doing much better.

However, the next day he began vomiting his medications, and was unhappy and irritable. It was thought that he had gastritis from the prednisone and was started on ranitidine. His parents thought he may be constipated and he was also started on lactulose. He had a normal neurological examination. Two days later, he was able to tolerate his medications, and was discharged home despite his irritability. Close outpatient follow-up was arranged. Two days after his discharge, he was seen in the nephrology clinic and was found to be extremely irritable and inconsolable. He had a normal examination, and his edema was markedly improved. He was readmitted to the hospital, and further investigations revealed the etiology of his symptoms.

Case 2: Long-standing neuropathy with acute onset of weakness

A 16-year-old girl with presumed Charcot-Marie-Tooth disease presented to the emergency department with an acute onset of lower limb weakness. She was unable to walk where previously she had been fully ambulatory.

One month before presentation, she had a three-week history of abdominal pain. Five days before presentation, she developed bilateral shoulder and upper back pain.

The morning of her presentation, she had difficulty getting up off the floor and getting in and out of the bathtub. She reported that her legs were numb and 'wobbly'. She had no presyncopal symptoms. She denied urinary incontinence. Bowel dysfunction was difficult to assess because she usually stooled once per week. She had no fevers or night sweats.

Her history was significant for orthopaedic surgeries. She was followed for bilateral pes cavus deformities and progressive right foot varus deformity for which she had required surgery several years earlier. Her presumed diagnosis of Charcot-Marie-Tooth disease was based on her orthopaedic findings and her family history. Her mother, maternal aunt and other relatives on her mother's side had been diagnosed by genetic testing. The patient herself had not had genetic testing and was not followed by a neurologist at the time of presentation. As a result, her premorbid neurological examination was unknown.

A physical examination at presentation revealed stable vital signs with a blood pressure of 110/66 mmHg. Her lower limbs were weak, with the right side weaker than the left. The proximal muscles were more severely affected than the distal muscles. She had decreased sensation to pinprick, light touch, and a temperature to the level of T8 to T10 on the left and T4 on the right. Proprioception was inconsistent in the toes, and vibration sense was also decreased in the toes, but was normal at the ankles. Her lower limb reflexes were absent (it was not clear whether she had reflexes present in the past). Plantar responses were flexor and anal tone was normal.

The laboratory investigations (complete blood count, electrolytes, calcium, magnesium, phosphate, liver enzymes, lactate dehydrogenase, creatine kinase and erythrocyte sedimentation rate) were unremarkable. A magnetic resonance imaging screen of her spine was normal. She was admitted to hospital for observation and further workup.

The day after her admission, the patient's lower limbs continued to weaken. She became incontinent. After four days, a magnetic resonance imaging screen was performed which revealed the diagnosis.

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CASE 1 DIAGNOSIS: NEPHROTIC SYNDROME WITH CEREBRAL SINOVENOUS THROMBOSIS

An eye examination performed by the ophthalmology consultant showed bilateral papilledema. A computed tomography scan revealed an extensive sinovenous thrombosis of his superior sagittal and transverse sinuses. There were no infarcts or hemorrhages. He was diagnosed with cerebral sinovenous thrombosis (CSVT) secondary to nephrotic syndrome. He was initially started on unfractionated heparin, and then switched to low-molecular-weight heparin (enoxaparin). He clinically improved in hospital and was discharged home one week later. He remained on enoxaparin for six months. He finished the initial course of prednisone for his nephrotic syndrome, and has not had any relapses to date.

Nephrotic syndrome is a common renal disorder in childhood characterized by proteinuria, hypoalbuminemia and edema. The majority of cases are attributable to minimal change glomerulopathy, and referred to as idiopathic nephrotic syndrome. The peak age of onset occurs at two to three years (1).

The mainstay of treatment for nephrotic syndrome is steroids. Prednisone is the drug of choice, and is usually administered at a dose of 60 mg/m^2 for six weeks, and then tapered off over the next 10 weeks. In some patients with severe edema, albumin infusions with furosemide are given to help mobilize fluids.

The major complications of nephrotic syndrome that contribute to morbidity and mortality include infections (peritonitis, cellulitis and sepsis) and thromboembolism (1).

Nephrotic children are prone to develop thromboembolic complications secondary to an acquired hypercoagulable state (1). There are several potential mechanisms for the hypercoagulable state including urinary loss of proteins that inhibit coagulation (antithrombin III), a raised fibrinogen concentration, destabilization of platelets by hyperlipidemia and intravascular volume depletion (which can worsen with aggressive diuresis). To date, no predictors for thrombosis have been established in children with nephrotic syndrome, and prophylactic anticoagulation remains controversial. In our patient, the platelet count was elevated, which was an additional risk factor for thromboembolism, and dipyridamole was started. However, there is little evidence that this is a beneficial treatment.

The most common site of thrombosis in nephrotic syndrome is renal vein thrombosis. CSVT is not common in nephrotic children, but nevertheless can carry an increased morbidity compared with clots in other locations.

A recent review of cases of CSVT in nephrotic syndrome in Canada (2) revealed four cases documented in Toronto, Ontario, between 1992 and 2004. Fluss et al (2) also reviewed all cases documented in the literature, and included an additional 17 cases in their analysis. They found that the majority of cases of thrombosis presented with the first episode or within the first six months of diagnosis of nephrotic syndrome. Clinical manifestations were nonspecific, and consisted of seizures in eight cases and signs of increased intracranial pressure (headache, vomiting, lethargy and irritability) in 16 cases. Focal neurological deficits were seen in seven children (cranial nerve palsy or hemiparesis). All patients were anticoagulated with either unfractionated heparin or low-molecular-weight heparin, and the outcome was good in the majority of patients. One patient was left with cognitive impairment, and another died from a pulmonary embolus.

