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.

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1. Introduction

Diabetic neuropathy (DN) is a major long-term complication of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (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].
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.

### Table 1

<table>
<thead>
<tr>
<th>Classification of diabetic neuropathy.</th>
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<tr>
<td>Generalized symmetrical polyneuropathy</td>
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<tr>
<td>Acute sensory</td>
</tr>
<tr>
<td>Chronic sensorimotor</td>
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<tr>
<td>Autonomic (cardiovascular, gastrointestinal, genitourinary)</td>
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<td>Proximal motor (amyotrophy)</td>
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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 glycosylation 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 endoneural, 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
Finally, investigations to clarify the factors implicated in the pathogenesis of macrovascular complications could lead to the identification of biochemical markers with high predictive value for early diagnosis of DN [30].

3. Natural history of DN

Different sensations are transmitted by different types of nerve fibres. Vibration sensations are transmitted by large myelinated fibres (Ab fibres), and thermal sensations by small myelinated (B) and unmyelinated (c) fibres [31]. Patients with diabetes and a selective large-fibre sensory neuropathy usually have absent or reduced vibration sensation, impaired balance, and diminished proprioception and position sense. In the more severe form, loss of position sense may result in sensory ataxia. Also, slow nerve conduction is usually clearly demonstrable due to the selective involvement of the large fast-conducting fibre population [32].

In small-fibre sensory neuropathy, diminished pain and temperature sensations are observed, which facilitates undetected trauma of the limbs. Early in the course of the disease, patients may present with subjective symptoms of numbness or feelings of “cold feet”, or “burning” or “bone-deep” pain. Conduction velocity may not be dramatically impaired, even at the stage when pain is an overriding feature, and therefore correlates poorly with clinical findings [33]. The greatest risk resulting from small-fibre neuropathy is foot ulceration and, subsequently, gangrene and amputation [34].

Many researchers have studied the presence of small- and large-fibre involvement in DN. Most studies agree that abnormalities in the function of unmyelinated fibres (pain, reduction of temperature sensation) precede those of large fibres (impaired vibration sensation). It has also been reported that adult patients with painful DN may lack signs of large-fibre damage [35]. In addition, it has been noted that, even in young T1DM patients soon after diagnosis, small – but not large – fibres are impaired, despite treatment for ketosis and hyperglycaemia [36]. On the other hand, Dyck et al. [37] reported that, in asymptomatic patients, DN can involve small and large fibres either independently of each other or in combination. They observed, however, that the progression of neuropathic damage – from small fibres initially to large fibres later – was not the case in many patients. Hendriksen et al. [38] noted that, although the perception of cold stimuli was sometimes selectively impaired in diabetic patients, no support could be found for the concept of progressive neuropathic damage from small-fibre dysfunction initially to loss of function in large fibres later. Furthermore, in another study, Dyck et al. [39] reported that vibration sensation threshold (VST) abnormalities were much more frequent than thermal (cold) detection threshold abnormalities in patients with mild DN whereas, in cases of more severe neuropathy, all sensory fibres were affected.

As for which part of the nerve is initially affected, researchers agree that the longer nerves in the lower limbs are affected first, followed by those in the upper limbs [38,40]. However, examination of the arms should not be ignored [41].

4. Diagnostic methods for peripheral diabetic neuropathy (PDN)

The consensus statement from the San Antonio conference of the American Diabetes Association and American Academy of Neurology [42] recommended that at least one parameter from each of the following five categories must be assessed to establish the presence of DN: symptom profile; neurological examination; quantitative sensory testing; nerve conduction studies (NCS); and quantitative autonomic–function testing.

The most reliable method for the assessment of peripheral neuropathy, even in the early asymptomatic stage, is the evaluation of nerve conduction velocity, which can be estimated by NCS, an electrophysiological method with excellent reproducibility. Other electrodiagnostic methods used to detect subclinical neuropathy are needle electromyography, which can reveal fibrillation, a sensitive indicator of axonal degeneration [43,44], and somatosensory evoked potentials (EPs), which can show delays in peripheral nerve conduction [45].

NCS, the most widely used electrodiagnostic tools for the detection of PDN, are strongly correlated with underlying structural changes, and are also sensitive, accurate, objective, reproducible and independent of patients’ cooperation [46–48]. Thus, NCS are considered the gold-standard method for the detection of peripheral neuropathy. On the other hand, it is an invasive method, difficult to perform and, therefore, unsuitable as a screening tool. In addition, it selectively examines only large-fibre dysfunction [49].

For this reason, alternative methods for the quantitative assessment of PDN are needed. VSTs, as measured with a biothesiometer, provide estimates of large-fibre neuropathy with 82% sensitivity and 75% specificity compared with NCS [50], while other devices for the estimation of VSTs offer less reliable information [51]. In addition, the specificity and sensitivity of VSTs in diagnosing PDN depend on the cutoff points used to define the abnormalities [52].

