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Case Report

# Neurogenic heterotopic ossification in Guillain-Barre syndrome: a rare case report

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**Abstract**

Neurogenic heterotopic ossification (NHO) is an abnormal development of bone in extra-skeletal tissues, related to neurological disease. NHO is frequently seen after traumatic brain injury or spinal cord injury. NHO may also occur as a rare complication of Guillain Barre Syndrome (GBS). Here, we present a 39 year old man with an acute onset of GBS who developed NHO around both hips two months after the disease onset. Our patient had a history of mechanical ventilation, incomplete tetraplegia and prolonged immobilisation. The pathogenesis of NHO is unclear. Various risk factors have been associated with the development of NHO; prolonged coma, long-term sedation, spasticity, degree of paralysis. NHO is a rare complication of GBS and physicians should be aware that it can develop especially in patients with severe paralysis and in need of mechanical ventilation. Pain and restriction of movements, especially in the hips, should bring NHO to the mind.

**Keywords:** Neurogenic Heterotopic Ossification, Guillain Barre Syndrome, Prolonged Immobilisation, Mechanical Ventilation, GBS

## Introduction

Neurogenic heterotopic ossification (NHO) is an abnormal development of bone in extra-skeletal tissues, related to neurological disease. NHO is frequently seen after traumatic brain injury (TBI) or spinal cord injury (SCI), with an incidence of 20-30% in SCI and 5-20% in TBI patients[1,2]. NHO may also occur as a rare complication of Guillain Barre Syndrome (GBS). Zelilig and colleagues followed 65 patients with GBS for three years, and only 4 (6%) of them had NHO[3]. Neurologic damage (TBI, SCI, GBS, stroke), trauma, tissue hypoxia, fever lasting more than five days, genetic predisposition, male sex, spasticity, prolonged coma and artificial ventilation are various risk factors associated with the development of NHO[4,5]. NHO often forms around the hip, knee and shoulder joints, and may cause pain and limitation in joint movements. The exact pathophysiological mechanism of NHO is not completely understood[1-4]. Here we present a 39 year old man with an acute onset of GBS who developed NHO around both hips two months after the disease onset.

## Case report

A 39 year old man was admitted to the emergency department with paraesthesia in all limbs, diplopia, and nausea since two days. Within a few hours the patient developed weakness in both the lower and upper limbs. His neurologic examination revealed bilateral abducens nerve paralysis, facial diplegia, flaccid areflexic paralysis of the limbs (corresponding to Medical Research Council grade 3/5 in all muscles of the upper extremities and 2/5 in lower extremities) and bilateral flexor plantar responses. The bowel and bladder were not initially involved. The patient underwent electromyography examination with the possible diagnosis of GBS. The electromyogram confirmed an acute, acquired, disseminated polyneuropathy syndrome involving sensory, motor and autonomic fibers, with prolongation of the distal motor latency, prolongation of the F-wave, decreased sensory

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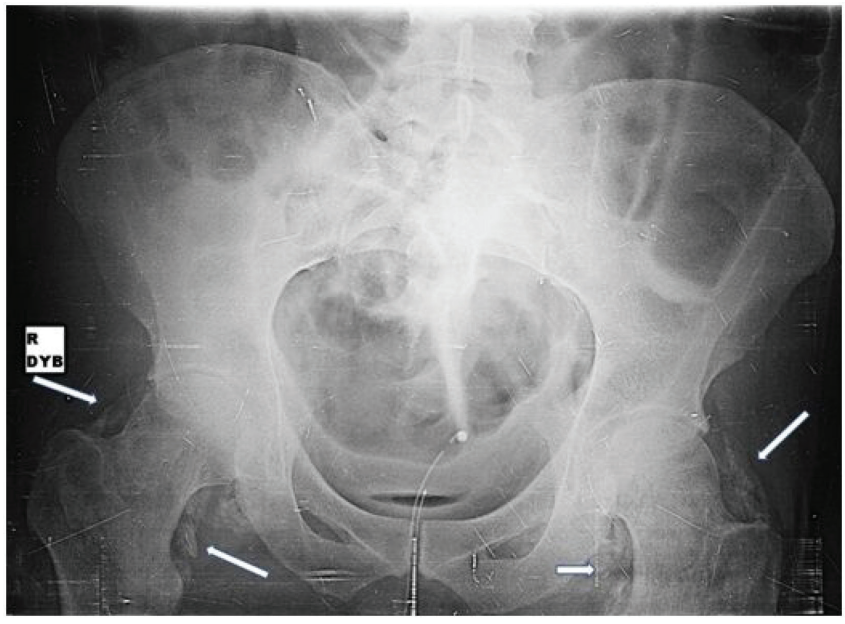


**Figure 1.** Arrows are pointing NHO on the anteromedial and anterolateral aspects of both femurs (The Brooker Classification Class 3).

