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Hymenoptera sting as atypical causative factor for Guillain Barré Syndrome and chronic inflammatory demyelinating polyneuropathy – A case report and insights on pathophysiology

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ABSTRACT

Introduction. Neurological manifestations secondary to Hymenoptera stings are rare. However, the literature describes cases of severe central and peripheral nervous system damage. Suspected pathophysiological mechanisms include hypoxic-ischemic damage, demyelination, and the direct neurotoxic effect of venoms. In this context, bee stings could be a possible atypical causative factor for Guillan–Barré syndrome and chronic inflammatory demyelinating polyneuropathy.

Case report. We present the case of a 32-year-old patient who declared the presence of a bee sting two weeks before the onset of neurological manifestations (flaccid quadriparesis, predominantly distal, with paresthesia at the same level) that were initially diagnosed as a Guillain Barré syndrome. Despite the treatment with immunoglobulins in the acute phase, the worsening of the motor deficit after one month required a new course of immunoglobulins, associating corticosteroids, with initially favorable evolution. However, the presence of a new relapse after eight weeks, correlated with changes such as albumin-cytological dissociation in the examination of the cerebrospinal fluid and the appearance of active denervation on the electroneuromyography study, established the final diagnosis of chronic inflammatory demyelinating polyneuropathy.

Conclusions. We consider the presented case proof of the relationship between the Hymenoptera sting and various peripheral nervous system pathologies. Inflammatory and demyelinating changes common to Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy appear to be the primary pathophysiological mechanism to explain this uncommon correlation.

Keywords: Hymenoptera sting, Guillain Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelination

List of abbreviations

CIDP	– chronic inflammatory demyelinating polyneuropathy
CNS	– central nervous system
CSF	– cerebrospinal fluid
GBS	– Guillain Barré syndrome
HIV	– Human Immunodeficiency Virus
IVIg	– intravenous immunoglobulins
MBP	– myelin basic protein
PNS	– peripheral nervous system

INTRODUCTION

Guillain Barré Syndrome (GBS) is an acute demyelinating disease characterized by inflammatory damage to the peripheral nervous system, particularly to the myelin sheath of the nerve fibers, thus explaining the various clinical manifestations [1]. The incidence of GBS is 1 to 2 cases per 100,000 per year

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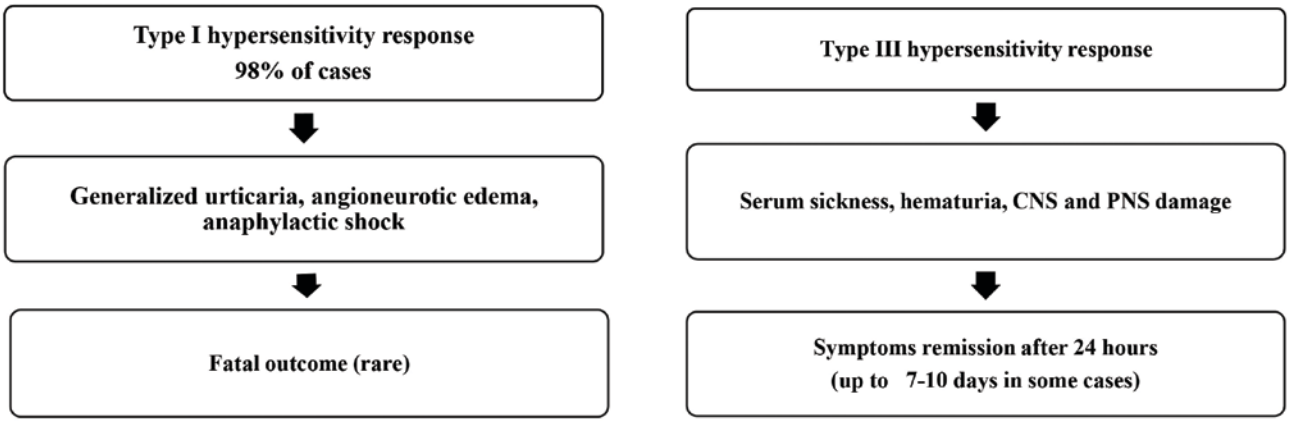

