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REVIEW ARTICLE

Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity

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Summary

Prior to a joint meeting of the Neurodiab Association and International Symposium on Diabetic Neuropathy held in Toronto, Ontario, Canada, 13-18 October 2009, Solomon Tesfaye, Sheffield, UK, convened a panel of neuromuscular experts to provide an update on polyneuropathies associated with diabetes (Toronto Consensus Panels on DPNs, 2009). Herein, we provide definitions of typical and atypical diabetic polyneuropathies (DPNs), diagnostic criteria, and approaches to diagnose sensorimotor polyneuropathy as well as to estimate severity. Diabetic sensorimotor polyneuropathy (DSPN), or typical DPN, usually develops on long-standing hyperglycaemia, consequent metabolic derangements and microvessel alterations. It is frequently associated with microvessel retinal and kidney disease – but other causes must be excluded. By contrast, atypical DPNs are intercurrent painful and autonomic small-fibre polyneuropathies. Recognizing that there is a need to detect and estimate severity of DSPN validly and reproducibly, we define subclinical DSPN using nerve conduction criteria and define possible, probable, and confirmed clinical levels of DSPN. For conduct of epidemiologic surveys and randomized controlled trials, it is necessary to pre-specify which attributes of nerve conduction are to be used, the criterion for diagnosis, reference values, correction for applicable variables, and the specific criterion for DSPN. Herein, we provide the performance characteristics of several criteria for the diagnosis of sensorimotor polyneuropathy in healthy subject- and diabetic subject cohorts. Also outlined here are staged and continuous approaches to estimate severity of DSPN.

Keywords diabetic polyneuropathy; diabetic sensorimotor polyneuropathy; atypical diabetic polyneuropathy; classification; definitions

Abbreviations: DPN – diabetic polyneuropathy; DSPN – diabetic sensorimotor polyneuropathy; MNCV – motor nerve conduction velocity; NIS – Neuropathy Impairment Score.

Introduction and objectives

A summary of this, and the other updates reported here, has been published earlier [1]. This update begins with the consideration of classification of diabetic polyneuropathies (DPNs) and then provides definitions, minimal criteria for diagnoses, and estimation of severity of typical DPN, i.e. diabetic sensorimotor polyneuropathy (DSPN). Subsequently, atypical DPN is described and discussed only briefly. This update alludes only briefly to focal and multifocal varieties.

Classification of diabetic neuropathies

The neuropathies developing in patients with diabetes mellitus are known to be heterogeneous by their symptoms, pattern of neurological involvement, course, risk covariates, pathological alterations, and underlying mechanisms [2–4]. We accept the Thomas *et al*. [5,6] and Boulton *et al*. [7,8] separation of DPNs into generalized polyneuropathies (DPNs) and focal (e.g. CrIII neuropathy and median neuropathy at the wrist from carpal tunnel syndrome) and multifocal varieties (e.g. multiple mononeuropathy, lumbosacral, thoracic, and cervical radiculoplexus neuropathies [5–9]). It is known that all patterns of neuropathy listed above also occur in patients without diabetes mellitus [10].

The evidence that generalized DPNs can be further classified into at least two major subgroups (typical and atypical) seems compelling [5–8]. Typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy and is thought to be the commonest variety of DPN, from cohort and population-based epidemiological studies [3]. It develops on a background of long-standing chronic hyperglycaemia, associated metabolic derangements, and cardiovascular risk factors [11–17]. It is postulated that metabolic derangements, secondary to chronic hyperglycaemia (polyol shunting, accumulation of advanced glycation end products, oxidative stress, lipid abnormalities among other metabolic derangements [17–20], and microvessel alterations [21–23]), are involved in the development of DSPN. The pathological alterations of microvessels are similar to those observed in diabetic retinopathy and nephropathy. In cross-sectional and longitudinal epidemiological surveys of population-based cohorts of patients with diabetes mellitus, total hyperglycaemia has been shown to be an important risk covariate [14,16], but vascular risk factors have been emphasized in other studies [13,15]. Progression of DSPN has been shown to be prevented or inhibited by rigorous glycaemic control [11,12,24,25]. DSPN has been found to be statistically associated with retinopathy and nephropathy [3,26].