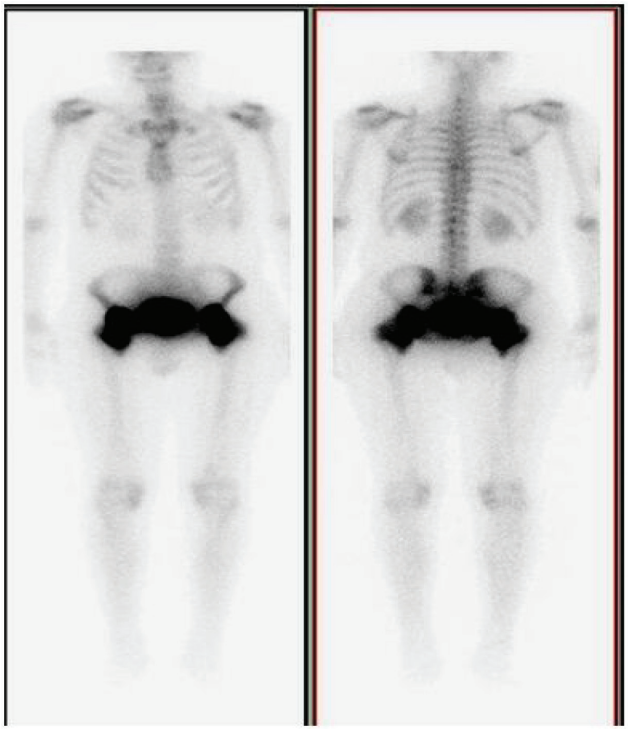

**Figure 2.** Three-phase bone scan study shows prominent Tc99m-MDP uptake in the acetabulum, proximal femur and trochanter bilaterally.

and motor nerve amplitude, disperse responses and reduced nerve conduction velocities. The cerebrospinal fluid revealed an elevated protein concentration with a normal cell count. Anti-ganglioside antibodies were negative. Intravenous immune globulin (IVIG) was then administrated at a dosage of 0.4 mg/kg/daily. The same day weakness progressed rapidly in his all extremities, rendering him unable to stand due to total loss of strength in all muscle groups. The 6$^{th}$ and 7$^{th}$ cranial nerves were involved in both sides, and respiratory muscle weakness appeared. This progressed to a respiratory failure that required mechanical ventilation. The patient remained in the intensive care unit for two months. IVIG was administrated again over 5 days for a total dose of 2 g/kg body weight, after five sessions plasmapheresis performed on every other day. Treatment with a booster IVIG (0.4 gr/kg/day) was continued every 15 days. Rehabilitation was also performed from the beginning of the disease. In addition oral prednisolone was administered at 1mg/kg/day, which was reduced by 5 mg every two weeks.

Two months after the onset of GBS, pain and decreased range of motion (ROM) emerged in both hips. NHO was diagnosed on the plain X rays of the pelvis. NHO was visible on the anteromedial and anterolateral aspects of both femurs (Figure 1). The serum calcium was 10.5 mEq/L (normative range 8.6-10 mEg/L) and the serum alkaline phosphatase was 61 IU/L (40-129 IU normative range). Intravenous ibandronic acid 150 mg was given weekly until the patient began to take orally. IV ibandronic acid was discontinued and etidronate disodium was administered 10mg/kg for 10 weeks. ALP and Ca levels were measured periodically. The

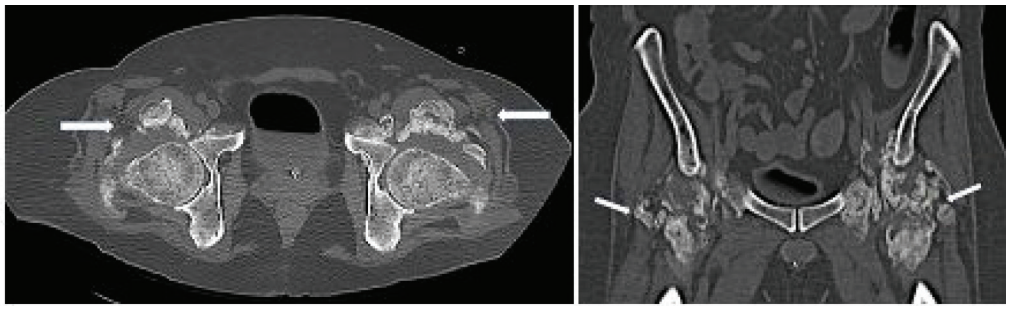

**Figure 3.** Under computed tomography guidance, corticosteroid injection was made to the periarticular portions of both hips (shown by arrows).

