

Review

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Clinical and Experimental Evidence of Hypoglycemic Neuropathy

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ABSTRACT

When compared with the extensive research on hypoglycemic impacts on Central Nervous System (CNS) and cardiovascular system, the effects of hypoglycemia on the Peripheral Nervous System (PNS) have not been investigated as thoroughly. Epidemiologic data and risk factors for hypoglycemic neuropathy are still lacking. Interestingly, hyperglycemia mainly results in the damage of sensory and autonomic nerve fibers, whereas hypoglycemia predominantly leads to the development of motor neuropathy. Most clinical features are concluded from patients with insulinoma, and neuropathology has shown axonal degeneration in large myelinated fibers. Experimental animal models support the clinical and histopathological findings. The exact pathophysiological mechanisms of hypoglycemic neuropathy remain elusive. The influence of hypoglycemia on peripheral nervous system warrants further investigations.

KEYWORDS: Hypoglycemic neuropathy; Hypoglycemia; Peripheral nervous system.

ABBREVIATIONS: CNS: Central Nervous System; PNS: Peripheral Nervous System; NCV: Nerve Conduction Velocity; IHH: Insulin-Induced Hypoglycemia; DPN: Diabetic Peripheral Neuropathy; DM: Diabetes Mellitus; HbA1c or A1C: Glycated hemoglobin; LDL-cholesterol: Low-Density Lipoprotein-cholesterol; HDL-cholesterol High-Density Lipoprotein-cholesterol.

INTRODUCTION

Hypoglycemia is a condition primarily affecting diabetic patients treated under excessive medication, such as insulin or other hypoglycemic agents.¹⁻³ Other causes of hypoglycemia include insulinoma, poor intake, infections, liver, and kidney diseases.¹⁻³

The incidence of hypoglycemia varies considerably among studies by means of using different biochemical criteria to define an event.^{4,5} The symptoms of hypoglycemia vary between individuals. Neurogenic (autonomic) symptoms include tremor, palpitations, hunger, and cold sweating. Neuroglycopenic symptoms often include behavioral changes, confusion, seizure, coma, and death.⁴ Compared to the abundant and extensive data on hypoglycemia effects on the Central Nervous System (CNS) and cardiovascular system, there is little evidence in humans and experimental animal studies toward hypoglycemic effects on the Peripheral Nervous System (PNS).^{6,7}

Diabetic Peripheral Neuropathy (DPN) is the commonly reported vascular complication affecting as many as 50% of patients with Type 1 and Type 2 Diabetes Mellitus (DM).^{4,5,8} The

common risk factors for DPN include diabetic duration, Glycated hemoglobin (HbA1c or A1C).⁹ Recently, cardiovascular risk factors, such as elevated blood pressure, hyper-triglyceridemia, Low High-Density Lipoprotein-cholesterol (HDL-cholesterol), High Low-Density Lipoprotein-cholesterol (LDL-cholesterol), and decreased estimated glomerular filtration rate also appear to be related to newly diagnosed Diabetic Peripheral Neuropathy (DPN) in type 2 DM independent of HbA1c.⁹⁻¹² Moreover, with diverse patterns of DPN in diabetes, it is possible that the development of DPN is not only influenced by hyperglycemia but by other factors, such as hypoglycemia, as well. Therefore, it is important to identify the role that hypoglycemia plays in DPN. In this article, we first introduce the clinical characteristics of hypoglycemic neuropathy. Then, we provide the evidence from animal studies. After which, we discuss the key issues of pathogenesis. Lastly, key points regarding hypoglycemic neuropathy are summarized in the conclusion.

