



EMG Case No. 70, August 2004

Presenting Symptom(s):

Difficulty in swallowing and ophthalmoplegia

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Appropriate Audience: Residents and practicing physicians

Learning Objectives: After completing this educational activity, participant will be able to: (1) formulate the differential diagnosis for multiple cranioneuropathies, (2) identify the relevant electrophysiologic data that correlate with acute inflammatory polyneuropathy with predominant cranial nerve dysfunction, and (3) learn the clinical and laboratory features of Miller Fisher syndrome.

This case is no longer available for CME credit.

History

A 37-year-old gentleman presented to the emergency room with a one week history of difficulty in swallowing solids and liquids. He was also complaining of gradual onset difficulty in speaking and describing his throat as feeling numb. He had a pulsating left-sided headache, blurring of his vision on the left, and pain in his left ear. He was having difficulty handling his secretions and speaking with a raspy and breathy voice in the emergency room. Direct laryngoscopy revealed erythema and edema of the laryngeal surface of the epiglottis. The patient was intubated for airway protection and treated with intravenous antibiotics and steroids. He had mild improvement of his symptoms and was extubated four days later. The patient is now complaining of bilateral facial weakness predominantly involving the ophthalmic region beside persistent dysphagia and dysarthria. He has diplopia, but denies decreased visual acuity, vertigo, sensory changes on his face, extremity or trunk, weakness, incoordination, tinnitus, and impaired hearing.

- Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.
- Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?

Commentary I

Given the persistent deficits in addition to his new symptoms, the concerning diagnoses that must be considered include brain stem ischemia, oropharyngeal neoplasm, extension of oropharyngeal infection into adjacent soft tissues, neuromuscular junction disorders, inflammatory polyneuropathy, autoimmune diseases such as sarcoidosis, and skull base neoplasm. Further history should provide information about systemic symptoms such as



unintentional weight loss and night sweat, risk factors for infections including HIV, occupational exposure, illnesses among family members, and travel history.

History, continued

The patient denies systemic diseases or symptoms. He also denies recent travel outside of Houston, HIV risk factors, exposure, nausea, vomiting or diarrhea, and illnesses among family members. However, he had upper respiratory tract infection symptoms and a fever of 100.5F three days prior to presentation.

- If necessary, revise your differential diagnosis based on the additional clinical history. On which details of the physical examination should you focus at this point?

Commentary II

An acute illness can precede inflammatory polyneuropathy, but in this case may be unrelated. The other diagnoses cannot be ruled out with history. The physical exam must include a careful evaluation of the head and neck for palpable masses. A thorough assessment of mental status, other cranial nerve, motor and sensory function must be performed.

Physical Examination

This gentleman is an overweight patient that is awake, alert, oriented to person, place and time. He appears apprehensive, but comfortable. He is attentive and follows directions appropriately. He has severe labial, lingual and guttural dysarthria, but no difficulties with phonation. He is able to repeat and name with limited phonation and has normal comprehension. The visual fields are full to confrontation. Pupils are equal, round, and reactive to light. Extraocular movements revealed decreased lateral rectus movement bilaterally. There is mild bilateral ptosis and the patient is unable to raise his eyebrows. The sclera is visible upon attempt to close his eyes. Bell's phenomenon is present. The patient is unable to smile or protrude his tongue. His gag reflex is bilaterally weak. Sensation is intact to light touch and pinprick. The muscle strength of sternocleidomastoid and trapezius muscles is 5/5 bilaterally. He has no skin rash and no enlarged lymph nodes. His cardiovascular examination is normal and lungs are clear to auscultation bilaterally. The extremities are warm and well perfused without edema.

- At this point, review your differential diagnosis and revise as appropriate.
- Are there additional observations on physical examination that might be helpful in narrowing your differential list?

Commentary III

On physical exam, this patient has minimal abnormalities on the head and neck exam. The rest of his general physical exam is likewise unremarkable. His neurologic exam, however, is notable for bilateral cranial nerve V, VI, VII, IX, X and XII impairment. His level of consciousness is normal. The pertinent differential diagnoses of multiple cranial neuropathies include brain stem ischemia, neuromuscular junction disorder, autoimmune related inflammatory polyneuropathy, skull base neoplasm, or infection related cranial neuropathy.

Additional physical exam that would be helpful include motor and sensory exam. Assessment of the deep tendon reflexes and coordination is also relevant.