rehabilitative management continued, including passive and active - assistive ROM exercises for major joints, breathing exercises and electrotherapy for all upper and lower limb muscles. When the patient was discharged from the ICU after two months, the muscle strengths improved in all extremities (grade 3/5 in the upper and 2/5 in the lower extremities). The patient could stand up with support; however could not walk or sit in low position due to pain and limitation in the movements of hip joints. Passive ROM of both hips was restricted to 40º of flexion and 20º of internal and external rotation. Three-phase bone scan study showed prominent Tc99m-MDP uptake in the acetabulum, proximal femur and trochanter bilaterally (Figure 2). Under computed tomography guidance, corticosteroid injection was made to the periarticular portions of both hips (Figure 3). The pain decreased and a 10º degree flexion was achieved after injection. At 6 months follow up, his rehabilitation program continues. He can walk with a walker, and sit without support.

## Discussion

The pathogenesis of NHO is unclear. The pathological phenomenon is abnormal formation and accumulation of bone in non-osseous tissues. It is generally agreed that after neurogenic injury an anti-inflammatory cascade of signalling starts, which stimulates the mesenchymal stem cells to differentiate into chondrocytes and osteoblasts; however recent studies showed that NHO is associated with neuroinflammation and neural crest bone formation[2,5-6]. Bone morphogenetic proteins (BMPs) are signalling factors that cells use for embryonic development and tissue regeneration. They play a role in cell proliferation, apoptosis, differentiation, cell fate determination and morphogenesis of all tissues including nervous and musculoskeletal systems[7]. It is suggested that damage to the bone from traumatic injury may release BMPs which will open blood-nerve barrier (BNB) and induce neuroinflammation in the nerves near to the injury site[2,5-6]. Neural crest stem cells and progenitors are found in endoneurium which is protected from external environment by the BNB. With opening of BNB , these cells, more BMPs and inflammatory cytokines will be released into blood stream. Elevated BMPs in blood also induce the production of brown adipose tissue (BAT) which promotes angiogenesis and hypoxic environment. Neuroinflammation cascade, elevation BMPs levels, production of BAT will accelerate neural crest stem cells to undergo osteogenic differentiation and form NHO[5-6]. Various risk factors have been associated with the development of NHO; prolonged coma, prolonged mechanical ventilation, long-term sedation, spasticity, degree of paralysis as well as other factors specific to the individual such as genetic or other unidentified factors[2-3,8-9]. Chauveau et al found higher expression of osteocalcin and osteonectin mRNA in bone cells of HO when compared to healthy bone cells. In an another study, Chauveau et al demonstrated higher levels of SP7, a transcription factor that is essential for osteoblast differentiation and skeletal development in HO samples when compared to normal ones[8,9]. Expression of the higher level transcript factors may be due to neuroinflammation and elevated BMPs.

GBS is an autoimmune inflammatory polyneuropathy that damages myelin and axons. Primary target can be myelin or axon[10]. BNB is altered and disturbed in immune mediated neuropathies such as GBS[11]. BMPs are potent inhibitors of oligodendrocyte differentiation and myelin protein expression. Expression of BMPs is increased in demyelination pathologies[12]. It can be hypothesized that although there is no traumatic injury or bone fracture in GBS; neuroinflammation in peripheral nerves, immune mechanisms, disruption of BNB and elevated levels of BMPs may cause NHO in GBS.

NHO is seen after TBI, SCI, stroke, poliomyelitis and GBS. Zeilig et al reported that 6% of patients with GBS had NHO during follow up[3]. All patients with GBS who developed NHO had a history of mechanical ventilation and prolonged immobilisation. Mechanical ventilation and long period of immobilization may change acid-base balance and impair oxygenation of tissue.

All patients with GBS had NHO at the hip. NHO usually affects hip and knee joints[1,2]. In a study by Ponrartana S, it

is found that BAT volume is strongly associated dimension of femur and amount of muscle at the midtight[13]. BAT promotes angiogenesis and hypoxic environment which makes a proper floor for NHO formation[5-6]. This may be a reason why patients mostly have NO around hip joints in which high BAT volume exits.

Diagnosis of NHO was made at an average of 3 months in Zeilig's study. There are other reports of patients who developed NHO after GBS[9,14]. All these cases share neurological damage, prolonged immobilisation and hip involvement in common. Our patient had NHO around both hips. He had a history of mechanical ventilation, incomplete tetraplegia and prolonged immobilisation.

The clinical signs and symptoms of NHO start to develop 4-12 weeks post injury with a peak occurrence at 2 months. NHO typically presents with a non-specific inflammatory reaction (pain, heat, swelling, erythema) which makes it difficult to diagnose as these symptoms are similarly present in sepsis, cellulitis, deep vein thrombosis and osteomyelitis. As the NHO progresses, ROM of the joint is decreased, and may even result in joint ankylosis 2. Our patient reported hip pain during physical therapy, 2 months after the onset of disease. We also detected limited ROM in the hips.

