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A MULTIMODAL APPROACH TO THE EARLY DIAGNOSIS OF DYSMETABOLIC POLYNEUROPATHIES

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Dysmetabolic polyneuropathies arise when persistent abnormalities of glucose, renal clearance, vitamin availability, thyroid function or other systemic metabolic processes impair peripheral nerves. The most familiar phenotype is distal symmetric diabetic polyneuropathy, but a similar length-dependent pattern can occur in chronic kidney disease, vitamin B12 deficiency and other endocrine or nutritional conditions. The diagnostic challenge is that the metabolic disorder may be real while the neuropathy has an additional and potentially treatable cause [1-7].

Early damage may involve thinly myelinated Aδ fibres, unmyelinated C fibres and autonomic axons before routine nerve-conduction studies become abnormal. Burning, thermal dysesthesia, allodynia, altered sweating or orthostatic symptoms can therefore precede loss of vibration, absent reflexes and weakness. A test designed for large myelinated fibres cannot be expected to exclude a disorder confined to small fibres [2, 8-10].

Objective

To define a clinically practical multimodal pathway for recognizing early dysmetabolic polyneuropathy and identifying patients who require specialized small-fibre or differential diagnostic testing.

Clinical entry point

The first task is to establish the phenotype. A typical metabolic neuropathy develops gradually, begins in the toes or feet, remains broadly symmetrical and progresses proximally. History should document the quality and timing of sensory symptoms, gait difficulty, weakness, autonomic complaints, medication exposure, alcohol use, nutritional risk and family history. Sudden or rapidly progressive onset, marked asymmetry, early proximal weakness, cranial-nerve involvement or a sensory level are atypical and should redirect the investigation.

Bedside examination should deliberately separate fibre functions. Pinprick and temperature test small sensory fibres; vibration with a 128-Hz tuning fork, joint position and Romberg testing assess large sensory fibres; strength and tendon reflexes characterize motor and reflex involvement. The 10-g monofilament is valuable for identifying loss of protective sensation and ulcer risk, but it is not a sensitive stand-alone test for early neuropathy [1, 4].

Table 1. Matching the suspected fibre phenotype to the diagnostic method

Clinical question	Preferred assessment	Early diagnostic contribution	Caution
Are large myelinated fibres affected?	Nerve-conduction studies and EMG	Confirms axonal or demyelinating large-fibre disease	May remain normal in isolated small-fibre neuropathy
Are thermal or pain pathways affected?	Pinprick/temperature examination and QST	Detects altered thermal thresholds and sensory gain or loss	QST is psychophysical and not fully localizing
Is there structural small-fibre loss?	Skin biopsy with IENFD	Provides objective morphometric evidence	Requires standardized laboratory processing
Is autonomic function involved?	Cardiovagal, orthostatic and sudomotor testing	Documents autonomic C-fibre dysfunction	Medication and hydration can confound results
Can a non-invasive research marker help?	Corneal confocal microscopy	Quantifies corneal small-nerve morphology	Thresholds and access are not yet uniform

Functional confirmation

Nerve-conduction studies remain central when weakness, impaired vibration, reduced reflexes or an uncertain pattern is present. A typical metabolic neuropathy is usually axonal, with reduced sensory amplitudes followed by motor involvement. Disproportionate slowing, conduction block or marked temporal dispersion raises concern for an acquired demyelinating neuropathy. Needle EMG is helpful when motor axon loss, radiculopathy or a superimposed focal process must be assessed.

When the examination suggests a small-fibre phenotype and conventional electrodiagnostic testing is normal, objective confirmation may be obtained with quantitative sensory testing, sudomotor or other autonomic tests, and skin biopsy. Devigili and colleagues showed that clinical signs combined with abnormal QST and/or reduced intraepidermal nerve-fibre density were more reliable than sensory symptoms alone [8]. Thus, a single abnormal test should be interpreted cautiously, especially when the clinical examination is normal.

Corneal confocal microscopy is a rapid, non-invasive method for quantifying small corneal nerve fibres. Meta-analytic and longitudinal data support its ability to identify subclinical diabetic nerve damage and to predict future neuropathy in research cohorts [11, 12]. Its use is promising for repeated observation, but local reference values, operator standardization and clinically actionable cut-offs remain necessary before broad routine adoption.