Tactile perception thresholds (TPT) are measured using different sizes of monofilaments. Each monofilament exerts a specific amount of pressure when bent on contact with the examined site. Patients are asked whether they can feel the pressure and their responses are recorded as either “yes” or “no”. TPT is a well-established method for the assessment of large-fibre dysfunction in adult patients [53]. Nevertheless, it has proved to be less reliable for assessing PDN in paediatric populations, with only 19% sensitivity and 64% specificity [51].

In contrast, thermal discrimination thresholds (TDTs) can identify small-fibre abnormalities that cannot otherwise be assessed by any of the other methods. Small-nerve-fibre damage has also proved to be important, as it is predictive of the degree of pain in painful PDN [54].
5. Prevalence of PDN

5.1. Nerve conduction studies (NCS)

The variety of diagnostic tests and different criteria used for the definition of PDN are responsible for the discrepancies in its prevalence across various studies. In adult patients with T1DM, the prevalence of neuropathy has been estimated to be as high as 100% when based on motor conduction velocities [37]. In children and adolescents with T1DM, significantly lower motor and sensory conduction velocities in all examined nerves have been reported in 57–68.4% of patients [55–57, 5]. Furthermore, electrophysiological evidence of polyneuropathy has been found in 32.4% of patients with newly diagnosed T1DM [9].

5.2. Vibration sensation and thermal discrimination thresholds

In the Diabetes Control and Complications Trial (DCCT) involving 1177 adults with T1DM, of the 1107 patients with electrophysiological findings of PDN, 782 (71%) had abnormal VSTs [58]. Furthermore, it has long been reported that adults with diabetes have reduced warm and cool sensitivity compared with non-diabetic age-matched controls [59].

The Danish Study Group of Diabetes in Childhood [60] looked at 339 children and adolescents with diabetes, aged 6–18 years with an average T1DM duration of 7.2 years, and found elevated VSTs in 62.5% of the studied population. However, in another longitudinal epidemiological study [10] of the evolution of diabetic microvascular disease, persistent VST impairment of the lower limbs was detected in only 6.2% of the 129 T1DM children examined. Such a difference may be attributed to the different cutoff points used for normal values as well as the fact that, in the latter research, VST was measured twice within a period of 18 months, and any findings that were consistently abnormal both times were recorded as pathological. In addition, the paediatric population in the latter study had a shorter diabetes duration (mean: 2.9 years).

In another study, Abad et al. [61] studied 35 neurologically asymptomatic T1DM children, aged 8–16 years, and a control group of 35 age-matched non-diabetic subjects. They measured warm-, cold- and heat-induced pain thresholds in the dorsal aspects of the right arm and foot. In this case, 43% of the T1DM patients presented with an abnormality of at least one sensory threshold.

6. Risk factors for the development of DN

Glycaemic control has been recognized as the most important risk factor for DN and other diabetic complications [62–64]. The DCCT [65] found that intensive insulin therapy delays the onset and slows the progression of DN by 60%. Also, it has been proposed that poor glycaemic control is associated with the morphological characteristics of a more severe form of DN [66]. In paediatric populations with T1DM, there has been a positive correlation between deterioration of glycaemic control and the development of neuropathy [67]. Poor metabolic control is associated with slower NCS results [68] and elevated VSTs [69]. Indeed, the term “metabolic memory” emphasizes the long-term beneficial effects of strict diabetic control on the prevention of DN [70]. In addition, patients who have generally good long-term metabolic control demonstrate a lower prevalence of neuropathy later in life.

The effect of diabetes duration on the progression of DN has been well documented. In a study by Barkai et al. [71], diabetes duration proved to be one of the risk factors for the development of neuropathy. Similarly, studies in paediatric populations have shown a positive correlation between T1DM duration and the development of DN. When Solders et al. [68] conducted a 10-year follow-up study in 144 newly diagnosed children with T1DM, they found low sensory conduction velocities in 25% of the children at the time of disease onset that improved over the first 2 years. After this time period, however, deterioration of motor and sensory conduction velocities was observed, with further reductions over time. Other researchers have confirmed deterioration in electrophysiological parameters with time as well [69]. Nevertheless, in cross-sectional studies, the results have been conflicting: some have demonstrated a positive correlation between T1DM duration and progression of peripheral neuropathy [72], some found a weak correlation [61] and others found no correlation at all [73]. These conflicting findings might be attributed to the short T1DM duration among patients included in paediatric studies. Also, as already mentioned above, as glycaemic control is a major risk factor for the development of diabetic complications, the conflicting published studies might also be attributed to the fact that none of them included multivariate analyses that took into consideration the effects of both diabetes duration and glycaemic control.