FIGURE 1. Hypersensitivity responses to Hymenoptera sting

worldwide, according to the latest epidemiological data [2]. While all age groups are affected, the incidence increases by approximately 20 percent with each 10-year increase in age after the first decade of life [3]. In addition, the incidence of GBS is slightly higher in men than women [3]. There is regional variation among variants of GBS, with axonal forms being more common in Asia than in North America or Europe, where demyelinating forms predominate [4]. About two-thirds of patients with GBS mention inflammatory or infectious events preceding the development of symptoms and signs of neuropathy [5].

Chronic inflammatory demyelinating polyneuropathy (CIDP) can be considered the chronic form of GBS. CIDP is usually characterized by a relapsing-remitting or progressive course of symmetrical proximal and distal muscle weakness [6]. The reported prevalence of CIDP ranges from 0.8 to 8.9 cases per 100,000 persons [7]. There is a male predominance, with a sex ratio ranging from 1.5 to 4 [8]. It primarily affects adults, and the incidence increases with age. The typical age of onset is not well established; some studies have reported the average age of presentation in the sixth decade, but CIDP can also occur in children [9].

No specific predisposing risk factors for CIDP have been identified. In this context, the authors discuss the role of the Hymenoptera sting as a possible atypical causative factor for GBD/CIDP. Although neurological manifestations secondary to Hymenoptera stings are rare, the literature reports cases of severe central and peripheral nervous system damage [10,11]. Suspected pathophysiological mechanisms include hypoxic-ischemic damage, demyelination, and the direct neurotoxic effect of venoms [12]. These side effects could be due to and explained by the fact that Hymenoptera venom contains both low molecular mass substances (biogenic amines, amino acids, phospholipids, kinins) and high molecular mass proteins (phospholipase, hyaluronidases, esterase, acid phosphatase), which are relevant in inducing and triggering allergic and toxic reactions to venoms [13]. In most cases, the allergy to insect venom is manifested by immediate type I hypersensitivity response: generalized urticaria, massive angioneurotic edema, or anaphylactic shock, sometimes with a fatal outcome [14]. As Figure 1 shows, only a small number of cases fall into type III hypersensitivity response, with remission of symptoms after 24 hours, up to 7-10 days, manifested clinically similar to serum sickness [15].

Besides hypersensitivity responses, neurological complications are even less common and rarer, affecting both the central (CNS) and peripheral nervous system (PNS). Among Hymenoptera sting-related CNS damage, some authors report several neurological severe manifestations, such as acute disseminated encephalomyelitis or cerebral infarction [16]. Regarding PNS damage, Hymenoptera venom was linked to peripheral neuritis, optic neuropathy, and myasthenia gravis [17].

In the context of scarce literature data available at present, this paper aims to present a possible atypical case of GBS/CIDP following a bee sting, with the subsequent discussion on the possible pathophysiological pathways that might explain this uncommon correlation.

CASE REPORT

We present the case of a 32-year-old patient from a rural area of eastern Romania who works as a beekeeper and who presented himself to the Neurology Clinic of the County Emergency Hospital for worsening flaccid quadriparesis, predominantly distal with paresthesia at the same level and difficulty walking. The symptoms had an acute onset approximately 3.5 months before the presentation, with the simultaneous appearance of paresthesia in the fingers and toes and a motor deficit in the upper and lower limbs, more severe distally than proximally, with an ascending character. A GBS was initially diagnosed, so he was treated with intravenous immunoglobulins (IVIg) 0,4 g/kg/day for five days. Of relevance for the

anamnesis, we mention the presence of a bee sting about two weeks before the onset of the neurological manifestations. The response to IVIg was satisfactory, significantly improving the motor deficit. However, after one month, an aggravation of the motor deficit reoccurred, this time associated with paresthesia in the four limbs, dysphagia for liquids and solids, and respiratory difficulties, which required endotracheal intubation. An additional treatment regimen with IVIg was applied in doses similar to the first attempt; however, this time, with associated corticosteroid therapy in a progressively reduced dose. Subsequent evolution was favorable, with the patient being weaned from the ventilator. Rehabilitation therapy followed, with improvement of motor deficit and increase of muscle tone, resumption of walking with bilateral support for medium distances and without support for short distances.

