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Post-infectious new daily persistent headache may respond to intravenous methylprednisolone

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Abstract New daily persistent headache (NDPH) is a subtype of chronic daily headache (CDH) that starts acutely and continues as a daily headache from the onset. It is considered as one of the most treatment refractory of all headache syndromes. The pathophysiology is largely unknown. Viral infections, extracranial surgery, and stressful life events are considered as triggers for the onset of NDPH. A few patients may have the onset of their symptoms during an infection. Here we report nine patients with NDPH like headache. All of them had a history suggestive of extracranial infections a few weeks prior to the onset of headache. All patients received intravenous methyl prednisolone (IV MPS) for 5 days. Intravenous MPS was followed by Oral steroids for 2–3 weeks in six patients. The relief of headache started between the second and fifth days of infusion in all patients. The steady improvement in headache continued and seven patients experienced almost complete improvement within 2 weeks. Two other patients showed complete improvement between 6 and 8 weeks after initiation of IV MPS therapy. We conclude that NDPH-like headache may occur as a post infectious process following a recent infection. We also speculate on the possible mechanisms of headache in our patients.

Keywords Headache · New daily persistent headache · Chronic daily headache · Post infectious illness · Corticosteroids · Methyl prednisolone

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Introduction

New daily persistent headache (NDPH) is a type of chronic daily headache (CDH). The term NDPH was first coined by Vansat in 1986 [1]. It falls into group 4 of the International Headache Society (IHS) classification system. It is characterized as "daily and unremitting from very soon after onset (within 3 days at most)". The pain is typically bilateral, pressing or tightening in quality and of mild-to-moderate intensity. There is considerable overlap in pain characteristics of NDPH and chronic tension type headache (CTTH) in the diagnostic criteria [2]. Abrupt onset of a primary CDH of long duration is the most important feature for the diagnosis of NDPH. The pathophysiology of NDPH is largely unknown. Viral infections, extracranial surgery, stressful life events, etc. are considered as the triggering factors for the onset of NDPH [3]. The prognosis and treatment of patients with NDPH are highly variable.

Primary NDPH may be a self-limiting type of headache that resolves without therapy within several months. However, recent observations suggest that primary NDPH may be the most treatment refractory of all primary headache disorders [4]. Here, we report nine patients with abrupt onset of daily headache of variable duration. All patients had history suggestive of infection prior to the onset of headache and responded to intravenous (IV) methyl prednisolone (MPS).

Materials and methods

Case 1 prompted us to look for similar case, and we observed nine similar patients over a period of about 1.5 years in whom a preceding infection was noted a few weeks prior to the onset of daily headache. Three patients are described in detail. The main characteristics features of other cases are summarized in Table 1. Written informed consent was taken from the patients to publish this report.

Case 1

A 36-year-old female presented to our outpatient neurology clinic with a complain of daily continuous headache of about 10-week duration. The headache was present