Atypical DPNs are different from DSPN in several important features, i.e. onset, course, manifestations, associations, and perhaps putative mechanisms [5–8,27–31]. They appear to be intercurrent varieties, developing at any time during the course of a patient's diabetes mellitus [30–32]. Onset of symptoms may be acute, subacute, or chronic, but the course is usually monophasic or fluctuating over time. Archer *et al*. [30] described a prototypic variety quite distinct from the usual course of DSPN. Their nine cases had painful neuropathies that were preceded by weight loss, a feature emphasized by Ellenberg [29] but also characteristic of diabetic lumbosacral radiculoplexus neuropathy [9]. Burning pain and contact hyperalgesia were typical features. Sensory loss was mild and there was no or little weakness. With conventional treatment they improved. Symptoms disappeared in months. Retinopathy or nephropathy was not observed. Nerve conduction abnormalities, if present, were mild. Younger *et al*. [31] biopsied cutaneous nerves of patients having some features of the Archer *et al*. patients. They reported lymphocytic infiltrates, albeit small, but possibly suggestive of an inflammatory (perhaps immune) pathogenesis. It is important to note that many of these patients developed their symptomatic sensory and autonomic polyneuropathies shortly after rigorous control of hyperglycaemia had been achieved, making it unlikely that chronic hyperglycaemia is a putative risk covariate – different from the causative factors of typical DSPN.

Investigators have described an increased prevalence of IFG or IGT in patients with small-fibre painful polyneuropathies [33–38]. Whether IFG or IGT causes an increased prevalence of DPN, and if it does, whether it causes typical or atypical DPN remains unsettled [34–42] for methodological reasons and contradictory results [39].

The focal and multifocal neuropathies associated with diabetes mellitus can be broadly subdivided into those in which repeated, mild, mechanical trauma, compression, or entrapment is causative and others possibly related to inflammation with or without associated ischaemia. The first group includes median neuropathy at the wrist, ulnar neuropathy at the elbow, and peroneal neuropathy at the knee. The second group may include mononeuropathy, e.g. cranial nerve III and multiple mononeuropathies, and radiculoplexus neuropathies of the lumbosacral (also called diabetic amyotrophy, Bruns Garland syndrome, and by other names), thoracic, and cervical segments. There is increasing evidence that inflammation, microvasculitis, and ischaemia are involved in these radiculoplexus neuropathies [9,43–46].

Typical DPN (i.e. diabetic sensorimotor polyneuropathy)

The San Antonio Conference defined DPN as 'peripheral or autonomic nerve damage attributable solely to diabetes mellitus' [47]. Boulton *et al*. [7] defined DPN as 'presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes'. The case definition of distal symmetric polyneuropathy (of which DSPN is a member) from the AAN, AAEM, and AAPMR report, and based on a formal review of the medical literature, states that 'the highest likelihood of polyneuropathy occurs with a combination of neuropathic symptoms, multiple signs, and abnormal electrodiagnostic studies' [48]. Whereas each of these definitions seems acceptable and intuitively correct, they do not separate typical DPN (i.e. DSPN) from atypical DPN, which we judge to be needed. Here, we also emphasize more precise nerve conduction abnormality criteria for subclinical DSPN (Stage 1a) and provide approaches useful for estimating the severity of DSPN. In addition, proficiency of the clinical examination of signs and symptoms and of nerve conduction testing is emphasized.

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We propose separate definitions for typical DPN (DSPN) and atypical DPN. DSPN is a symmetrical length-dependent sensorimotor polyneuropathy attributable to chronic hyperglycaemia, associated metabolic derangements, cardiovascular risk covariates, and microvessel alterations. An abnormality of nerve conduction which may be subclinical (asymptomatic and without signs or symptoms of polyneuropathy) appears to be the first objective and quantitative indication of DSPN and is a necessary condition for the confirmed diagnosis of DSPN. The occurrence of diabetic retinopathy and nephropathy in a given patient strengthens the case that a patient's sensorimotor polyneuropathy is attributable to diabetes mellitus. However, the association among these complications is not strong enough to allow diagnosis of DSPN from knowing that diabetic retinopathy or nephropathy occurs in the same patient, i.e. other causes of polyneuropathy must be excluded.