CLINICAL EVIDENCE OF HYPOGLYCEMIC NEUROPATHY

There are very few reports on the effects of hypoglycemia on the human PNS. In 1946, Silfvorskiöld reported hypoglycemia related motor symptoms in insulinoma patients.¹³ In 1956, Mulder, et al. presented similar cases and proposed the motor symptoms may be related to neuritis by abnormal high insulin levels.¹⁴ Afterwards, more and more patients with insulinoma were reported.¹⁵⁻¹⁹ In 1982, Jaspan, et al. reported a case and reviewed previously reported twenty-eight cases with insulinoma and frequent hypoglycemia.²⁰ The average age of the cases was 38 year old with a mild male predominance. The most typical presentation started with obvious distal paraesthesia with or without significant sensory loss, followed by motor-predominant distal symmetric peripheral neuropathy with obvious muscle atrophy. Unlike the usual pattern of diabetic polyneuropathy, the upper extremities are generally more involved than the lower ones, but foot drop can occur frequently. Moreover, neuropsychiatric symptoms with fluctuated or episodic confusion were easily noted. The onset and course of neuropathy varied. Most patients ran sub-acute or chronic polyneuropathy pattern in 3-6 months. Some patients got acute polyneuropathy after coma recovery. But these patients also experienced many hypoglycemia episodes before.²⁰ Thus, whether severe hypoglycemia alone is sufficient to lead to polyneuropathy was still questionable. After removal of the insulinomas, sensory symptoms tend to regress greatly but definite improvement in motor weakness was uncommon.¹³⁻²⁰ Nerve Conduction Velocity (NCV) study showed distal symmetric predominantly axonal motor neuropathy from most of their reports.¹³⁻²⁰ There was also electromyographic evidence for denervation of skeletal muscles.^{15,16} Normal cerebrospinal fluid protein suggested peripheral axonal injury rather than dorsal root ganglion involvement.¹⁰⁻¹² With respect to neuropathology, axonal degeneration in large myelinated fibers and neurogenic atrophy in muscle had been shown in peripheral nerves of insulinoma patients.²¹⁻²³

In contrast, other researchers revealed that insulinoma

related hypoglycemia neuropathy affected both motor and sensory fibers or mainly the sensory symptoms in mice and humans.^{19,24} This is the same situation of diverse presentations of neuropathy in diabetic patients. Some diabetic patients show mainly sensory disturbances and/or autonomic dysfunctions, others show mixed sensorimotor symptoms or motor problems predominant. It is possible that some of the clinical findings are not exclusively the consequence of hypoglycemia but also in combination of hyperglycemia and hypoglycemia states.¹² Hypoglycemic effect may contribute to the diverse pattern of diabetic peripheral neuropathy in humans. Further studies are needed to investigate the co-existence effects of hypoglycemia in diabetic neuropathy.

EVIDENCE FROM ANIMAL STUDY

Investigators have used various experimental animal models, such as healthy and diabetic rats or mice to elucidate hypoglycemic neuropathy.¹⁰⁻¹² Normal and diabetic rats underwent experimental hypoglycemia with excessive insulin injection exhibit either abnormal NCV or nerve structure change with a combination of Wallerian-type axonal de-and regeneration.²⁵⁻²⁷ The pathological change indicates that hypoglycemia affects the neuron rather than the Schwann cell and the axonal degeneration affects large myelinated fibers preferentially.²⁸⁻³⁰ Furthermore, motor axons are more severely damaged than sensory axons in the peripheral nerve trunks.²⁸⁻³⁰ Both the duration and the severity of the hypoglycemia can influence the occurrence of neuropathy.^{29,30} These findings of animal studies are highly compatible with hypoglycemic neuropathy reported by Jaspan.²⁰

When looking at the rats, pathological changes of hypoglycemic neuropathy at the nerve trunk level are much more obvious than at the spinal root level, including ventral horn and dorsal root ganglion.²⁶⁻³¹ This discovery is again compatible with cerebrospinal fluid and pathologic results in human beings.¹⁰⁻¹²

The investigators also studied the Insulin-Induced Hypoglycemia (IIH) effects on non-diabetic and diabetic rats by analysis of tibial nerves. They demonstrated that the Wallerian-type axonal degeneration happens only in treated diabetic rats, especially more severe in the daily insulin injection group. Other investigators studied hyperglycemic rats, and selectively gave them either small or high doses of insulin to the point of hypoglycemia, or just left them remained hyperglycemic state without insulin.³² In the hypoglycemic rats, loss of large myelinated fibers and decreased NCVs were noted, while the other groups had mainly sensory fiber abnormalities.^{32,33}

