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Chronic inflammatory demyelinating polyneuropathy in childhood can present acutely: A report of three cases

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Abstract

Three patients with chronic inflammatory demyelinating polyneuropathy (CIDP) with acute onset initially diagnosed as Guillain-Barre syndrome were presented. Case 1 had profound weakness over 8 weeks but followed a monophasic recovery course and was almost full recovery at 6 months and remained well one year later, whereas Case 2 recovered with two relapses at 4 and 5 months followed by full remission at 6 months. Case 3 had almost monthly relapses over 2 years, requiring monthly intravenous immunoglobulin and 4 courses of intravenous methylprednisolone. Despite frequent relapses, clinical evidence of areflexia and neurophysiologic evidence of chronic neuropathy, Case 3 remained strong during remission. No causes were found except Case 2 may be due to reactivated latent Epstein-Barr virus. Unlike those with subacute or indolent onset, CIDP with acute onset may represent a very distinct variant with good outcome. We believe that acute onset CIDP variant and Guillain-Barre syndrome most likely represent parts of a continuum, arbitrarily separated by their time course. The supporting arguments are presented; diagnosis and management difficulties are briefly discussed.

INTRODUCTION

Criteria for the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) were developed in 1991 by an ad hoc subcommittee of the American Academy of Neurology and the mandatory clinical feature is the progressive or relapsing motor and sensory neuropathy of over at least 2 months duration.[1] There were no specific features regarding types of onset and clinical courses. Hence, it is now increasingly thought to be heterogenous with various clinical patterns being described.

CIDP most frequently starts insidiously and evolves slowly, either in a slowly progressive (more than 60% of patients) or relapsing manner (approximately one third of patients), with partial or complete recovery between recurrences.[2] However it can present acutely. In Leicester Royal Infirmary, UK, only 3 cases of CIDP in children have been identified and all were initially diagnosed as Guillain-Barre Syndrome (GBS). In many ways, CIDP can be considered the chronic equivalent of acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common form of GBS. The supporting arguments for this comment, diagnosis difficulties and management dilemma are discussed.

CASE REPORT 1

A 10 year-old Caucasian boy presented with one to 2 weeks history of ascending limb weakness, pin and needle of legs and painful knees. On arrival, he was able to walk but often tripped over. Examination revealed that he had grade 3-4/5 motor weakness, worse at lower limbs and proximal muscles. Three days later, he became profoundly weak and was unable to stand and walk. The motor power was markedly reduced to grade 1/5 in lower limbs and 2/5 in upper limbs as well as hypotonia and absent reflexes.

Cerebrospinal fluid (CSF) analysis showed an markedly elevated protein (4.0 g/l) with normal leukocyte count (0 cells/mm^3). Nerve conduction study/electromyography (NCS/EMG) showed more axonal than demyelinating sensorimotor polyneuropathy with active denervation seen. A diagnosis of GBS was made. Intravenous immunoglobulin (IVIG) 2g/kg over 5 days was commenced but there was no improvement. He remained bed and wheelchair bound but he never

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had any bulbar weakness, facial weakness and respiratory failure. His motor deficit remained severe (power 1-2/5).

One month after admission, he was given intravenous methylprednisolone 250 mg four times per day for 5 days followed by oral prednisolone 40 mg daily for one week and tapered off gradually by 10mg weekly. He improved gradually and one month later (total 2 months after admission), his motor power improved with proximal muscle power 4-5 but still unable to walk and was wheelchair bound.

He continued to make good progress. Around 4 months after the admission, he was able to walk, although he was unsteady and still required wheelchair occasionally. He was able to climb stairs, holding to a handrail. Around 6 months after first presentation, he had minimal weakness but was still disturbed with neuropathic pain. At age 11 years, he still had neuropathic pain, requiring amitriptyline and gabapentin.

CASE REPORT 2

15 year-old Caucasian male presented with 5 days history of ascending symmetrical weakness, numbness and tingling sensation of lower extremities. He had non-specific febrile illness 3 months earlier. He became profoundly weak 2 days after admission and was wheelchair bound with facial diplegia and external ophthalmoplegia. There was tightness of chest and breathing difficulty but no significant respiratory weakness or bulbar palsy. Examination revealed areflexia and limbs weakness (power grade 3-4/5). A clinical diagnosis of GBS syndrome was made.

