Rapid screening for inflammatory neuropathies by standardized clinical criteria

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Abstract

Background: Delay in recognition and treatment of inflammatory neuropathies increases morbidity and mortality. We have developed and standardized 3 clinical screening criteria that rapidly detect inflammatory neuropathies. **Methods:** We reviewed all patients with definite large fiber neuropathy in 2 different patient populations: 1 from a private neurology clinic and the other from a tertiary care center. Patients were divided into 2 groups: those with an inflammatory neuropathy and those with a noninflammatory neuropathy. We specifically noted the 3 key neuropathy characteristics: onset, distribution, and associated systemic features (ODS). We studied the sensitivity and specificity of ODS in differentiating between inflammatory and noninflammatory neuropathies.

Results: A total of 206 patients were included: 51 from the private clinic and 155 from the tertiary care center.

The sensitivity of using ODS in detecting an inflammatory neuropathy was 96% and the specificity was 85%. The positive predictive value of ODS was 0.8 and negative predictive value was 0.97. **Conclusions:** Rapid screening for inflammatory neuropathies by ODS clinical criteria is highly sensitive and has a high negative predictive value for noninflammatory neuropathies. ODS uses simple clinical criteria to rapidly screen for patients with a potentially treatable form of neuropathy and accelerate their diagnostic evaluation. **Classification of evidence:** This study provides Class IV evidence that 3 neuropathy characteristics—onset, distribution, and associated systemic features—accurately identify patients with inflammatory neuropathies. *Neurol Clin Pract* 2016;6:384-388

Up to 20% of patients with large fiber peripheral neuropathy have an autoimmune or inflammatory etiology.¹ Rapid recognition of these patients permits prompt initiation of appropriate workup and immunosuppressive treatment and prevents morbidity. Moreover, unnecessary investigation and treatment of patients who are unlikely to have an inflammatory neuropathy is costly and occasionally harmful.^{2,3}

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This study examines whether focusing on 3 key clinical questions will reliably differentiate inflammatory neuropathies from noninflammatory neuropathies.

An acute or subacute onset of a neuropathy, especially if the onset is asymmetric or if the neuropathy has associated systemic features or both, should raise a red flag and investigation for inflammatory neuropathy.⁴ However, it is unclear how well these characteristics detect patients with inflammatory neuropathies.

This study examines whether focusing on 3 key clinical questions will reliably differentiate inflammatory neuropathies from noninflammatory neuropathies. The 3 key questions are summarized by onset, distribution, and systemic features (ODS). ODS+ patients should have one or more of the following: the onset should be acute or subacute (less than 8 weeks to reach the plateaus); the distribution should be non-length-dependent, meaning the symptoms are proximal and distal (such as in chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]) or multifocal or asymmetric (such as in mononeuritis multiplex); or there should be systemic features such as weight loss or skin changes.

We hypothesized that ODS can be a highly sensitive screening tool for inflammatory neuropathies, expediting diagnostic evaluation and management of ODS+ patients. ODS could also have a highly negative predictive value, which could potentially minimize unnecessary diagnostic evaluation in ODS− patients.

METHODS

Standard protocol approvals, registrations, and patient consents

The study was approved by the University of North Carolina (UNC) institutional review board.

We reviewed the charts of all patients who were diagnosed with large fiber neuropathy at UNC and at a privately owned clinic seen between October 2013 and June 2015. Patients had definite evidence of large fiber neuropathy on nerve conduction study based on our laboratory normative data corrected to the patient's age. Patients with entrapment neuropathy, radiculopathy, small fiber neuropathy, or motor neuron disease were all excluded from the study. We noted whether the patient had an acute or subacute onset as defined above, a non-length-dependent distribution of symptoms and signs, or any systemic features. Systemic features included one or more of the following: skin changes, weight loss, autonomic symptoms (mainly orthostatic hypotension), fever and chills, or joint inflammation. O, D, and S all had equal weight when positive and patients who had at least O, D, or S positive were considered ODS+. Patients were separated into ODS+ and ODS−. The 2 groups were compared and it was noted whether they had an inflammatory or autoimmune neuropathy vs a noninflammatory neuropathy (table). Inflammatory neuropathies included Guillain-Barré syndrome, CIDP and its subtypes, multifocal motor neuropathies, vasculitic neuropathies or those associated with connective tissue disease, paraneoplastic neuropathies, autoimmune ganglionopathies, and inflammatory plexopathies (diabetic and nondiabetic). We performed a sensitivity and specificity as well as false-negative and false-positive statistical analysis.

Research question

The primary research question concerns whether focusing on 3 key clinical questions will reliably differentiate inflammatory neuropathies from noninflammatory neuropathies. In this design, this will result in Level IV evidence.

The sensitivity of onset, distribution, and systemic features (ODS) for inflammatory neuropathies was 96% and the specificity was 85%.