For epidemiological surveys or controlled clinical trials of DSPN, we advocate the use of nerve conduction as an early and reliable indication of the occurrence of subclinical DSPN. To be reliable as the indicator of subclinical DSPN (Stage 1a), nerve conduction evaluation must be carried out rigorously using appropriate testing conditions and techniques using suitable criteria and reference values corrected for applicable variables of age, gender, height, and weight – the topic discussed in the next section. Volunteered symptoms and elicited signs are needed to confirm the diagnosis and to estimate severity. Other neurophysiological tests (e.g. quantitative sensation and autonomic tests) are useful in characterizing neuropathic expression. As for nerve conduction evaluations, so also for the clinical evaluation of signs and symptoms, careful attention needs to be given to the issue of proficiency of examiners. In a recent study of the proficiency of neuromuscular experts as compared to their 75% group diagnosis or as compared to confirmed nerve conduction abnormality, their diagnoses were more variable and less reproducible than usually assumed or desirable – indicating a need for careful instruction, consensus development, and quality assurance of the clinical evaluation, in conducting epidemiological surveys or randomized controlled clinical trials [49–51]. In an earlier but smaller study assessing proficiency with agreement on methods of examination and diagnosis and using confirmed nerve conduction abnormality as a guide in training, high levels of concordance among clinical examinations were achieved [52].

Atypical DPNs

Atypical DPN has not been as well characterized and studied as has typical DPNs (i.e. DSPN). It is possible that atypical DPN is actually not a single entity but several varieties. This condition appears to be an intercurrent and monophasic or fluctuating disorder, tending to preferentially involve small sensory and autonomic nerve fibres, by not being closely associated with chronic hyperglycaemia or associated with the microvessel abnormalities found in DSPN.

Abnormality of nerve conduction as minimal criteria for the diagnosis of subclinical DSPN

The evidence that nerve conduction abnormality of limb nerves is the most objective and quantitative indication of DSPN comes from studies of DPN cohorts [53–57] and population-based study of healthy subject and diabetes mellitus cohorts [52,58–61].

For purposes of using nerve conduction studies for the research diagnosis of subclinical DSPN (Stage 1a), it is necessary that they are performed proficiently, using suitable criteria for abnormality based on adequately obtained reference values corrected for applicable variables and that the results are clearly presented and interpreted. In performance of nerve conduction studies, particular attention needs to be given to adequate maintenance of limb temperature, correct and exact placement of stimulating and recording electrodes, accurate measurement of distances, use of just supramaximal electrical stimulation, recognition of normal anatomic variations (e.g. nerve crossovers), avoidance of recording of spurious responses, and adequate documentation and record keeping. Assuming that nerve conduction values have been proficiently assessed, it is then necessary to express abnormality by comparison with adequately obtained reference values and to use these values to determine whether DSPN is present based on appropriate criteria for its diagnosis – the subject explored further in subsequent paragraphs.

The nerve conduction criteria, which might be used for the diagnosis of DSPN in epidemiological surveys, randomized controlled trials, and even for medical practice, were recently assessed in databases of previously studied healthy subjects and a population-based cohort of diabetic subjects (RDNS) – cohorts from Olmsted County, MN, USA [3,16,58]. Ideal nerve conduction criteria for DSPN would use attributes representative of neurophysiological abnormality in DSPN employing attributes that are frequently abnormal in the condition. In an HS cohort, use of the criterion should result in low frequency of abnormality, i.e. few false positives, providing values of abnormality near the set percentile abnormality, e.g. 2.5th or 1st percentile. In a population-representative cohort of patients with diabetes mellitus, the criterion should sensitively detect DSPN – in perhaps one third or more of the cases. In the Nerve Conduction Criteria Study, the authors were especially concerned about the frequency of false positives (type 1 error) because multiple attributes and multiple nerves are usually assessed in nerve conduction studies.