PATHOGENESIS OF HYPOGLYCEMIC NEUROPATHY

IIH is one of the most common forms of hypoglycemia in diabetes. Thus, it is also the most frequently aroused research interest to explain the pathophysiology of hypoglycemic neuropathy.^{11,12} In addition, histopathological findings induced by IIH are similar to those findings in cases of hypoglycemic

agents, other than insulin or insulinoma, in human.^{10,12} It indicates that pathogenesis of hypoglycemia neuropathy induced by IIH does not represent a species-specific effect.¹⁰⁻¹² We highlight the key issues herein, and more detailed descriptions of pathogenesis of hypoglycemia neuropathy induced by IIH have been described elsewhere in another review article.¹²

Mechanisms Involved in the Pathogenesis are Complex and Multifactorial

Because hypoglycemia is involved, energy depletion appears to be a likely mechanism in IIH induced hypoglycemia neuropathy; however, other mechanisms such as ischemia, might also play an important role as well.¹⁰⁻¹²

The depletion of energy within neurons may result in altered intraneural concentrations of various metabolites and lead to axonal degeneration seen during IIH.¹² Furthermore, neuron axons and Schwann cells are not only physical neighbours but also influence and support each other.^{34,35} Hence, the myelin breakdown seen on Schwann cells during IIH may be caused directly by ATP depletion or caused indirectly by ATP depletion in neurons.¹⁰⁻¹² Local ischemia caused by decreased nerve blood flow leads to local hypoxia, which may result in axonal degeneration and myelin breakdown.^{36,37} This phenomenon caused by ischemia change corresponds with energy deprivation as the cause of the changes in IIH related neuropathy.^{12,34}

However, it is somewhat difficult at present to explain why large diameter myelinated motor fibers are particular vulnerable to IIH only based on mechanisms of energy deprivation or nerve ischemia.¹² If energy deprivation or nerve ischemia is the only mechanism involved in pathogenesis, it may be expected that small myelinated axons, which have higher per-volume metabolic rates than large myelinated axons, are more susceptible to oxygen deprivation or ischemia.^{12,35} Since the opposite appears to be true, it is reasonable to hypothesize that the underlying mechanism involved in the pathogenesis of IIH related hypoglycemic neuropathy is complex and multifactorial.

Hypoglycemia Or Hyperinsulinemia is the Main Cause of PNS Changes

Previous studies have considered insulin to be a major cause in PNS images.²⁶⁻³¹ However, growing evidence suggests that insulin is beneficial for PNS function and serves as a promoter of axonal regeneration after injuries.¹⁰⁻¹² On the contrary, hypoglycemia during normal insulin levels causes axonal degeneration in the PNS.¹² Thus, the present available data seems to support that hypoglycemia, not hyperinsulinaemia, plays a more important role in IIH peripheral neuropathy.¹⁰⁻¹² It raises the question of whether hypoglycemia rather than hyperinsulinaemia or a combination of the two is the main cause of peripheral nerve injury. Further studies are needed to clarify this important issue.

In conclusion, the mechanisms involved in the patho-

genesis remain poorly understood. Deeper understanding in pathogenesis from basic research is needed.

CONCLUSION

Clinical observational studies in human suggest that large myelinated motor fibers appear to be vulnerable to hypoglycemia. This is different from the common pattern of diabetic polyneuropathy with predominant sensory and autonomic neuropathy. Experimental animal models confirm the clinical observations. Future studies are needed to investigate the effects of frequency, severity and duration of hypoglycemia events on the progression, and the outcomes of hypoglycemic neuropathy in clinical setting. More experimental studies are also needed to provide mechanistic insights into the pathophysiology of hypoglycemic effects toward PNS.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DISCLOSURES

All authors report no disclosures.

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