Table 1 Main features of patients 4–9

	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age (year)	24	26	32	25	29	20
Sex	M	M	F	M	M	F
Duration of headache (weeks)	6	16	20	10	14	10
Details of headache	hol, press, cont, mod, occ. exacer	hol, press, cont, mild-mod	hol, press, cont, mild-mod, occ. exacer	hol, press, occ, puls, cont, mod, occ. exacer	hol, press, cont, mild-mod	hol, press, cont, mild-mod
Associated symptoms	No	nau, phot	No	nau	nau, phot	No
Preceding illness						
Type of illness	Rhinitis	Pharyngitis	Pharyngitis	Gastroent	Rhinitis	Gastroent
Time interval with headache onset (weeks)	4	5	3	2	3	3
Duration of illness	3–4 days	10 days	2 weeks	2–3 days	1 weeks	4–5 days
Any investigations	Not done	Normal	Leucocytosis	Not done	Not done	Not done
Treatment	cetr, para	antb, ibup	antb, para	Not any specific	Detail not known	Metr
Investigations						
MRI brain	Normal	Normal	Normal	Normal	Normal	Normal
(use of contrast)	No	No	No	Yes	Yes	Yes
	(at 6 weeks)	(at 12 weeks)	(at 20 weeks)	(at 9 weeks)	(at 14 weeks)	(at 10 weeks)
CSF	Normal	Not done	Not done	Normal	Not done	Normal
Others	Normal	Normal	Normal	Normal	Normal	Normal
Prior treatments						
Drugs used	amt, val, nap, ind	ibu, nap, top, dot, pred	ibu, ind, pro, amt, pred	amt, Ibu, para,	ibu, nap, ind	para, val, amt
Response	No	Minimal	Minimal	No	Minimal	No
Treat. with IV MPS (1,000 mg daily)	5 days	5 days	5 days	5 days	5 days	5 days
Followed with oral prednisolone	No	40 mg/d for 3 weeks	60 mg/d for 3 weeks	No	40 mg/d for 2 weeks	60 mg/d for 2 weeks
Beginning of response	2nd day of infusion	4th day of infusion	5th day of infusion	3rd day of infusion	4th day of infusion	3rd day of infusion
Total response	com in 2 weeks	mar in 1 week, com in 2 weeks	mar in 2 weeks	mar in 1 week	mar in 1 week, com in 2 weeks	com in 2 weeks
Follow up	no hd in 3 months	occ. mild hd in 3 mths. No after that in next 3 months	occ. mild-mod, hd in next 8 weeks. No after that in next 4 months	occ. mild hd in 6 weeks. No hd in next 4 months	no hd in 4 months	no hd in 6 months

Amt amitryptiline; *antb* antibiotics; *cetr* cetrizine; *com* complete; *cont* = continuous; *d* days; *dot* dothiepine; *exacer* exacerbations; *F* female; *Gastroent* gastroenteritis; *hd* headaches; *hol* holocephalic; *ibup* ibuprofen; *indo* indomethacin; *M* male; *mar* marked; *metr* metronidazole; *mod* moderate; *mths* months; *nap* naproxen; *nau* nausea; *occ* occasional; *para* paracetamol; *phon* phonophobia; *phot* photophobia; *pred* prednisolone; *press* pressing; *puls* pulsatile; *top* topiramate; *val* valproic acid; *vom* vomiting

from the onset, and was described as pressing, holocephalic, and as mild-to-moderate for most of the time. However, exacerbations to severe intensity (for a few minutes to a few hours) were noted on a few occasions. The patient denied the presence of nausea, vomiting, photophobia, phonophobia, or any cranial autonomic features even during the exacerbation phase. There was no prior history of headache or family history of headache.

The patient gave history of sore throat, cough, and low to moderate grade fever (up to 102°F) of about 1 week duration. These symptoms subsided with treatment (azithromycin and ibuprofen) 2 weeks prior to the onset of daily headache. The patient did not feel any type of headache during that febrile period. Routine hematological and biochemical investigations done at that time were normal except for the presence of leucocytosis.

Prior treatment with various drugs (including indomethacin and a short course of oral prednisolone) provided little or no improvement on headache. Physical examination did not reveal any abnormality. Repeat hematological and biochemical investigations were normal. Magnetic resonance imaging (MRI) of the brain with and without gadolinium (done after 10 weeks of the headache) was reported as normal. Cerebro spinal fluid (CSF) revealed mild pleocytosis (10 cells- all lymphocytes). All other routine parameters of CSF were normal. As IV MPS is one of the treatment options for chronic daily headache, giving a trial of IV MPS was planned. The patient received a 5 days' course of IV MPS (after taking an informed written consent). IV MPS (1,000 mg) was given in 500 ml normal saline over 3 h. The headache started to subside on the third day of infusion and the patient felt marked improvement after 5 days' course of infusion. IV MPS was followed by Oral administration of prednisolone (60 mg daily) with gastric protection (omeperazole). The headache subsided completely in the next 2 weeks. Oral prednisolone was gradually tapered off (25% every alternate day) after 3 weeks. In further 1-year follow-up, she did not experience any headache.