The later evolution, despite initial significant improvement in neurological deficits, was marked by a new episode that appeared 2.5 months after discharge. The patient returned to the Neurology Clinic for worsening neurological symptoms with acute onset (for approximately 4-5 days), similar to the complaints from the first admission. The presence of a new relapse after eight weeks, correlated with changes in paraclinical examination, such as albumin-cytological dissociation in the cerebrospinal fluid (CSF) examination, together with the appearance of active denervation on the nerve conduction studies, established the final diagnosis of CIDP.

DISCUSSION

In the current article, the authors present an interesting case, which could be evidence for the link between GBS/CIDP and Hymenoptera sting. Although the cause of CIDP and its variants remains unknown, evidence supports the hypothesis that these disorders are immunologically mediated and may have multiple triggers [18]. The adaptive immune system's cellular and humoral components appear to be involved in the pathogenesis of CIDP and its variants [19]. The involvement of cellular immunity is supported by evidence of T cell activation, crossing of the blood-nerve barrier by activated T cells, and expression of inflammatory cytokines, such as tumor necrosis factor, interferons, and interleukins [20]. The implication of humoral immunity is demonstrated by the roles of immunoglobulin (Ig) and complement deposition on myelinated nerve fibers. This was highlighted by passive transfer experiments, where conduction blocks and demyelination were induced by injecting serum or purified IgG from CIDP patients into rats [21]. Still, the specific immunological triggers for CIDP remain unclear in most patients.

On the contrary, in the case of GBS, up to two-thirds of patients have a history of respiratory or gastrointestinal tract infection before the onset of neurological symptoms [22]. According to the International Guillain Barré Syndrome Outcome Study (IGOS), 76% of patients reported a trigger event four weeks before GBS was diagnosed. This included upper respiratory tract infection in 35 percent of the cohort and gastroenteritis in 27 percent, respectively [23]. Table 1 summarizes the most relevant findings from that study.

TABLE 1. Relevant prior events linked to neurological symptoms in GBS patients

Prior event	Serological evidence of a specific infectious agent
Respiratory tract infections 35%	Campylobacter jejuni 25%
Gastroenteritis 27%	Cytomegalovirus 4%
Medication (Tumor necrosis factor antagonist therapy; Tacrolimus and suramin; Isotretinoin; Immune checkpoint inhibitors)	HIV-1 (predominantly in immunocompromised patients)
Surgical interventions (in particular orthopedic and gastrointestinal surgery)	Epstein-Barr virus 1%
Vaccines 3%	Mycoplasma pneumoniae 10%

The exact mechanisms that explain the onset of neurological symptoms following Hymenoptera stings are unknown. Among the suspected pathophysiological pathways, we mention the relevance of specific allergenic proteins in the venom that might induce the production of IgE antibodies. These antibodies can cross-react with myelin basic protein (MBP) and cause various neurological symptoms [24]. There is a possibility that patients may not remember some stings in the past, which may pre-sensitize the patient to that particular venom and lead to an immediate hypersensitivity reaction characterized by the cross-reaction between IgE antibodies and MBP with subsequent neurological complaints.

Searching the literature, we found an interesting case of a 3-year-old girl who developed acute GBS following a bee sting, the main symptoms being difficulties in walking, climbing stairs, and getting up from a sitting position. The diagnosis was established with the help of nerve conduction studies [25].

