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# The use, misuse and abuse of paraneoplastic panels in neurological disorders. A retrospective study

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ABSTRACT

*Objectives:* The field of paraneoplastic neurological syndromes PNS has grown exponentially with the increased identification of associated antibodies. Testing for these antibodies is commonly done in "panels" to increase sensitivity, and these panels have become a routine test on CSF samples obtained for a variety of clinical indications. Excessive testing has raised concerns about the correct utilization of these panels. Our study investigates the appropriateness of use of paraneoplastic panel in an academic, tertiary-care medical center.

*Patients and Methods:* We retrospectively reviewed charts of all patients who had autoimmune paraneoplastic panel testing in one year period. We collected date on demographics, clinical presentations and ancillary testings on all reviewed charts. Then, we devised an algorithm based on available data to define cases where testing had been unnecessary or likely unnecessary.

*Results:* We collected 60 cases that had undergone autoimmune paraneoplastic testing serum and/or CSF. Testing was unnecessary in 10 cases (16%), in which presentations had a definitive confirmatory tests. Testing was unlikely necessary in 11 cases (18%), in which all ancillary testing was normal in 6 cases, and presentation was not compatible with any known syndrome in 5 cases. Collectively, paraneoplastic panel testing was of extremely low yield on more than one third of the cases where where w testing was done.

*Conclusion:* Our results adds to the growing concerns about the utilization of paraneoplastic panels, and the urgent need for enhanced screening and establishing a framework that can guide neurologists on when testing can have a sufficient yield to warrant it. Such framework should be built using diagnostic algorithms based on risk, clinical manifestations, characterization of autoantibodies and their associations.

## 1. Introduction

The field of autoimmune paraneoplastic neurological syndromes (PNS) has grown exponentially in the last two decades. [1] This expansion is driven by the continuous identification of new antibodies targeting various components of central and peripheral nervous system. There is currently more than 20 antibodies available for commercial testing. [2,3] Unfortunately, many of these disorders have overlapping symptomatology with each other and with other non-autoimmune pathologies [4]. In order to improve the sensitivity and reduce the cost of antibody testing, it is commonly done through "panels which encompass a variety of antibodies targeting synaptic, cell-surface and intracellular targets [5].

Although there are proposed criteria for defining PNS, [6] there are no set criteria for when testing is recommended. This is compounded by the increased recognition of atypical presentations of some patients who tested positive for paraneoplastic antibodies, or "non-classical" PNS [7]. Therefore, ordering paraneoplastic panel testing has become a rampant practice among neurologists, driven by the rapidly expanding phenotype of PNS [8], the overlap with other neurological disorders, and the fear of missing an underlying malignancy [9,10].

However, the increased utilization comes with increased costs, and increased possibility of false positive results. The later drives further testing such as surveillance imaging, and exposes patients to unnecessary treatments. This is important as sensitivity of these panels was estimated to be 34–65% when case adjudication was based on clinical criteria, [5] and false positive results were as high as 70% [11].

We attempted to characterize the clinical and ancillary features of all patients who underwent paraneoplastic testing in our institution, and then looked into the appropriateness of use of paraneoplastic panel testing.

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## 2. Material and methods

### 2.1. Population

We enrolled charts of all adult patients (> 18 year old) who had CSF testing between 7/1/2017 and 6/30/2018 at SUNY Upstate Medical University Hospital. Charts of subjects on whom autoimmune (Paraneoplastic) panels done were individually reviewed. We examined demographics, clinical presentation and reason for CSF testing, duration of illness preceding presentation, prior history of malignancy, and all related ancillary testings including MRI brain, EEG, video-EEG, EMG/Nerve Conduction Studies, CSF profile and results of the paraneoplastic testings.

### 2.2. Clinical presentation

We adopted the Paraneoplastic Neurologic Syndrome Euronetwork Database classification of paraneoplastic disorders; [12] and thus divided subjects based on their clinical presentation as being tested primarily for one of the following syndromes:

1) Limbic encephalitis, or encephalomyelitis [13]
2) Cerebellar degeneration [14]
3) Myelitis syndrome, brainstem encephalitis, opsoclonus myoclonus syndrome, motor neuron disease, and stiff-person syndrome (PNS) [15–17]
4) Optic neuritis or cancer-associated retinopathy [18]
5) Peripheral nervous disorders including sensory neuro-/neuronopathy, dysautonomia and neuromyotonia [19]
6) Lambert-Eaton myasthenia syndrome, Dermatomyositis/ polymyositis and necrotizing myopathy [20,21]

### 2.3. Appropriateness of testing

Determining appropriateness of testing is a challenging task in light of lack of evidence on the positive and negative predictive values of a specific clinical presentation or a clinical test in many of the subtypes of PNS. However, a thorough literature review provides some guidance on scenarios in which testing can be of extreme low yield. For example, CSF analysis was found to be abnormal in 97% of subjects with PNS in regard to protein (< 50 mg/dl), cell count (< 5 white cells) or presence of oligoclonal bands. [22] More over, MRI brain is abnormal in 70–80% of subjects with limbic encephalitis, and EEG is abnormal in the majority of patients with encephalitis [13,14]. Taken together, the lack of abnormalities on MRI brain, EEG and CSF analysis carries an extremely low likelihood of paraneoplastic encephalitis. Actually, an abnormality on one of them was considered a required criteria for diagnosis as suggested by Delmau [23]. Similarly, a normal nerve conduction study coupled with normal electromyography render sensory neuropathy/ neuronopathy, and neuromyotonia unlikely [24–26]. However, normal studies do not exclude other neuropathies such as autonomic, or CIDP-like neuropathies [27]. Unfortunately, there is no enough data on other subtypes of paraneoplastic disorders to extrapolate similar rules of thumb.