In conclusion, CSVT is a known complication of nephrotic syndrome. As in the present case, the signs and symptoms can be nonspecific, and patients do not necessarily present with seizures or neurological deficits. A high index of suspicion is needed, and head imaging should be ordered when CSVT is suspected because prompt initiation of therapy can decrease morbidity.

CLINICAL PEARLS

- Patients with nephrotic syndrome are prone to develop thromboembolic complications.
- CSVT is a rare, but a well-described complication of nephrotic syndrome.
- Symptoms of CSVT can be nonspecific and careful attention should be paid to any neurological symptoms, including irritability in patients with nephrotic syndrome.
- Treatment of CSVT with anticoagulants can lead to good outcomes.

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CASE 2 DIAGNOSIS: TRANSVERSE MYELITIS IN A TEENAGER WITH CHARCOT-MARIE-TOOTH

A repeat magnetic resonance imaging (MRI) screen four days after admission was characteristic of transverse myelitis (TM) with increased signal intensity on T2-weighted images from C6–T4. She was treated with a five-day methylprednisolone pulse followed by two courses of intravenous immunoglobulin. She was treated with rehabilitation medicine, and slowly improved during her stay. Follow-up three months later found her much improved; although she was still dependent on a walker. She continued to have a neurogenic bowel and bladder. Genetic testing confirmed her diagnosis of Charcot-Marie-Tooth (CMT) type 1A.

The present case describes a teenager with CMT who presented with acute and rapidly progressive lower limb weakness and sensory dysfunction. Her physical examination findings were complicated by her presumed baseline absence of reflexes and underlying motor and sensory peripheral neuropathy.

CMT encompasses a group of hereditary peripheral neuropathies. Clinically, patients develop very slow, progressive wasting and weakness of distal muscles, sensory loss, skeletal deformities, and decreased or absent reflexes. Nerve conduction studies are consistent with a demyelinating polyradiculoneuritis. Conduction blocks are rarely seen. Cerebral spinal fluid (CSF) contains high protein and no pleocytosis. Root hypertrophy may be seen on an MRI screen with little, if any, enhancement with gadolinium.

A diagnosis of Guillain-Barré syndrome (GBS) was initially considered. GBS is an acquired, immune-mediated polyradiculopathy. Patients present with acute, progressive, flaccid weakness and areflexia. It may be accompanied by pain and paresthesias. On examination, all sensory modalities may be disturbed. However, sensory loss can lag behind the symptoms of weakness. Usually weakness begins distally in the lower limbs. Symptoms usually manifest days to weeks after respiratory or gastrointestinal infection. High protein and a normal cell count are found in the CSF. Nerve conduction studies are consistent with a demyelinating polyradiculoneuritis, with frequent conduction blocks. There may be enhancement of the nerve roots with gadolinium on MRI.

TM is a focal inflammatory disorder of the spinal cord which disrupts motor and sensory tracts below the site of the lesion. The thoracic area is most commonly affected. The symptoms usually develop acutely and progress quickly over the first few days. Back pain at the level of the lesion is observed. Often, there is bladder and bowel dysfunction.

TM has been associated with a preceding viral, bacterial and certain parasitic infections. It has also been linked with immunizations. A history of respiratory or gastrointestinal illness precedes 30% to 60% of cases, and approximately 30% of cases are preceded by a history of minor trauma.

MRI of the spine may reveal hyperintensities on T2-weighted images and occasionally gadolinium enhancement. MRI evidence of inflammation and cord edema may be delayed for several days after clinical onset of symptoms (as in the present case), highlighting the importance of repeat imaging in children for whom clinical suspicion remains high. CSF pleocytosis with elevated lymphocytes is usually present and CSF glucose levels are normal. Protein levels in the CSF may be normal or elevated. In a small percentage of patients, oligoclonal bands are present in the CSF, particularly those at high risk for the future diagnosis of multiple sclerosis.

A course of an intravenous high-dose steroid, such as methylprednisolone, is the usual treatment. Recovery may be noted within eight weeks, but improvement may be seen over years. Residual deficits, such as urinary dysfunction, are not unusual. Approximately 30% of children with TM remain paraplegic, and over 70% are left with some degree of bladder dysfunction, with approximately 50% requiring bladder catheterization. Poorer prognosis has been associated with a complaint of back pain, a more rostral sensory level, a younger age of onset, CSF pleocytosis and more extensive MRI findings.

Distinguishing GBS from TM at initial presentation may be difficult. GBS is more likely in the setting of ascending weakness, with sensory symptoms being predominantly 'dysesthesia' rather than sensory loss. Neurogenic bowel or bladder symptoms are rarely seen. Autonomic symptoms, such as arrhthymias and hypotension, may occur and can be life-threatening; thus, all patients must be carefully monitored. Typical neurophysiological findings of demyelination, as well as high protein and the absence of pleocytosis in the CSF further support the diagnosis of GBS. In contrast, persistent, asymmetric parapesis, a spinal sensory level, and neurogenic bowel and bladder dysfunction are more suggestive of TM. Typical MRI findings and CSF pleocytosis are further suggestive of the diagnosis.

CLINICAL PEARLS

- Acute weakness and sensory changes are not features of genetically defined polyneuropathies, such as CMT.
- Differentiation between TM and GBS requires a detailed clinical and radiological examination.
- TM should be suspected when a patient presents with a spinal sensory level, neurogenic bladder and bowel dysfunction. Typical MRI findings and CSF pleocytosis can confirm the diagnosis.
- GBS usually presents with ascending weakness, and is confirmed by typical neurophysiological findings and high protein with a normal white blood cell count in the CSF.

RECOMMENDED READING

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