CSF studies showed a normal leukocyte count (4 cell/mm^3) with an elevated protein (1.49 g/l) and no oligoclonal bands. NCS and EMG showed a sensory-motor polyneuropathy, mainly axonal with possible patchy demyelination and no active denervation.

He was treated with IVIG (400mg/kg of body weight per days for 5 days). There was a gradual improvement over 3 months. He was able to walk independently over short distances. However he relapsed at 4 months following viral infection but responded rapidly to second course of intravenous immunoglobulin. He had another relapse at 5 months and had profound weakness and was wheelchair dependant with poor respiratory effort requiring non-invasive positive pressure ventilation.

Repeated CSF studies showed an elevated protein (0.78g/l) and leukocyte count (13 cells/mm^3). Polymerase chain reaction (PCR) of CSF detected 1000 Ebstein-Barre virus (EBV) DNA copies per ml. Blood serology showed that Epstein-Barr nuclear antigen IgG was detected by enzyme immunoassay but there was negative EBV viral capsid antigen. NCS/EMG at 4 months showed a worsening mixed axonal and demyelinating neuropathy.

Third course of IVIG was given but there was minimal response. Two weeks later, he was started on oral prednisolone (40mg daily for 5 days and reduced by 10mg every 5 days) and Gabapentin for pain and tingling sensation. One week later, he improved and was discharged without respiratory support. Six week later, he was in full remission while he was on prednisolone 5mg daily. At last follow-up at 9 months, he was in full remission without medication.

CASE REPORT 3

An 8 year-old girl presented with one week history of rapidly progressive ascending motor weakness and a couple of months of unexplained lethargy. At presentation, she was unable to lift up a glass of milk, brush hair, and her gait was unsteady. Examination revealed hypotonia, hyporeflexia and power of grade 3-4/5 over all four limbs.

CSF analysis showed an elevated protein (0.71 g/l) and normal leukocyte count (0 cells/mm^3). EMG/NCS showed more demyelinating than axonal sensorimotor polyneuropathy, upper limbs worse than lower limbs with active denervation. A diagnosis of CIDP was made.

She was first treated with IVIG 2 g/kg over 5 days, and she rapidly felt better next day and was discharged 5 days later with normal gait.

Three weeks later, she presented with 2 days history of motor weakness and was given second course of IVIG followed by oral prednisolone (40 mg daily for one week, and was tailed off gradually). She presented again with third relapse one month later while she was still on prednisolone. Intravenous methylprednisolone (30mg/kg/day for 5 days followed by oral prednisolone 1mg/kg for 10 days and tailed off slowly) was given. She responded rapidly and was in full remission for the next 3 months. Second intravenous methylprednisolone was given for her relapse and she responded rapidly but this time she was only in remission for 3 weeks. Subsequently third and fourth methylprednisolone was tried at 6 months apart, but they were no longer able to maintain remission. She had monthly relapses and appeared to respond rapidly to IVIG (2g/kg/day

for 5 days) but relapsed every month. She had a total of 17 relapses over a period of 2 years.

At 10 months after first presentation, repeated NCS/EMG showed more axonal than demyelinating sensorimotor neuropathy with chronic neurogenic changes. Repeated CSF analysis showed a slightly elevated protein (0.68 g/l) with normal leukocyte (3 cells/mm^3). During relapses, she presented with short history of weakness, paresthesia and tingling of extremities. She had difficulty in walking and climbing stairs during relapse. Limbs power was of grade 4+, and there were areflexia/hyporeflexia. In between relapses, she was in full remission, was able to swim and run. She have less relapses at last review at age 10.5 years.

Genetic and serology studies

All 3 patients were subjected to extensive genetic and serology studies and the results were negative. Genetic studies included hereditary motor sensory neuropathy type 1 (Cases 2,3) and hereditary liability to pressure palsies (Case 2). Serological evaluation included EBV (Cases 2,3), Cytomegalovirus (Cases 2,3), Campylobacter Jejuni (Cases 1,2,3), toxoplasmosis (Case 3), Influenza A and B (Cases 2,3), Mycoplasma pneumoniae (Cases 2,3), Herpes simplex (Case 3), Varicella zoster (Case 3), Borrelia Burgdoferri (Case 3), anti-MAG antibody (Cases 1,2,3), anti-ganglioside GM1 antibody (Cases 2,3), and antinuclear antibodies such as smooth muscle antibody, mitochondrial antibody, liver Kidney microsomal antibody, parietal cell antibody (Case 3).