In light of the above, we deemed testing to be inappropriate based on chart reviews if the subject had a clear and unequivocal etiology of his presentation based on CSF testing or MRI findings. We deemed testing likely unnecessary if 1) presentation was compatible with encephalitis syndrome, but EEG, MRI brain AND CSF testing were all normal, or 2) if presentation was not compatible with any known paraneoplastic syndrome and with lack of history of malignancy.

## 3. Results

665 medical charts were reviewed. Among these, 60 subjects had CSF testing of paraneoplastic panel (9%). Neurology service was involved in the care of all 60 subjects. Female to male ratio was 31/29. All subjects had the lumbar puncture in the hospital setting, except for 3 subjects who had it in outpatient setting. The reason for CSF sampling was as following: 14/60 for seizures work-up, 15/60 for altered mental status, 4/60 for psychosis or psychiatric presentation, 26/60 for focal neurological symptoms and 1/60 for headache [Fig. 1].

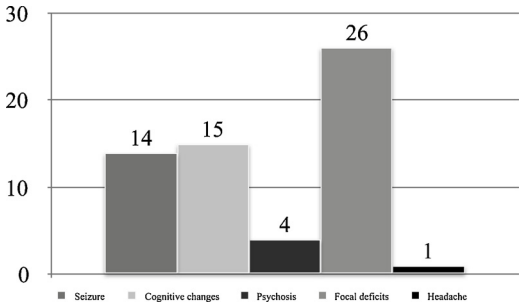


**Fig. 1.** The clinical presentation leading to CSF sampling.

The paraneoplastic syndrome that was sought was encephalitis for 37/60, cerebellar syndrome 2/60, Myelitis/brainstem encephalitis 3/60, optic neuritis 5/60, and peripheral neuropathy in 8/60. The other 5/60 were not consistent with any paranesolpastic syndrome [Fig. 2].

Regarding appropriateness of testing, 21/60 cases (35%) met our criteria for unnecessary or unlikely necessary testing:

Testing was unnecessary in 10 cases (16%), in which presentations had a definitive confirmatory tests (1 case with VZV antibody in CSF, 1 case with malignant cytology in CSF, and 8 cases with definitively diagnostic MRI lesions including primary or metastatic tumors, infections and CJD).

Testing was unlikely necessary in 11 cases (18%), in which all ancillary testing was normal in 6 cases, and presentation was not compatible with any known syndrome in 5 cases. The later consists of cases presented with intractable headache, concomitant optic neuritis and mono neuritis multiplex, isolated diplopia, bladder atonia with normal EMG of lower extremities, and emotional lability with intermittent dysarthria and ataxia.

Finally, 4/60 cases tested positive; 1 NMDA antibody, which was deemed to be false positive as the patient recovered spontaneously without immunomodulation treatment, and remained symptom-free on follow-up, 1 striational muscle antibody (serum only) which was also irrelevant to the clinical presentation as the patient manifested with refractory epilepsy and no neuromuscular symptoms, [28] and 2 GAD-65 (serum only, and negative in CSF). The last two patient both were diagnosed while critically ill, and both expired shortly after the diagnosis. It remains unclear if they were true positives. Their clinical presentation was rapid alteration in mental status, and the testing was done to rule out limbic encephalitis.

## 4. Discussion

Autoimmune paraneoplastic neurological syndromes encompass a wide variety of heterogenous disorders. Clinical diagnosis of PNS depends largely, but not fully, on obtaining antibodies levels in serum or

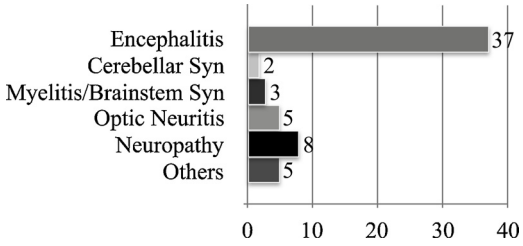


**Fig. 2.** The suspected paraneoplastic syndromes which led to panel testing.

CSF, [29] which has become a flourishing practice among neurologists in a multitude of clinical scenarios.

The cost of serum and CSF panels can reach $1,300 per case, [30] and that without taking into account the cost of imaging, other testing or immunotherapy that may arise in false positive cases. At the current time, there is an unprecedented surge in reporting “unexpected cases” that tested positive for paraneopalstic antibodies in literature, which only adds to the anxiety of practicing neurologists of missing such a consequential diagnosis.

Our study was not meant to analyze the sensitivity or specificity of paraneoplastic panels, but rather to look into the rationale of ordering them. We found that in our academic tertiary institution, one third of the cases where paraneoplastic panels were obtained, testing was inappropriate or likely unnecessary.

It is imperative to note that the methodology of our study does not allow determining when testing was appropriate, as there are no agreed-upon criteria to determine such. Instead, we only determined when testing appeared unnecessary.

Our results are consistent with other studies showing the positivity rate of paraneoplastic panel to be low, [31,32], and add to the growing concerns about the utilization of paraneoplastic panels [33–35], and the urgent need for enhanced screening and establishing a framework that can guide neurologists on when testing can have a sufficient yield to warrant it.

Such framework should be built using diagnostic algorithms based on risk, clinical manifestations, characterization of autoantibodies and their associations. [31]

## Ethical standards

The study was declared as exempt from review by the institutional review board IRB of SUNY Upstate Medical University.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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