Case 2

A 32-year-old female presented with an 8-week history of continuous headache. The headache was daily and almost continuous since the beginning. It was described as holocephalic, and pressing type. The headache fluctuated from mild to severe in intensity. However, it was of moderate intensity for most of the time. She never felt complete relief from headache since the beginning. The patient occasionally felt nausea, photophobia, and phonophobia. There was no prior history of headache, family history of headache, or history of trauma to head.

The patient had a history suggestive of upper respiratory tract infection (URTI) in the form of recurrent sneezing, nasal discharge, myalgia, and fever. These symptoms were present for about 4–5 days and subsided with over-the-counter medications (cetrizine and paracetamol) about 3–4 weeks prior to the onset of daily headache. The patient did not remember experiencing any headache at the time of URTI.

Physical and neurological examination did not reveal any abnormality. Routine hematological and biochemical investigations were normal. MRI brain (with and without gadolinium) was reported as normal (done after 8 weeks of onset of headache). CSF examination revealed mild pleocytosis (14 cells- all lymphocytes). Prior treatment with various drugs (naproxen, ibuprofen, amitriptyline) had not produced any significant response on the headache. We gave a trial of indomethacin, sodium valproate, and short course of prednisolone. There was just minimal improvement with these drugs. Later on, we gave a trial of IV MPS (1,000 mg daily for 5 days). The patient responded positively, and the headache started to improve within 48 h after the first infusion of IV MPS and it subsided completely after the fifth infusion of IV MPS. Intravenous MPS was not followed by any oral drug. However, headache recurred in mild form after a few days. Oral methyl prednisolone (48 mg daily) was started and the headache subsided within 3 days. Oral methyl prednisolone was withdrawn after 2 weeks. In further 5-month follow-up, she did not feel any type of headache. Repeat CSF done after 4 weeks returned to normal level.

Case 3

A 33-year old woman presented with about 5-month history of holocephalic, non-pulsatile, continuous, mild-to-moderate headache with occasional exacerbations. The headache was almost continuous since the beginning and never had period of remission. The exacerbations, in bouts of a few minutes to a few hours, had a frequency of about one to two attacks per week. The exacerbations were occasionally associated with nausea, photophobia, and phonophobia. However, the feature related to cranial autonomic involvement was not noted. There was no prior history of headache, family history of headache or history of trauma to head. On direct questioning, the patient admitted to having sneezing, nasal discharge, cough, fever, and myalgia a few weeks prior to the onset of headache. These symptoms were treated with over-the-counter medications and the patient was not investigated for that. There was no other significant past medical history. Physical examination revealed no abnormality. Routine hematological and biochemical investigations were normal. CT brain (at 4 weeks), MRI brain without gadolinium (at

5 months), and CSF examination (done in early part of the headache) were reported normal. Prior treatment with various drugs (paracetamol, naproxen, ibuprofen, dothiepin, sodium valproate topiramate, prednisolone, etc.) had produced minimal effect on the headache.

The patient received a trial of IV MPS (1,000 mg daily for 5 days), followed by oral methyl prednisolone (16 mg tds) with gastric protection. The patient started to feel improvement after fifth infusion of IV MPS. This improvement continued and there was almost complete improvement after 2 weeks. After this, oral methyl prednisolone was gradually withdrawn. However, the headache recurred in continuous pattern with occasional exacerbations. Oral methyl prednisolone was restarted at the dose of 16 mg tds. The headache again subsided completely within 1 week. However, the steroid was withdrawn because of the beginning of gastritis after 3 weeks. The headache again reappeared. However, this time headache was very mild. No treatment was started on this occasion. The headache subsided completely in the next 2 months.