The Nerve Conduction Criteria Study [62] evaluated eight nerve conduction criteria for the potential diagnosis of DSPN and the frequencies of abnormalities were tabulated in the HS and diabetic subject cohorts. In the diabetic

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Table 1. Nerve conduction abnormality in the RDNS and RDNS-HS cohorts using different criteria

	RDNS-HS[a] ($N = 330$)			RDNS ($N = 456$)	
	No. (%) abnormal			Prevalence at first visit	
	5th/95th	2.5th/97.5th	1st/99th	2.5th/97.5th	1st/99th
Criteria 1: ≥1 of 12 nerve conduction attributes abnormal[b]	123 (37.3)	57 (17.3)	30 (9.1)	60.1	42.5
Criteria 2: ≥1 abnormal in 2 separate nerves	37 (11.2)	8 (2.4)	3 (0.9)	34.6	22.1
Criteria 3: ≥1 abnormal in 2 separate nerves (1 is sural)	24 (7.3)	7 (2.1)	2 (0.6)	26.3	15.6
Criteria 4: Peroneal CV abnormal and sural amplitude abnormal	2 (0.6)	2 (0.6)	1 (0.3)	11.8	3.9
Criteria 5: Σ 2 nerve conduction normal deviates abnormal (peroneal CV and sural amplitude)	17 (5.2)	9 (2.7)	4 (1.2)	37.9	31.1
Criteria 6: Σ 2 nerve conduction normal deviates abnormal (peroneal CV and tibial CV)	17 (5.2)	9 (2.7)	4 (1.2)	34.2	21.1
Criteria 7: Σ 5 nerve conduction normal deviates abnormal	17 (5.2)	9 (2.7)	1 (0.3)	28.3	17.5
Criteria 8: Σ 6 nerve conduction normal deviates abnormal	17 (5.2)	9 (2.7)	4 (1.2)	30.9	23.5

[a]On the basis of theoretical considerations (Bonferonni's modelling) the following abnormal frequencies would be expected based on type 1 error and lack of linkage among attributes studied.
[b]Of $330 \times 12 = 3960$ nerve attributes tested, 197 (5.0%) are abnormal at the 95th, 75 (1.9%) at the 97.5th and 36 (0.9%) at the 99th.

subject cohort, the frequencies of nerve conduction abnormality using 2.5th/97.5th cut-offs were peroneal motor nerve conduction velocity (MNCV), 26.3%; sural amplitude, 25.4%; tibial MNCV, 24.8%; ulnar MNCV, 21.3%; peroneal F-latency, 16.9%; and ulnar F-latency, 16.0%. Among the pairs of these six nerve conduction attributes, there was highly significant agreement for the diagnosis of DSPN.

Eight criteria for DSPN were compared (Table 1). Criterion 1 – '≥1 abnormality of any one attribute from any nerve' – did not perform well. It was inadequate in the following respects. Abnormality could be due to mononeuropathy. Use of this criterion resulted in an excessive number of false-positive diagnoses. In the HS cohort (expected to have no patients with DSPN) and using this criterion and percentiles of ≤5th/≥95th, ≤2.5th/≥97.5th, and ≤1st/≥99th, abnormality frequencies of 37.3, 17.3, and 9.1% resulted – a large type 1 error. Assuming specificity to be the same for the diabetic as they were for HS (a reasonable assumption because the technique of testing and references values were the same), this criterion produced too high a frequency of abnormality among diabetic patients (Table 1).

Criterion 2 – '≥1 abnormal attributes in ≥2 separate nerves tested'. Inspection of the table shows that this criterion performs much better than Criterion 1. Using the ≤5th/≥95th percentile cut-off, the false positives are probably excessively high in both the HS and the diabetic subjects, but using lower percentile abnormality the error rate is acceptable. Criterion 3 – 'an abnormality ≤1st/99th percentile of any attribute of two separate nerves, one of which must be the sural nerve' (AAN, AAEM, and AAPMR). Using the ≤5th/≥95th percentile this criterion results in excessive false positives among HS and using the ≤1st/≥95th criteria in the diabetic subjects, too low a frequency of DSPN is obtained. Criterion 4 – 'abnormality of peroneal MNCV and sural amplitude'. Use of this criterion results in low sensitivity in both healthy subject and diabetes mellitus cohorts (Table 1). Criteria 5–8 are composite scores of nerve conduction attributes (Table 1). Irrespective of which composite score was used, specificity was close to the preset percentile abnormality level in the HS cohort. In the diabetic subject cohort, good specificity and sensitivity were achieved, especially for Σ 2 nerve conduction normal deviates ≥97.5th, i.e. peroneal MNCV and sural amplitude.