An increase of VSTs with age, in both the upper and lower extremities, has been shown in both adult patients with diabetes [74] and in healthy controls [75], and has also been confirmed in paediatric populations [72]. The age effect on the presence of nervous system impairment due to T1DM is nonetheless controversial. A study [76] in which recently diagnosed T1DM children were examined by electrophysiological methods reported no relationship between age and neural dysfunction. Ludvigsson et al. [77] have also shown that, in a paediatric population, there was no correlation between VST abnormality and current age or age at T1DM onset. In contrast, another report [55] found that the age at the time of disease onset was significantly related to the development of subclinical PDN affecting specific nerves. Some researchers [78] also observed that patients aged 5–14 years at the time of T1DM onset had an increased complications risk compared with those diagnosed at either a much younger age or after puberty.

Male gender has also been considered an additional risk factor for the development of PDN. This has been attributed to the observation that increased sorbitol production and decreased myo-inositol content appear to be sex-hormone-dependent [79]. However, in one large study, female patients were shown to be more prone to diabetic complications [78]. Also, in children and adolescents with T1DM, there are only a few studies investigating the impact of gender on DN and with conflicting results. Indeed, Solders et al. [68] showed no correlation between gender
and VST or NCS impairment, whereas Olsen et al. [60] reported that males were more prone to developing neuropathy.

Height is another risk factor for the development of PDN. The DCCT Research Group [74] found that subjects with peripheral neuropathy, in addition to being older in age, male and with longer diabetes duration, were also taller than those without PDN. Duck et al. [80] reported that height should be included in the prospective evaluation of nerve conduction parameters in paediatric patients, as it was the most significant independent variable on latency analysis. Bloom et al. [75], who studied VSTs in healthy subjects, observed that the thresholds on the foot were related to height. This led them to speculate that the lower thresholds and smaller variance in thumb readings were due to the shorter sensory pathway in the arm. In children with T1DM, some trials have indicated a positive correlation between height and the development of neuropathy [81], although other researchers disagree [61].

Puberty has also been shown to affect the development of DN. In a study of 112 children and adolescents with T1DM, late puberty proved to be an independent risk factor for peripheral sensory abnormalities [82]. A previous study [83] had shown that puberty modified the correlation of muscle capillary basement membrane thickness, an indicator of microvascular pathology, with Hba1c levels. The authors suggested that sex hormones [79] or growth factors [84] might be able to modulate the long-term effects of hyperglycaemia on vascular disease. Furthermore, it is well documented that near-normoglycaemia is difficult to achieve during puberty, as this period is characterized by both relative insulin resistance and reduced treatment compliance [85,86].

7. Association of DN with other diabetic complications

In adults with T1DM, PDN frequently coexists with autonomic neuropathy [87], and there have been similar findings in paediatric populations. It has been reported that adolescents with distal DN had significantly lower heart rate variation during deep breathing than the rest of the study population [85].

Microvascular T1DM complications have also been reported to be interassociated. Olsen et al. [88] studied 339 young patients (aged 12–26.9 years) with T1DM and found that the presence of subclinical neuropathy, as determined by abnormal VST values, correlated with the presence of diabetic retinopathy ($P=0.01$) and high diastolic blood pressure ($P<0.01$). Renal dysfunction was also associated with the former parameter. According to a subsequent report on the same population [60], an increased urinary albumin excretion rate was a major risk factor for the development of VST impairment. In fact, a large study based on 8114 patients with T1DM from 6707 families [78] has provided a possible explanation. The presence of one T1DM complication significantly increased the risk of other microvascular complications due to a shared genetic background. In addition, poor metabolic control was the most important common risk factor for all the described diabetic complications. On the other hand, in a study by Young et al. [89] of T1DM children and adolescents, there was an association between the development of neural and microvascular complications, based on the presence of poor glycaemic control; however, when the influence of diabetic control was eliminated, the correlation disappeared. Other researchers have agreed that the presence of DN does not significantly increase the risk of other diabetic complications [56].

The major role of metabolic control in the development and progression of diabetic complications is unanimously accepted. Clinical studies conducted since the 1970s by the paediatric diabetology group at the Free University of Brussels [90] have demonstrated that screening for subclinical retinopathy, neuropathy and nephropathy should be started at puberty, and continued for up to at least 3 years after T1DM diagnosis for the early detection of subclinical disorders and their possible reversal by improved metabolic control. Thus, the occurrence of irreversible, potentially incapacitating, lesions might be prevented.

8. Reversibility of DN abnormalities

The theory of an initial metabolic and partially reversible effect on nerve function by the diabetic state has been supported by the study of Solders et al. [68]. The improvement in sensory nerve conduction in children with newly diagnosed T1DM within the first 2 years after insulin initiation suggested that there are no permanent structural changes in the nervous system during the early years of T1DM, thereby also suggesting that the correction of metabolic disturbances might restore the damage.