Discussion

All of our cases fulfilled all the features of IHS criteria for NDPH, except one stating that the headache should be of >3 months' duration in a few patients (case 1, 2, 4, 7, 9) at the time of first consultation in our outpatient clinic. If we consider the time required for the complete improvement (in follow up), all cases except case 4 fulfilled the time defined in the diagnostic criteria for NDPH. Although >3 months' duration is a must in the diagnostic criteria, daily and unremitting headache from or almost from the moment of onset is considered the most characteristic of NDPH. All our patients had acute onset of headache and the headache was continuous since the beginning. None of these patients was suffering from medication overuse headache. The incidence of medication overuse is probably less in patients with NDPH. The medication overuse was significantly lower with NDPH than that observed with other type of CDH in Kung et al.'s study [5]. NDPH-like headache may be a presentation of another primary headache disorder such as migraine, tension headache, or benign thunderclap headache. However, a diagnosis of migraine, tension headache, or other primary headache disorder presenting as NDPH is very difficult to make in the absence of past history of that primary headache disorders. None of our patients had past history of any type of primary headache.

Relation of headache with infection

Headache can be an accompaniment to both intracranial and systemic infection. When the causative (intracranial) infection is effectively treated, or remits spontaneously, but headache persists for more than 3 months, then chronic post infectious headache is diagnosed. The only subgroup of chronic post infectious headache is chronic post-bacterial meningitis headache. In this group, the headache is a direct continuation of headache attributed to bacterial meningitis. There is little evidence for persistent headache following other intracranial or systemic infections. However, IHS acknowledged a possibility of post-non-bacterial infection headache in the Appendix (A9.4.2) [2].

An association of NDPH with infection is widely reported in the literature. About 30–43% of NDPH patients may have their headache onset after an infection, and infectious etiology has been suggested in a subset of patients with NDPH [3, 6]. Santoni-Santoni-william identified evidence of extracranial or systemic infections in 108 patients. All patients responded to antibiotics (as inclusion criteria). Headache was a solitary symptom in about 36% patients [7]. The serological tests for various viruses have been done in patients with NDPH. Evidence of Epstein-Barr virus (EBV) infection (active or past infection) has been demonstrated in various observations. Diaz Mitoma et al. [8] demonstrated evidence of active EBV infection in 27 of 32 patients with NDPH compared with 8 of 32 controls. Mack [6] identified 40 patients with NDPH. Seventeen patients had the onset of headache during an infection. Of these patients, over half had positive EBV serology at the onset of symptoms. EBV antibody titers indicating past infection were identified in 71% of seven patients tested in Li-Rozen et al.'s case series of 56 patients [3]. However, later on various other viral infections such as HSV, CMV, etc. were noted in patients with NDPH [9]. Based on these observations, viral infections have been implicated as a possible cause for NDPH. However, a possibility of EBV reactivation secondary to stress resulting from chronic headache has also been suggested for positive EBV titer in patients with NDPH [8].

The relation of headache in post infectious illness has not been elaborated well in the literature. Various post infectious CNS disorders may have headache as one of the accompanying symptoms. However, headache as an isolated or a presenting complain of post infectious illness has not been well acknowledged in the literature. The classical post infectious central nervous system disorders are acute disseminated encephalomyelitis (ADEM) and acute transverse myelitis (ATM). IHS recognizes headache as a symptom of ADEM. According to the 'notes' of IHS classification, headache is not usually a presenting or dominant symptom [2]. However, review of the literature suggests that headache may be a presenting symptom (with other symptoms) or a predominate feature in patients with ADEM. Headache was reported as one of the presenting symptoms in about 27–58% in patients with ADEM [10].

Johnsen et al. [11] reported four cases of subtle ADEM in children. In two of them, the main or presenting complain was headache of a few months' durations. A computed tomography (CT) scan of the head in both patients was normal. However, a MRI brain revealed a few hyper intense white matter lesions.

Are headache and other clinical profiles of NDPH comparable to ADEM?