Etiological screening

A focused laboratory screen should include fasting glucose or HbA1c, complete blood count, renal and liver profiles, electrolytes, thyroid function, vitamin B12 and serum protein immunofixation. If routine glucose testing is non-diagnostic in a painful distal sensory phenotype, impaired glucose tolerance testing may be considered. Borderline B12 requires assessment with methylmalonic acid, with interpretation adjusted for renal function [5, 15, 16].

Tests beyond the basic screen should be selected by phenotype rather than ordered indiscriminately. Inflammatory markers, autoimmune studies, infections, toxicology, genetic analysis, cerebrospinal fluid examination or nerve imaging become relevant when progression is rapid, distribution is asymmetric, motor involvement is prominent, systemic inflammatory signs are present or family history suggests inheritance.

Three-level clinical decision

Level 1 is bedside recognition: metabolic risk plus a compatible length-dependent symptom or sign pattern. Level 2 is objective functional classification with nerve conduction for large-fibre disease or targeted small-fibre/autonomic testing when conventional studies are normal. Level 3 is etiological attribution, which requires concordance between the neurological phenotype and the documented metabolic disturbance while reasonable alternatives have been assessed.

Follow-up should use the same clinical scale and testing conditions. Change in pain intensity alone is not sufficient to judge nerve recovery because symptoms can improve while sensory loss progresses. Repeated examination of fibre-specific signs, gait, protective sensation and selected objective measures provides a more defensible picture of progression or stabilization.

Interpreting discordant findings

Discordance between symptoms, examination and laboratory tests is common in early neuropathy. Burning pain with normal nerve conduction is not automatically a false-positive clinical presentation; it may reflect a process restricted to small fibres. Conversely, an isolated abnormal thermal threshold is not sufficient to establish neuropathy because attention, cognitive state, skin temperature and test technique influence QST. The appropriate response is to revisit the anatomical pattern, repeat a focused examination and select a structurally or autonomically complementary test rather than simply accumulating unrelated investigations.

An abnormal nerve-conduction result also requires phenotypic interpretation. Reduced distal sensory amplitudes with relatively preserved conduction velocities fit an axonal length-dependent process, whereas disproportionate slowing, conduction block or temporal dispersion is atypical for a straightforward metabolic neuropathy. In the latter situation, labeling the disorder as diabetic or uremic solely because the patient has a metabolic disease may delay recognition of a treatable inflammatory demyelinating neuropathy.

Causal attribution should therefore be graded. A metabolic association is plausible when exposure precedes symptoms and the neurological pattern is compatible. It becomes stronger when severity or progression parallels metabolic burden and competing causes have been reasonably assessed. Attribution remains uncertain when the distribution is atypical, the metabolic abnormality is mild, or another medication, nutritional deficiency, monoclonal protein or hereditary pattern offers a better explanation.

Monitoring and practical application

Baseline documentation should identify the exact fibre functions that are abnormal. For a painful small-fibre phenotype, follow-up may combine a standardized pain measure with pinprick or temperature findings and one objective small-fibre or autonomic method. For large-fibre disease, vibration, proprioception, reflexes, gait and protective sensation are more informative. Repeating every available test is rarely necessary; the monitoring tool should be selected because it can answer a defined question about progression, safety or response.

Clinical risk reduction begins while the aetiological work-up is in progress. Patients with sensory loss need education about skin and foot inspection, suitable footwear, burn prevention and fall risk. Autonomic symptoms require medication review and evaluation of hydration and cardiovascular contributors. Correction of glycaemia, renal dysfunction, thyroid disease or nutritional deficiency should be coordinated with the relevant clinician, because symptomatic analgesia does not replace treatment of the underlying metabolic exposure.

For scientific reporting, the terms possible, probable and confirmed neuropathy should be tied to explicit evidence. Authors should state whether the cohort was defined by symptoms, signs, nerve-conduction abnormalities, small-fibre tests or a combination of these. This transparency improves comparison between studies and prevents apparent differences in prevalence from being mistaken for biological disagreement when they actually arise from different case definitions.

Conclusion

Early dysmetabolic polyneuropathy is best identified through concordant clinical, functional and etiological evidence. Nerve-conduction studies define large-fibre involvement, while QST, autonomic testing, skin biopsy and corneal confocal microscopy address the diagnostic gap created by early small-fibre disease. A phenotype-driven strategy detects reversible causes, limits unnecessary testing and prevents a normal electrodiagnostic study from prematurely closing the investigation.

Adabiyotlar, References, Литературы:

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