Hymenoptera stings lead to a multitude of neurological symptoms via the mechanism of immediate or delayed hypersensitivity responses. The most common form of polyneuropathy associated with these stings is the acute inflammatory demyelinating type. In this regard, we found the case of a 6-year-old girl who developed progressive, symmetrical, ascending weakness within three days after a bee sting. Serial nerve conduction studies have confirmed acute mo-

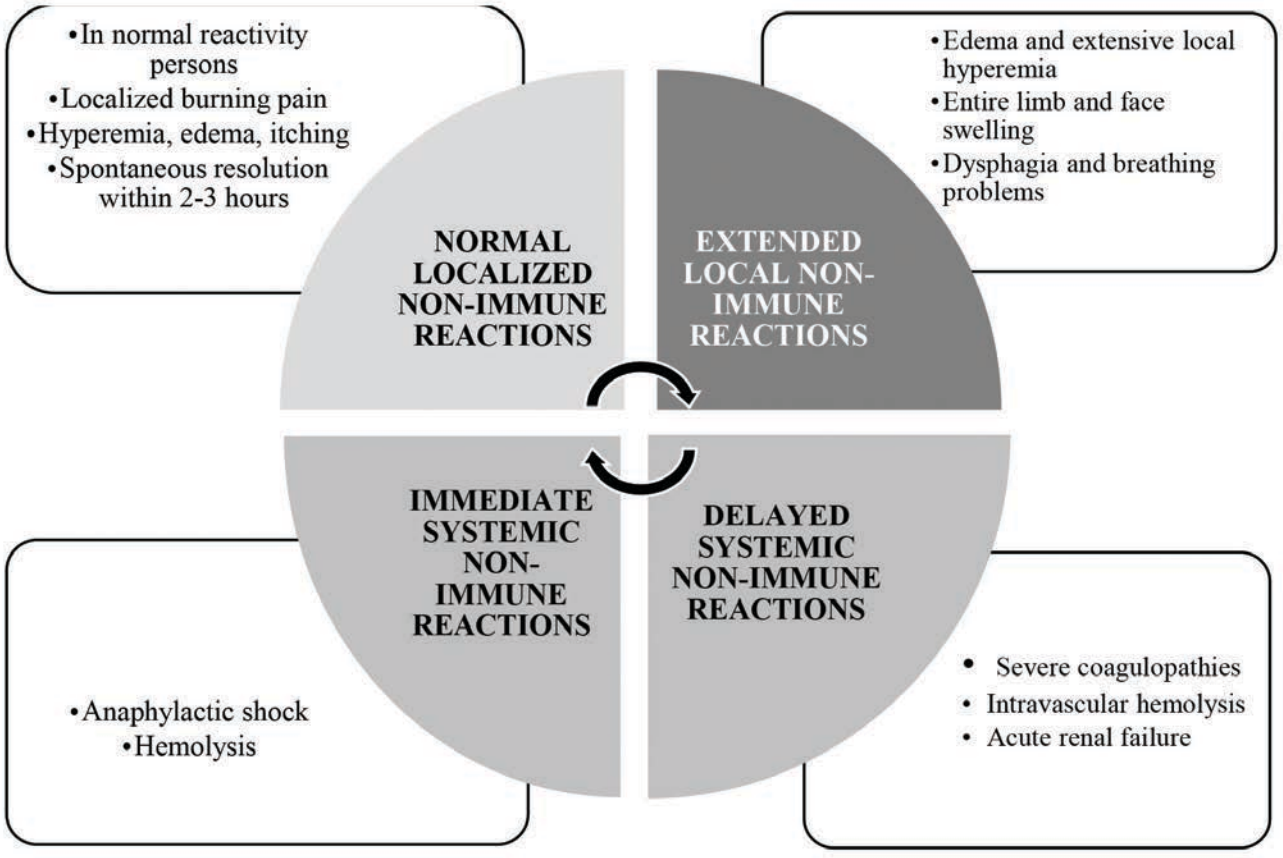

FIGURE 2. Overview of potential mechanisms that explain the onset of neurological symptoms after Hymenoptera sting

tor-predominant axonal polyneuropathy, while IVIg treatment stopped symptoms progression and ensured a gradual recovery [26]. This highlights that even a single bee sting can lead to an acute axonal variety of polyneuropathy in children.