As noted earlier, the most characteristic feature of NDPH is "daily and unremitting from very soon after onset (within 3 days at most)". The onset of ADEM is comparable to NDPH. The onset of ADEM is rapidly progressive and usually develops over hours to maximum deficits within days (mean, 4.5 days) [12]. The clinical characteristics of headache in patients with ADEM are not described in detail in the literature. However, it is presumed to be of mild-to-moderate intensity (like NDPH) [2]. NDPH and ADEM are both reported predominantly in children and early adulthood. Moreover, headache in ADEM is more predominant in children than adult [12]. NDPH is a slightly female-predominant disorder. However, a few case series have demonstrated male predominance or equal male–female ratio [13, 14]. The male–female ratio was almost equal in our case series. The associated symptoms described in patients with NDPH (such as photophobia, phonophobia, nausea, vomiting, stiffness, concentration problem, blurred vision, insomnia, tinnitus, numbness, tingling, vertigo, focal sensory or motor symptoms, etc.) are well-described features in patients with ADEM [3]. As noted earlier, serological marker of EBV (recent or past infection) is the most common viral marker in NDPH. EBV infection is considered as a main antecedent infection even in patients with ADEM [15]. The role of neuroimaging in patients with NDPH is to rule out secondary causes of headache. In general, there is a suggestion for CT brain for acute headache and MRI brain for chronic headache disorders (especially when associated with red flag signs) [16]. NDPH is a chronic headache disorder with acute onset. Therefore, the type of neuroimaging and timing to perform it may be vital in patients with NDPH. There is no suggestion or recommendation for neuroimaging in patients with NDPH. Many case series did not mention any detail about neuroimaging. In a few case series, neuroimaging was not done in all the patients [3, 13]. The case series that reported neuroimaging in their patients did not give details of neuroimaging, especially the timing when neuroimaging was performed (and including type of neuroimaging and use of gadolinium). In our all patients (except case 4) MRI brain was done only after 8 weeks of onset of headache. It was reported as normal in all the cases. CSF examinations were done in a very few case reports/series in the literature, and it was reported as normal. CSF examinations were done in our six patients (between 6 and 9 weeks of onset of the symptoms). Two of them showed mild pleoctyosis with normal opening pressure, protein and glucose. Repeat CSF examination was done in one of these patients that returned to normal in 4 weeks durations. This CSF abnormality is comparable to CSF abnormality of ADEM. Rozen and Swidan have demonstrated elevation of tumor necrosis factor-α (TNF-α) in patients with NDPH [17]. Similar observation has been observed in patients with ADEM [12].

The natural course of ADEM cannot be compared with that of NDPH as course of untreated ADEM is largely unknown [12]. Treatment with high dose steroid is not reported in the patients with NDPH in the literature. However, steroids (including IV MPS) are known as effective therapeutic agents for treating various types of chronic or sustained headaches such as status migrainous, chronic migraine, medication overuse headache, hemicrania continua, etc. [18, 19]. This prompted us to use IV MPS in case 1. The positive response encouraged to use this drug in other similar type of patients. Before initiating IV MPS therapy, we attempted to rule out the possibility of active infections of the brain and other parts of the body by careful history taking and investigations. There was a temporal relation in the beginning of relief in the headache and administration of IV MPS. The relief of headache started between the second and fifth day of infusion in all the patients. The steady improvement in headache continued and seven patients felt almost-complete improvement within 2 weeks. In other two patients (cases 6 and 7), complete improvement was noted between 6 and 8 weeks after initiation of IV MPS therapy. Six patients received oral steroids (either prednisolone or methyl prednisolone) for 2–3 weeks. Withdrawal of oral steroid led to recurrence of the headache on two occasions in one patient (case 3). The improvement pattern of headache in our patients was comparable to that of ADEM.

Are these secondary headaches?

The diagnostic criteria for secondary headaches in the IHS classification include (A). Headache with one (or more) of the following characteristics and fulfilling criteria C and D. (B) Another disorder known to be able to cause headache has been demonstrated. (C) Headache occurs in close temporal relation to the other disorder and/or there is other evidence of a causal relationship. (D) Headache is greatly reduced or resolves within 3 months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorders [2].

For most secondary headaches, the characteristics of the headache itself are poorly described in the literature.