Non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates and radiation therapy are current treatments to prevent and treat NHO. NSAIDs target to stop the inflammation of NHO. We did not use NSAIDs in this case because there is an increased risk of bleeding and impairing renal function. Bisphosphonates inhibit the formation of bone mineralisation. Although we used bisphosphonates in the early stage of NHO, the condition progressed. Once NHO has mineralised (detected radiographically) bisphosphonates will be less effective. Surgical excision is the only option if the functional impairment and pain cannot be resolved. Surgical excision is usually delayed until the growth and maturation of NHO is complete. This purpose of waiting for maturity is to minimise the rate of recurrence after surgical excision; however recent studies indicate that there is no correlation between this timing and NHO recurrence[14-18]. Surgical excision can be made before maturation of progressive NHO. Our patient will be a candidate for surgical excision if he cannot gain independent ambulation.

## Conclusion

NHO is a rare complication of GBS, and physicians should be aware that it can develop especially in patients with severe paralysis and in need of mechanical ventilation. Pain and restriction of movements, especially in the hips, should bring NHO to the mind.

## References


1. Gil JA, Waryasz GR, Klyce W, et al. Heterotopic Ossification in Neurorehabilitation. R I Med J 2015; 98(12):32-4.
2. Brady RD, Shultz SR, McDonald SJ, et al.Neurological heterotopic ossification: Current understanding and future directions. Bone 2017 May 16. pii: S8756-3282(17)30173-4. doi: 10.1016/j.bone.2017.05.015.
3. Zeilig G, Weingarden HP, Levy R, et al. Heterotopic Ossification in Guillain Barre Syndrome:incidence and effects on functional outcome with long-term follow-up. Arch Phys Med Rehabil 2006;87(1):92-5.
4. Ryu SR, Kim JH, Choi IS, et al. Heterotopic ossification as an unusual complication after Guillain-Barré syndrome: a case report. Arch Phys Med Rehabil 2008; 89(3): 564-7.
5. Davis EL, Davis AR, Gugala Z, et al. Is heterotopic ossification getting nervous?: The role of the peripheral nervous system in heterotopic ossification. Bone 2017; 15. pii: S8756-3282(17)30242-9.
6. Huang H, Cheng WX, Hu YP, Chen JH, Zheng ZT, Zhang P. Relationship between heterotopic ossification and traumatic brain injury: Why severe traumatic brain injury increases the risk of heterotopic ossification. J Orthop Translat 2017;12:16-25.
7. Hogan BL. Bone morphogenetic proteins:multifunctional regulators of vertebraye development. Genes Devop 1996;10(13):1580-94.
8. Chauveau C, Broux O, Delecourt C, et al. Gene expression in normotopic and heterotopic human bone: increased level of SP7 mRNA in pathological tissue. Mol Cell Biochem 2008;318(1-2):81-7.
9. Chauveau C, Devedjian JC, Blary MC, et al. Gene expression in human osteoblastic cells from normal and heterotopic ossification: Exp Mol Pathol 2004; 76(1):37-43.
10. Ohnmar H, Roohi SA, Naicker AS .Massive heterotopic ossification in Guillain-Barré syndrome: a rare case report. Clin Ter 2010;161(6):529-32.
11. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. Lancet 2016;388(10045):717-27.
12. Kanda T. Biology of the blood-nerve barrier and its alteration in immune mediated neuropathies. J Neurol Neurosurg Psychiatry 2013;84(2):208-12.
13. Grinspan JB. Bone Morphogenetic Proteins:Inhibitors of Myelination in Development and Disease. Vitam Horm 2015;99:195-222.
14. Ponrartana S, Aggabao PC, Hu HH, Aldrovandi GM, Wren TA, Gilsanz V.Brown adipose tissue and its relationship to bone structure in pediatric patients.J Clin Endocrinol Metab 2012;97(8):2693-8.
15. Mukhi PK. Desantis NM. An unusual presentation: Heterotopic ossification in a patient with inflammatory demyelinating polyradiculoneuropathy. AJPMR 1996; 75(2):155-6.
16. Sullivan MP, Torres SJ, Mehta S, et al. Heterotopic ossification after central nervous system trauma. Bone Joint Res 2013;1;2(3):51-7.
17. Cipriano CA, Pill SG, Keenan MA. Heterotopic ossification following traumatic brain injury and spinal cord injury. J Am Acad Orthop Surg 2009;17(11):689-97.

18. Chalidis B, Stengel D, Giannoudis PV. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: a systematic review of the literature. J Neurotrauma 2007;24(11):1675-86.

19. Almangour W, Schnitzler A, Salga M, et al. Recurrence of heterotopic ossification after removal in patients with traumatic brain injury. Ann Phys Rehabil Med 2016; 59(4):263-9.