DISCUSSION

The research criteria of CIDP include (1) progressive or relapsing motor and sensory dysfunction of more than one limb of a peripheral nerve nature, developing over at least 2 months; (2) cytoalbuminologic dissociation; (3) electrophysiological evidence of acquired demyelination; and (4) pathologic features of demyelination and remyelination.[1] There are no specific requirements regarding types of onset and clinical courses. CIDP most frequently starts insidiously and evolves slowly, either in a slowly progressive (more than 60% of patients) or relapsing manner (approximately one third of patients), with partial or complete recovery between recurrences.[2] However it can present acutely as shown in our cases.

The duration of 2 month is arbitrarily chosen probably because between 50% to 75% patients with GBS develop maximal weakness within 2 weeks and 90% to 98% by 4 weeks.[3] A small number of patients will continue to progress for longer than 4 weeks. This latter group overlaps to some degree with CIDP.[3] Other arguments that support CIDP is chronic equivalent of AIDP are that firstly, GBS and acute onset CIDP share similar physiologic studies, CSF results and pathologic features which basically show laboratory evidence of demyelination. Secondly, both GBS and CIDP are an acquired immune-mediated polyneuropathy, and thirdly acute onset CIDP and severe fulminant/axonal GBS have an almost similar course and prognosis. Hence, like many other experts[2,3], we believe acute onset CIDP and fulminant GBS most likely represent parts of a continuum, arbitrarily separated by their time course.

Diagnosis difficulties may arise. Case 1 was profoundly weak at one month despite IVIG. He responded gradually after intravenous methylprednisolone given at one month after presentation. Case 1 could have fulfilled the chronic progression of 2 months duration. However it is pragmatic to initiate the further treatment for CIDP earlier. Case 2 had good recovery at first 3 months but developed relapses at fourth and fifth months. Like Case 3, Case 2 also fulfilled the criterion of relapsing nature of at least 2 months duration. The chronicity and progression of the CIDP were also supported with worsening picture of serial EMG/NCS in Cases 2 and 3. Like many centers, we do not perform sural nerve biopsy.

Case 2 is believed to be due to reactivated EBV infection. The main supporting evidence is high level of EBV DNA detected in CSF. Negative anti-viral capsid antigen IgM and positive Ebstein-Barre nuclear antigen IgG by enzyme immunoassay in our case are consistent with the diagnosis. Conventionally, EBV-specific immunofluorescence serology test is used to detect antibodies to EBV viral capsid antigen IgM (indicating recent infection), to Epstein-Barr nuclear antigen IgG (indicating past infection) and to early antigen IgG (Early antigen; indicating viral activity). The presence of early antigen IgG indicates reactivated EBV infection.[4] Positive EBV PCR has been demonstrated in the serum of patients with reactivated EBV infections.[5] Hence, we believe PCR may be substituted to diagnose reactivated EBV infection.[5]

Childhood CIDP may responds effectively to IVIG, corticosteroids and plasmapheresis[2,3] and generally has a favourable long-term outcome.[2,3] It remains unclear which treatment should be a first-line regimen in the treatment of CIDP.[3] We think it is best to start with IVIG (2g/kg over 2-5 days depending on severity; shorter course if there is dramatic improvement) followed by corticosteroids (oral prednisolone as in Case 1 or intravenous methylprednisolone 30mg/kg/day for 5 days followed by oral prednisolone 1mg/kg for 10 days) if no substantial functional improvement is noted. The practical reasons include (1) it is impossible to differentiate between acute onset CIDP and GBS; (2) GBS only responds to IVIg but not corticosteroids; and (3) both CIDP and GBS respond to IVIG. Hence IVIG should be tried first. However the responses are not always predictable. For example, Case 1 did not respond to first course of IVIG but showed good response to IV methylprednisolone. Case 2 responded well to first two courses of IVIG but did not do so at second relapse. Case 3 responded to first course of intravenous methylprednisolone but did not do so with subsequent three course of intravenous methylprednisolone. On the other hand, case 3 responded well to IVIG. All these cases seemed to have good long term outcome.

In conclusion, acute onset (less than 4 weeks) CIDP and GBS most likely represent parts of a continuum[3], arbitrarily separated by their time course. Overall, good response to IVIG and corticosteriods and good prognosis are anticipated. Some acute onset CIDP could be related to a reactivated EBV. Detailed serology study of EBV is indicated.

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