Therefore, diagnostic criterion A does not contribute much to establish causation. However, criteria B, C, and D effectively establish causation [2]. As mentioned earlier, post infectious illnesses are known to produce headache (criterion B). Viral infection is a common occurrence in the general population. Viral infections may occur 4–6 times per year on average in children. Therefore, the medical history of presumed viral infection may be positive in about 33–50% of time in children at any time. Therefore, a causal relation of any disease entity with viral or other infections should be considered very cautiously. A latency period of less than 30 days has been suggested as a possible link between a febrile event and a post infectious entity [20]. Our cases all have less than 30 days of latency. Therefore, a possibility of causal link exists in our patients. As far as criterion D is concerned, seven patients showed almost complete relief from headache within 2–3 weeks of initiation of IV MPS therapy. Other two patients showed marked improvement in 2–3 weeks and improvement continued for next few months. One patient (case 2) showed recurrence of headache after completion of 5 days' course of IV MPS. This patient responded again to oral steroid. Withdrawal of oral steroid resulted in recurrence of the headache on two occasions in case 3. This temporal relation of initiation of steroid therapy and relief from the headache suggests that IV MPS was pivotal in relief of the symptoms. However, we cannot rule out other possibilities for the remission phase—especially spontaneous remission. A self-limiting form of NDPH is well described in the literature. There is no data or clinical features that may predict which patient is going to have self-limiting form of NDPH. Even the self-limiting form may take up to 24 months to show spontaneous remission [1]. Therefore, we should be very cautious in claiming any drug as being efficacious or inefficacious in patients with NDPH, especially in case reports/series. In the absence of any structural abnormality in neuro-imaging in our patients, it is difficult to speculate on that our patients have restricted form of ADEM. However, the similarity in the epidemiological features, clinical pattern of headache, associated clinical features (such as photophobia, phonophobia, nausea, vomiting, stiffness, concentration problem, etc.) in the literature, and our patients indirectly points that a subset of patients with NDPH may have a restricted form of ADEM, manifesting as an isolated headache. High incidence of evidence of EBV infection in both disorders further strengthens this view. Elevation of TNF-α in Rozen and Swidan case series and mild pleocytosis in our two cases in CSF are other supporting points for this notion. History of antecedent infections and a temporal relation of relief with high-dose intravenous steroid in our patients are two new observations that further reinforce the possibility of headache of post infectious origin. The response to IV MPS was early and marked in the patients with history of shorter duration (less than 4 months). This indicates that early initiation of the therapy may be vital in providing remission phase.

Mechanisms

Our cases and review of the literature suggest that headache of NDPH is comparable to that of ADEM. Therefore, headache in our patients and a subset of patients of NDPH may be a part of paucisymptomatic encephalomyelitis. It is difficult to speculate on the possible mechanisms of headache in our patients as the mechanisms of headache even in ADEM (and other demyelinating disease) and NDPH is not well explored in the literature. Acute onset of headache in patients with NDPH is highly suggestive of some etiology. It is puzzling for the treating physician not to find any abnormality in neuroimaging and laboratory investigations [4]. CNS immune activation is considered as a possible mechanism for the development of ADEM. The demonstration of proinflammatory cytokine in CSF in the Rozen–Swidan study suggests CNS activation in the patients with NDPH. Di Lorenzo et al. reported a case of NDPH secondary to heat stroke and suggested a possibility of immune reaction as a mechanism [21]. In patients with acute onset of headache, usually CT scan is advised, but CT scan is not a good diagnostic tool for investigating a possible demyelinating lesion. MRI brain with double dose contrast is preferable for a demyelinating lesion. MRI brain done in late part of the demyelinating disease may not reveal any abnormality, as lesions tend to resolve with time [11]. In most of our patients, MRI brain was done after 2 months. MRI brain with double-dose gadolinium in early part of the disease is required. ADEM is known to involve meninges, and meningeal features (such as nausea, vomiting, photophobia, meningeal signs) are common features in the patients with ADEM [10–12]. Lymphocytic meningitis has been demonstrated in the patients with ADEM [10]. Most of our patients had nausea, photophobia, or phonophobia. Although meningeal sign was absent in our patients, neck stiffness (with nausea, photophobia, phonophobia) was a common accompanying feature (50%) in Li and Rozen's case series of NDPH [3]. This indirectly suggests a possibility of meningeal involvement in a subset of patients with NDPH, including our cases. The presence of CSF pleocytosis in our two cases may be an indication of secondary NDPH.