From the results of the Nerve Conduction Criteria Study, the authors concluded that composite sum scores of normal deviates (from percentiles) and nerve conduction attributes performed best for diagnosing DSPN, although performance of Criterion 2, '≥1 abnormal attribute in ≥2 separate nerves', and Criterion 3 (when modified) was also acceptable. In clinical practice, less rigid criteria may be justified (Table 1, footnote a).

Estimating severity of DSPN

For medical practice and for conducting epidemiological surveys and randomized controlled clinical trials, measurement of the severity of DSPN in a given patient is

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needed to estimate severity of symptoms, signs, neurophysiological test results, and overall severity of DSPN. This need is not met by simply tallying patients as having, or not having, DSPN – severity also needs to be ascertained. Two approaches have been described – staged [63] and continuous measurement approaches [64].

The staged approach

Stage 0 = criteria for subclinical DSPN have not been met – an abnormality of nerve conduction not being present.

Stage 1a = criteria for subclinical DSPN have been met, but the patient does not have signs or symptoms of DSPN. If Criterion 3 (from previous sections) for DSPN is chosen, sural amplitude must be ≤1st percentile and any one other nerve conduction attribute assessed is ≤1st or ≥99th percentile with corrections made for applicable variables. If one of the composite scores is used (Criterion 5–8), the composite normal deviate score must be ≥97.5th or ≥99th percentile – whichever is chosen.

Stage 1b = criteria for subclinical neuropathy have been met and neuropathic signs without neuropathic symptoms are present.

Stage 2a = criteria for subclinical neuropathy have been met and the patient has neuropathic symptoms with or without neuropathic signs.

Stage 2b = criteria for subclinical neuropathy have been met and patient has unequivocal weakness of ankle dorsiflexion (Table 1, footnote a).

Continuous measurement of the severity of DSPN

An alternative method to assess the severity of DSPN is to use a continuous measure of neuropathic signs without or with nerve conduction or other neurophysiological test abnormalities. The Neuropathy Impairment Score (NIS) and NIS of the lower limb provide a sum score of scored weakness of a predetermined list of muscle groups, scored decrease of muscle stretch reflexes, and scored abnormality of sensory modalities of sensation of fingers and toes. Judgements are to be corrected for the influence of age, gender, anthropomorphic variables, and physical fitness. The NIS or NIS of the lower limb scores have been extensively described [65] and extensively used in epidemiological surveys and therapeutic trials of chronic inflammatory demyelinating and monoclonal gammopathies of undetermined significance neuropathies [52,66] and also in DSPN [65,67]. Paper and electronic forms of NIS and symptoms and disability scores have been extensively used in epidemiological surveys and randomized controlled clinical trials [68]. With some modifications, the MRC scale has been used to score overall muscle weakness [69]. Several other sum scores of impairment have been developed and published. The symptoms (and in some cases signs) of DSPN can be scored using the Neuropathy Symptoms Score [70], Neuropathy Symptoms and Change [68], the Michigan Score [71], and the Toronto Clinical Neuropathy Score [72–74].

