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Review

Peripheral neuropathy in children with type 1 diabetes

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Abstract

Diabetic neuropathy (DN) is a major complication of type 1 diabetes mellitus (T1DM) with significant morbidity and mortality in adulthood. Clinical neuropathy is rarely seen in paediatric populations, whereas subclinical neuropathy is commonly seen, especially in adolescents. Peripheral DN involves impairment of the large and/or small nerve fibres, and can be diagnosed by various methods. Nerve conduction studies (NCS) are the gold-standard method for the detection of subclinical DN; however, it is invasive, difficult to perform and selectively detects large-fibre abnormalities. Vibration sensation thresholds (VSTs) and thermal discrimination thresholds (TDTs) are quicker and easier and, therefore, more suitable as screening tools. Poor glycaemic control is the most important risk factor for the development of DN. Maintaining near-normoglycaemia is the only way to prevent or reverse neural impairment, as the currently available treatments can only relieve the symptoms of DN. Early detection of children and adolescents with nervous system abnormalities is crucial to allow all appropriate measures to be taken to prevent the development of DN.

Keywords: Type 1 diabetes; Children; Peripheral neuropathy; Review

Résumé

Neuropathie périphérique chez les enfants atteints de diabète de type 1.

La neuropathie diabétique (ND) est une complication majeure du diabète de type 1 (T1DM), avec une morbidité et une mortalité significatives à l'âge adulte. La neuropathie clinique est rarement observée dans des populations pédiatriques, tandis que la neuropathie subclinique est fréquente, spécialement chez les adolescents. La ND périphérique implique l'altération des grandes et/ou des petites fibres nerveuses, qui peut être diagnostiquée par différentes méthodes. La mesure des vitesses de conduction nerveuse (ECN) est la référence pour le dépistage des ND subcliniques, mais elle est invasive, difficile à conduire et elle détecte sélectivement les anomalies des grandes fibres nerveuses. Les mesures des seuils de sensibilité aux vibrations (SSV) et de la discrimination thermique (SDT) sont plus rapides, plus faciles et ainsi plus appropriées en tant que méthodes de dépistage. Maintenir un niveau glycémique proche de la normoglycémie est la seule manière de prévenir ou d'inverser les altérations nerveuses, puisque les traitements disponibles actuellement ne font que soulager les symptômes de la ND. La détection précoce des anomalies du système nerveux chez l'enfant et l'adolescent est donc cruciale pour prendre toutes les mesures nécessaires pour éviter le développement de la ND.

Mots clés : Diabète type 1 ; Enfants ; Neuropathie périphérique ; Revue générale

1. Introduction

Diabetic neuropathy (DN) is a major long-term complication of type 1 and type 2 diabetes mellitus (T1DM and T2DM, respectively) resulting in significant morbidity and increased mortality in adulthood. DN is the most frequent type of neuropathy in Western countries, affecting up to 60% of all patients with diabetes [1]. Impairment of the eyes, kidneys and nerves has also been reported in young people with diabetes [2]. While clinical complications are rarely seen among T1DM children, there is evidence that pathogenesis and early signs can develop during childhood and accelerate during puberty [3]. Early symptoms and signs of peripheral neuropathy have been reported in 10% of children with T1DM [4] and usually include lower limb pain, paraesthesia and/or hyperhidrosis [5].

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Table 1
Classification of diabetic neuropathy.

Generalized symmetrical polyneuropathy	Focal and multifocal neuropathy
Acute sensory	Cranial
Chronic sensorimotor	Truncal
Autonomic (cardiovascular, gastrointestinal, genitourinary)	Focal limb
	Proximal motor (amyotrophy)
	Coexisting chronic inflammatory demyelinating polyneuropathy

Diabetes can affect both the peripheral and autonomic nervous system. Numerous classifications of the variety of syndromes affecting the peripheral nervous system in diabetes have been proposed in recent years. The classification shown in Table 1 was based on that originally proposed by Thomas and modified by the American Diabetes Association [6,7]. The term "diabetic neuropathy" usually refers to polyneuropathy, the most frequent neurological deficit caused by diabetes. In the Rochester Diabetic Neuropathy Study of T1DM patients with diabetic neuropathy, 54% had polyneuropathy, while 22% and 11% had asymptomatic and symptomatic carpal tunnel syndrome, respectively, 7% had visceral autonomic neuropathy and 3% had other types of neurological damage [8]. Polyneuropathy and autonomic neuropathy have been reported in children with T1DM in several studies [9,10], whereas carpal tunnel syndrome is extremely rare in childhood diabetes [8].