Besides this, mechanisms responsible for other post infectious illness (such as reactive arthritis) may be responsible for the generation of the headache. Reactive arthritis (ReA) is a non-purulent joint inflammation secondary to a primary infectious process elsewhere in the body. The proposed mechanisms for the generation of

ReA is the persistence of pathogenic organisms or its products in the joint/synovium leading to local immune response [22]. The course of ReA is comparable to that of NDPH: short or self-limiting form, continuous, and remitting form [22]. Although acute ReA may be associated with low TNF-α, chronic ReA shows high production of TNF-α (like NDPH) [23]. Therefore, we speculate a local immune reaction in the meninges for the generation of headache in our patients and a subset of NDPH. The response to steroid is another point to suggest immunological or inflammatory pathophysiology in our patients as high dose of IV MPS or other steroid is well known therapeutic option in many post infectious illness. NDPH usually begins with infection (flu like illness). The non-headache symptoms resolve but headache remains. We can call it as 'immediate post infectious NDPH'. However, in our case series headache appeared only after 2–5 weeks of febrile illness (delayed post-infectious NDPH). Delayed onset of headache after a febrile period may be because of milder immune response, thus more amenable to steroid therapy.

The very high levels of steroid obtained by MPS probably act in some different ways. Boumpas [24] suggests that very high dose steroid increases NF-kappaB binding protein in the cytosol that may reduce the amount of pro-inflammatory transcription factors. Buttgereit et al. [25] have suggested that very high dose of steroid will lead to activation of membrane-bound steroid receptor and physico-chemical interactions with cellular membrane to increase immunosuppression.

Chronic administration of steroids is known to result in a number of side effects. The first reported use of mega doses of IV steroid was in 1969 to prevent renal allograft rejection and this type of therapy was termed as 'Big Shot'. Since the beginning of the use of high-dose pulses of corticosteroid, there was anticipation that there would be significant and limiting side effects. Although various types of side effects are reported with IV MPS, it is generally considered as safe as majorities of the side effects are transient and self-limiting and do not require specific treatment. A few case reports of sudden death have been reported following rapid administration of MPS (administered over less than 10 min). Therefore, it should not be administered rapidly. Ideally, it should be infused slowly over 2–3 h (not less than 30 min) [26, 27]. Recently, Hussain et al. [28] reported three patients with chronic severe migraine who developed aseptic osteonecrosis (AON) with short-term, intermittent pulse doses of steroids. We should be cautious for this disabling condition in patients who have received steroids for disabling and chronic headache, as both chronic severe headache and steroid use may be risk factors for AON. None of our patients showed any side effects related to IV MPS. One patient (case 3) showed mild gastrointestinal symptoms with oral steroid on follow-up.

Although we observed our patients prospectively, it has a number of limitations. We did not compare it with other patients with NDPH. We observed eight more patients with NDPH (but without history of any antecedent infection) during the same observation period. Only two patients received IV MPS and both showed only minimal response to the therapy. Our all patients admitted to having antecedent infections before the onset of headache. However, we do not have any serological evidence for that. Another limitation in our observation is headache of shorter duration. Our five patients had a history of less than 3 months at the time of consultation. Duration of headache in other four patients was between 14 and 20 months. Besides these, we cannot rule out even the possibility of other cause of headache (secondary) responsive to steroid, as full evaluation for secondary headache was not done.

If our observations and treatment response of IV MPS can be confirmed in other cases, it could be a therapeutic option for the patients with NDPH-like headache with history of antecedent infections, especially if caught in early stage. It will also open a window to take a trial of other immunosuppressive drugs in refractory cases of NDPH. It is also hoped that these cases may serve as a catalyst for early investigations (MRI with gadolinium, CSF examinations, search for biological markers, etc.) to clarify the issue.

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Conflict of interest None.

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