RESULTS

We studied 206 patients: 51 from the private clinic and 155 from the tertiary care center (figure). The etiology of the neuropathies and positivity for ODS are listed in the table. The sensitivity of ODS for inflammatory neuropathies was 96% and the specificity was 85%. The positive predictive value of ODS was 0.8 and negative predictive value was 0.97. The 3 patients who had an inflammatory neuropathy but were not ODS+ had a distal demyelinating neuropathy (distal acquired demyelinating symmetric neuropathy), which was found on nerve conduction studies. The 19 patients who did not have an inflammatory neuropathy but were ODS+ had the following: 7 inherited neuropathy (3 of those had hereditary neuropathy with liability to pressure palsies [HNPP] where the onset was acute or distribution was multifocal), 4 toxicity from chemotherapy, 3 lymphomatous neuropathy, 1 multiple perineurioma, 2 idiopathic neuropathies, 1 amyloid neuropathy from multiple myeloma, and 1 diabetes and end-stage renal disease with systemic features.

DISCUSSION

The rapid screening for inflammatory neuropathies by ODS clinical criteria has a high sensitivity. These criteria also have high negative predictive value for noninflammatory neuropathies. ODS is

Table Patient characteristics

Etiology	Private clinic (n = 51), n (%)	Academic clinic (n = 155), n (%)	Total (n = 206), n (%)	ODS+ ^a
Idiopathic ^b	16 (31)	10 (6)	26 (13)	2
Inherited	4 (8)	55 (35)	59 (29)	7
Diabetic	23 (45)	5 (3)	28 (14)	0
Neoplastic ^c	0	6 (4)	6 (3)	4
Toxic/metabolic ^d	4 (8)	8 (5)	12 (6)	6
Paraneoplastic	0	6 (4)	6 (3)	4
Primary inflammatory ^e	2 (4)	47 (30)	49 (24)	46 ^f
Diabetic inflammatory	1 (2)	2 (1)	3 (1)	3
Vasculitis or connective tissue disease	1 (2)	16 (10)	17 (8)	17

Abbreviation: ODS = onset, distribution, and systemic features.

^aODS+ patients with one or more of the following criteria: acute/subacute onset of neuropathy, non-length-dependent neuropathy, or associated systemic symptoms.

^bIn some of those patients, the clinical behavior strongly suggested an inherited neuropathy but genetic testing was either unrevealing or not performed.

^cEither primary nerve tumors or direct invasion of nerves by lymphoma.

^dRelated to chemotherapy, uremia, alcoholism, B₆ toxicity, or copper deficiency.

^eChronic inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, multifocal motor neuropathy with or without conduction block.

^fNerve conduction studies showed distal demyelination in the remaining 3 patients.

Figure Flow chart summarizing the study population

ODS = onset, distribution, and systemic features.

not meant to replace careful clinical examination and electrophysiology, but it is a simple and rapid screening method for patients with a potentially treatable form of neuropathy. It could be used by non-neuromuscular specialists and may help reduce unnecessary tests in ODS– patients.

The ODS criteria, in combination with nerve conduction studies, if performed prior to the neuromuscular evaluation increased the sensitivity of detecting inflammatory neuropathies to 100% in our population. The nerve conduction studies will detect distal acquired demyelinating peripheral neuropathies that may go undetected by ODS. These will also detect whether the patient has an asymmetric neuropathy that may be subclinical. The low specificity of ODS is explained by noninflammatory neuropathies, which can occasionally be asymmetric or multifocal or associated with systemic features or even acute or subacute such as HNPP or lymphomatous neuropathy. It is, of course, possible that some of these patients also have an associated inflammatory component or coincidental inflammatory disorders. Other causes of multifocal neuropathies that were not present in our population but are important to keep in mind are the ones related to infectious agents or, rarely, amyloid depositions.^{5,6} In HNPP, the history is suggestive and the nerve conduction studies showing the conduction block at entrapment site should prompt the clinician about this diagnosis. In the other form of multifocal neuropathies, even if the cause is not inflammatory, it remains serious (infection, amyloid) and should raise a red flag as well. So ODS not only screens for inflammatory neuropathies but can also warn the physician that the diagnostic evaluation should be expedited.

Patients with systemic features can have different neuropathies that are not related to immune-mediated processes such as amyloid neuropathy in the case of multiple myeloma or renal disease.^{7,8} These are usually easily recognized when taking a thorough history or with basic blood tests.

In regard to the acute or subacute onset of the neuropathy that was not inflammatory, the etiology was in general related to chemotherapeutic toxicity. However, here again, the history in this situation will suggest the etiology of the neuropathy and hence obtaining a good history will reduce the false-positive of ODS and increases the specificity of the tool. One needs to be aware of the coasting phenomenon of certain drugs to avoid confusion and unnecessary testing or treatment.⁹

ODS can help physicians taking care of patients with peripheral neuropathies to quickly determine if a patient is likely to have an inflammatory neuropathy. ODS is not meant to replace a neurologic examination and electrophysiology but it can be used to accelerate evaluation of ODS+ patients and potentially reduce health care costs in ODS– patients. A larger,

prospective study is needed to verify our findings and to assess whether ODS can positively affect health care cost.

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AUTHOR CONTRIBUTIONS

Chafic Karam: conceptualization, data interpretation, manuscript drafting and revision. Louis A. Tramontozzi III: conceptualization, data interpretation, manuscript drafting and revision.

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