Indeed, the reversibility of clinical peripheral neuropathy with intensified glycaemic control has been reported in two adolescents with unusually severe DN [91]. These patients both had poor metabolic control, pain in the lower limbs, and abnormal sensation and nerve conduction velocities. Only when near-normoglycaemia was achieved by the introduction of intensive insulin treatment were clinical improvements and normalization of nerve function observed. This finding may be explained by the hypoxia hypothesis of DN pathogenesis [20]. Thus, experimental hyperglycaemic, but not normoglycaemic, hypoxia can give rise to alterations in fast K+ conduction and after-potentials in axons related to axoplasmic acidification. This could lead to the generation of ectopic impulses and contribute to the occurrence of positive symptoms such as pain [92]. This also suggests that the maintenance of normoglycaemia blocks the pathogenetic pathway and alleviates symptoms.

9. Treatment and prevention of DN

In general, DN in T1DM children and adolescents is subclinical and rarely symptomatic [3]. However, in adulthood, neuropathic pain can cause considerable interference with sleep, daily activities and quality of life. In addition, nociceptive neuropathy can lead to injury, together with vascular complications, gangrene and even amputation. Thus, the available treatments and future prospectives for patients with diabetic neuropathy are important.

As DN is asymptomatic in children and adolescents with T1DM, the prevention or delay of symptoms is the primary issue. The establishment of near-normoglycaemia in the early stages
of DN has been shown to be the only approach that slows its progression while also alleviating the clinical symptoms [93].

In adults with diabetes, the treatment of DN includes symptomatic relief of neuropathic pain and therapies that might influence the natural history of neuropathy. Different drugs are licensed for pain relief in adults with painful DN, while others are still under experimental use. Antidepressants such as the tri-cyclics [93] and duloxetine have been established as first-line therapy for neuropathic pain [94]. Antiepileptic drugs, such as topiramate [93], oxcarbazepine [95], and the newly prescribed gabapentin and pregabalin [96] are also effective. Neuropathic pain is generally insensitive to opioids, although tramadol, a weaker centrally acting non-narcotic opioid, has proved beneficial [97]. Alternative therapies, such as the topical use of capsaicin, acupuncture and electrical treatments, can also be used for pain relief [93].

Other treatments targeted at influencing the natural history of this complication are still in the experimental stages except for thioctic acid, a lipoic acid that appears to delay or even reverse PDN through multiple antioxidant actions [98]. In Germany, thioctic acid has been licensed for the treatment of DN for more than four decades, and several studies favour its efficacy and safety [99–101].

Aldose reductase inhibitors have been extensively studied over the past few decades. They disrupt the conversion of glucose to sorbitol in the polyol pathway. Although numerous studies have been published confirming their effectiveness [102,103], they have not yet been established in clinical practice in Western countries.

As already mentioned, AGEs are involved in the pathogenesis of DN, and trials of anti-AGE agents offer promising results [104]. The angiotensin-converting enzyme (ACE) inhibitors have also been reported to have beneficial effects on the electrophysiological parameters of patients with DN [105].

The efficacy of C-peptide, the precursor of insulin, has also been examined, as insulinopenia per se apart from hyperglycaemia is involved in the pathogenesis of DN [106]. Trials in rats have demonstrated that C-peptide can prevent or even reverse painful and nociceptive DN [107]. The use of growth factors, such as nerve growth factor and insulin-like growth factor (IGF)-1, also appear to be promising in the treatment of DN. In addition, the use of L-carnitine appears to be effective in T1DM children with subclinical neuropathy [108]. Protein kinase C inhibitors have been reported to have positive results in patients with DN [109], whereas glucagon-like peptide (GLP)-1 [110] and activating transcription factor 3 [111] have been used experimentally in rats with encouraging outcomes.

10. Conclusion

Peripheral neuropathy is a major complication of diabetes mellitus and affects patients in adult life. However, the first signs can develop in childhood and especially during adolescence. Thus, it is suggested that annual screening for the early detection of nervous system impairment should be established for all adolescents with T1DM and for diabetic children with a disease duration of more than 3 years. Screening should include simple non-invasive tests such as neurological examination, VSTs and TDTs. Patients with abnormal or marginally abnormal results and/or objective symptoms of DN should be further examined by NCS. In addition, those with confirmed subclinical neuropathy should be encouraged to achieve near-normoglycaemia by intensive insulin treatment, as good metabolic control is the only way to prevent or delay DN as well as other diabetes complications. Available treatments to date provide relief from symptoms, but they cannot reverse the progression of DN.

Disclosure of interests

The authors declare that they have no conflicts of interest concerning this article.

References