Inoculation of allergens is done together with the venom through the Hymenoptera sting. Usually, the resulting lesions are localized, but more generalized systemic reactions, even with fatal outcomes, were also recorded in allergic persons sensitized by previous stings [27]. Allergy to insect venom develops quickly, but most allergic individuals can gradually build tolerance to the poison; this is considered the result of steadily induced production of IgE and specific blocking IgG antibodies [28].

Although uncommon, neurological symptoms after Hymenoptera stings are pretty diverse, involving both the CNS and the PNS, and can be life-threatening. Moreover, most occur in younger people and children [29].

Hypoxic-ischemic damage is another relevant pathological mechanism in neurological symptoms associated with Hymenoptera venom inoculation. Wasp venom contains vasoactive, inflammatory, and thrombogenic peptides and amines, including histamine, leukotrienes, and thromboxane [30]. Infarction after the Hymenoptera sting might be caused by vasoconstriction and platelet aggregation secondary to the injection of various allergens contained within the venom. Infarction could also result from circulatory failure and respiratory distress from an anaphylactic response. Another explanation for wasp sting cerebral ischemia could be the involvement of the superior cervical ganglion, which controls the sympathetic innervation of the distal internal carotid artery [31]. Multiple unilateral stings in the neck region may stimulate the superior cervical ganglion, resulting in increased endothelial permeability in the distal-internal carotid artery. Concomitantly, the wasp sting-associated systemic immune response and activated platelets would promote thrombosis in the sensitized internal carotid artery [32].

A third mechanism explaining the onset of neurological complaints after bee stings could be the direct toxic effect due to the large venom load. Massive envenomation by Hymenoptera is reported to cause acute and delayed reactions such as encephalopathy, hemolysis, rhabdomyolysis, and acute renal failure [33].

Finally, CNS and PNS demyelination are the third category of pathological mechanisms described. Figure 2 summarizes the most important Hymenoptera sting-triggered pathophysiological mechanism that might lead to neurological symptoms.

Hymenoptera antigens could initiate the production of antibodies that cross-react with MBP. However, immune responses may be induced by phospholipase A activation in the venom, with subsequent

release of encephalogenic basic proteins or other antigens resulting from myelin membranes [34]. Sporadic neurological cases were reported in earlier studies; for example, Reisman found anti-myelin antibodies in an 8-year-old boy who developed ataxia, areflexia, and ophthalmoplegia 72 hours after four bee stings [35]. In addition, Means et al. reported a case with recurrent and progressive bilateral weakness and numbness of the arms and legs following yellow jacket stings [36]. The autopsy revealed areas of demyelination in the central and peripheral nervous system with necrosis and inflammatory infiltration in the brainstem and spinal cord. Massive pulmonary embolism was also found as the cause of death.

The results of conducted clinical and paraclinical investigations in our patient showed no signs of hypoxic-ischemic damage or a direct toxic effect on the PNS. Therefore, demyelinating changes common to GBS and CIDP are suspected.

CONCLUSION

According to current literature data, the Hymenoptera sting could be an essential trigger for PNS disorders, especially inflammatory demyelinating neuropathies. In this regard, several GBS and CIDP case reports link the onset of suggestive neurological symptoms to inoculation of Hymenoptera venom. However, despite some incipient hypotheses, the exact pathophysiological mechanism remains to be determined.

We consider the presented case report additional proof to strengthen the correlation between Hymenoptera sting and GBS/CIPD. Simultaneously, the current case highlights the difficulties the neurologist faces when diagnosing peripheral nerve disorders in the initial phase. However, we ascertain the scarce number of cases reported in the literature on this topic and many unknowns related to possibly involved pathological mechanisms. To confirm the causative relation between Hymenoptera sting and GBS/CIDP, future research should focus on a better understanding of the molecular pathways altered by Hymenoptera venom and their link to acute or chronic demyelination of the PNS.

Conflict of interest: The authors declare no conflict of interest.

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