Composite scores of representative attributes of nerve conduction have also been shown to be useful in estimating the severity of polyneuropathies [75–78]. It is not possible to develop a sum score of attributes of nerve conduction without some transformation of the data. Composite scores of nerve conduction can be derived if percentile values are expressed as normal deviates from percentiles corrected for applicable variables and abnormality is expressed in the same tail of the normal distribution. A composite score of neurophysiological tests is especially useful in epidemiological surveys and randomized controlled trials. Because DSPN is the summation of different symptoms, signs, and test abnormalities, use of composite normal deviate scores allows combining representative signs and test results. A further important use of composite scores is that it allows assessment of change in severity even within the range of normal and extending into abnormality. The percentile position of this composite measure must be independently set by studies of the composite score in reference populations. An example of such a composite score for use in DSPN is Σ 5 nerve conduction normal deviates. The Σ 5 nerve conduction normal deviate score is made up of peroneal nerve velocity, amplitude, distal latency, tibial distal latency, and sural amplitude, with the five nerve conduction attributes expressed as normal deviates. In a similar manner, it is possible to add other neurophysiological measures to the composite nerve conduction score. In Σ 7 NTs normal deviate, Σ 5 nerve conduction normal deviate is added to by the normal deviate score of vibratory detection threshold of the toes and heart rate deep breathing decrease.

On the assumption that NIS abnormality correlates with neurophysiological test abnormalities, a composite score combining the two has been proposed and used in epidemiological surveys and controlled trials, e.g. NIS of the lower limb + Σ 7 NT normal deviate score.

Conclusions

The Neurodiabetes Consensus (Toronto) Group on DPNs supports the earlier classification of DPNs by Thomas *et al*. [5,6] and Boulton *et al*. [7,8] into generalized and focal and multifocal, and further separating DPNs into typical (DSPN) and atypical DPNs. For epidemiological surveys and controlled trials, we define DSPN as chronic, symmetric, length-dependent sensorimotor polyneuropathy developing from metabolic derangements and microvessel alterations related to chronic hyperglycaemia and cardiovascular risk factors. Metabolic derangements and microvessel alterations appear to be similar and common to those of retinopathy and nephropathy. As the pattern of DSPN is not unique in diabetes mellitus, other causes need to be excluded.

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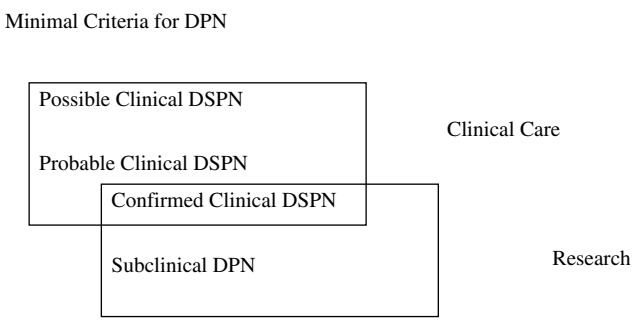

Figure 1. Minimal criteria for diabetic polyneuropathy

Atypical DPN are intercurrent generalized polyneuropathies having an acute or subacute onset and a monophasic or relapsing course that may develop at any time during a patient's diabetes mellitus. These atypical neuropathies need further studies emphasizing natural history, classification, and outcome. Like DSPN, so also in atypical DPN other causes of neuropathy need to be excluded.

Definitions of minimal criteria for DSPN

1. Possible Clinical DSPN
   Symptoms *or* signs of DSPN. Symptoms may include: decreased sensation, positive neuropathic sensory symptoms (e.g. 'asleep numbness', 'prickling' or 'stabbing', 'burning' or 'aching' pain) predominantly in the toes, feet, or legs. Signs may include: symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes.
2. Probable Clinical DSPN
   A combination of symptoms *and* signs of distal sensorimotor polyneuropathy with any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes.
3. Confirmed Clinical DSPN
   An abnormal nerve conduction study and a symptom or symptoms or a sign or signs of sensorimotor polyneuropathy. Severity of DSPN can be assessed by staged or continuous approaches described above and by dysfunction and disability scores [65].
4. Subclinical DSPN (Stage 1a)
   No signs *or* symptoms of polyneuropathy. Abnormal nerve conduction, as described above, is present (Figure 1).

Atypical DPNs

Before further classification of atypical DPNs, setting minimal criteria for diagnosis and estimating severity, further characterization from epidemiological surveys and mechanistic studies are needed. The issue of painful, autonomic, and nerve morphological abnormalities are discussed in subsequent articles.

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Conflict of interest

The authors have no conflicts of interest.

Appendix

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