The course of DN can be classified into two broad stages: subclinical and clinical. The former implies electrophysiological abnormalities of nerve function with no clinical symptoms of peripheral nerve disease, whereas clinical neuropathy is defined as an abnormal neurological examination consistent with peripheral sensorimotor polyneuropathy plus either abnormal nerve conduction in at least two peripheral nerves or unequivocally abnormal autonomic neural tests [10,11]. The aim of the present review is to describe the prevalence, epidemiology and diagnosis of peripheral DN in children and adolescents with T1DM, and to report on its risk factors and prevention.

2. Pathogenesis of DN

Autonomic and somatic neuropathies are thought to have a common aetiopathogenesis, albeit one that is not yet completely understood. According to the metabolic theory, when tissues with diabetic complications are exposed to hyperglycaemia, sorbitol accumulates because of the conversion of intracellular glucose to sorbitol and, thus, myoinositol levels fall [12,13], thereby resulting in tissue damage through an as yet unclear mechanism. When proteins are exposed to elevated glucose concentrations, their glucosylation occurs in proportion to the average glucose concentration [14]. Also, it is known that glycosylated myelin is recognized by specific receptors and endocytosed by macrophages [15]. This may explain the segmental myelin loss seen in human DN. Hyperglycaemia-induced formation of advanced glycation end-products (AGEs) modifies not only myelin, but also tubulin, neurofilament and actin. Modification of the latter cytoskeletal protein leads to axonal atrophy, degeneration and impaired axonal transport, while glycation of laminin results in impaired regenerative activity [16]. Recently, the receptor for AGEs (RAGE) has been found to colocalize with AGEs in peripheral nerves. AGE interaction with RAGE activates the transcription of proinflammatory genes, thereby increasing cellular oxidative stress [17,18], which eventually leads to functional and structural abnormalities in peripheral nerves. Moreover, it has been proposed that non-enzymatic glycation of structural nerve proteins can lead to direct impairment of axons and microvessels. Experimental diabetes has been associated with the non-enzymatic glycation of tubulin and actin, and hyperphosphorylation of neurofilament, all of which are post-translational modifications of critical cytoskeletal proteins [19].

According to the hypoxia hypothesis, the nerves of patients with diabetes become ischaemic because of inflammation and dysfunction of the endoneurial, perineurial and epineurial blood vessels [20]. The decrease in endoneurial oxygen tension appears to correlate with reductions in motor conduction velocity, myoinositol content, axoplasmic transport, sodium–potassium ATPase activity and oxygen consumption in the sciatic nerves of diabetic rats [21]. In addition, functional abnormalities, such as increased permeability to radioiodinated albumin, have been reported in new blood vessels that develop in a diabetic milieu. Similarly, sciatic nerves in diabetic rats are excessively leaky to albumin [16]. These abnormalities can result in local ischaemia and excess release of endothelin, a potential vasoconstrictor, and nitric oxide. Thus, elevated levels of endothelin have been reported in patients with diabetes [22]. Endothelin receptors are found on the vasa nervorum and, in diabetes, endothelin vasoconstriction produces prolonged neural ischaemia and infarction [21].

However, these theories are not mutually exclusive and, instead, are complementary to each other [23]. Nitric oxide has been proposed as the potential bridge between the metabolic and vascular theories [24]. Initially, the excess rise in nitric oxide levels may lead to vasodilatation but, later on, this action fails as it is altered by AGEs and also because the vessels probably become progressively resistant to this effect [16].

Other factors that may contribute to peripheral nerve dysfunction are oxidative stress [24] together with genetic factors. However, antioxidant enzymes protect against the rapid onset of DN by reducing oxidative stress. Genetic variations that affect the activity or expression of antioxidant enzymes may therefore be associated with susceptibility to neuropathy [25]. Furthermore, autoimmunity plays an important role. Children with T1DM have been found to have elevated serum levels of anti-elastin antibodies, indicative of elastin degradation, which correlates with DN [26]. Moreover, alterations in linoleic acid metabolism lead to changes in membrane phospholipids and also to impairment of the microcirculation [27]. The role of other factors, such as abnormalities in nerve growth factors [28,29] and the possible direct neurotrophic effects of insulin and insulin-related growth factors, also appear to be relevant