Physical Examination, continued

Motor examination revealed normal muscle tone and bulk. There is mild weakness of arm abductor and hip flexors bilaterally. Otherwise the strength is 5/5. The sensation is intact to light touch and pinprick. Deep tendon reflexes are diminished. Finger-to-nose and heel-to-shin movements and finger tap are impaired. Gait is wide based and unsteady.

- If necessary, revise your differential diagnosis based on the additional physical findings.
- Design your approach to the electrophysiologic examination based on the existing data.

Commentary IV

The additional physical exam reveals minimal proximal muscle weakness with depressed reflexes. There does not appear to be any sensory deficits on exam. The differential diagnoses remain unchanged. However, among the inflammatory polyneuropathies, Miller-Fisher syndrome seems more likely because of the presence of ophthalmoparesis in addition to gait impairment out of proportion relative to the degree of weakness and sensory loss. At the current juncture, laboratory studies (including lumbar puncture) and diagnostic tests such as neuroimaging and electrophysiologic studies are indicated to elucidate the etiology for this patient’s symptoms. An electrophysiological investigation of the lower cranial nerves and sensory and motor nerves will be helpful in defining the nature and anatomy of the involvement.

Electrophysiologic Data

SENSORY NERVE CONDUCTION STUDIES							
NERVE	SIDE	STIM SITE	RECORD	cm	AMPL	LAT	CV
Sural	R	Ankle	Lat. Mal.	14	Absent	Absent	
	L	Ankle	Lat. Mal.	14	Absent	Absent	
Ulnar	L	Wrist	5 th digit	14	18(>15)	2.9 (<3.7)	

MOTOR NERVE CONDUCTION STUDIES							
NERVE	SIDE	STIM SITE	RECORD	cm	AMPL	LAT	CV
Blink reflex (mixed)	R	Supraorbital notch	Orbicularis oculi		Absent	Absent	Absent
	L	Supraorbital notch	Orbicularis oculi		Absent	Absent	Absent
Facial	R	Preauricular	Orbic oculi		Absent	Absent	Absent
	L	Preauricular	Orbic oculi		Absent	Absent	Absent
Ulnar	L	Wrist	Hypothenar	8	7.6(>5)	2.8(<4.5)	
		B. elbow	Hypothenar		8.1(>5)	6.4	64
		A. elbow	Hypothenar		7.2(>5)	8.4	70
Tibial	R	Ankle	Abd. Hall.	12	7.9(>5)	3.7(<6.1)	
		Knee	Abd. Hall.		6.6(>5)	10.6	45



Peroneal	L	Ankle	EDB	8	2.9(>5)	4.3(<6.0)	
		Knee	EDB		2.4(>5)	10.4	49
F-wave (peroneal)						Absent	
F-wave (facial)						Absent	

NEEDLE ELECTROMYOGRAPHY									
INSERTional activity: N, sust, unsust FIB: 0, 1+, 2+, 3+, 4+ OTHer: 0 or fascic, myotonia, myokymia EFFort: N, decr RECruitment: N, inc or dec 1+, 2+, 3+, 4+ AMPlitude: N, inc or dec 1+, 2+, 3+, 4+ DURation: N, inc or dec 1+, 2+, 3+, 4+ POLyphasia: N, inc or dec 1+, 2+, 3+, 4+									
R/L	MUSCLE	INSER	FIB	OTH	EFF	REC	AMP	DUR	POL
L	Orbicularis oris	Incr	3+	0	N	Decr	N	N	N
L	Orbicularis oculi	Decr	0	0	N	No Muap			
L	Nasalis	Incr	3+	0	N	No Muap			

- On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.
- Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)
- Make the final revisions of your diagnostic impression(s).

Diagnostic Impression

Electrophysiologic studies revealed sensory involvement (absent sural bilaterally) despite normal clinical sensory exam. Motor nerve conduction studies are not affected. F-waves and blink reflex are absent. EMG of facial muscles revealed denervation. A repetitive stimulation and EMG of the limb muscles would also be helpful; however, the patient is too uncomfortable with the needle examination and considering the clinical course performed electrophysiologic studies could give enough information. After consulting with the primary physician of the patient, a decision was made to stop the EMG examination at this point. Combined with clinical findings, these data suggest Miller-Fisher syndrome. However, it is impossible to totally exclude the other possible diagnoses without further lab studies. Therefore, multiple imaging studies including a CT of the chest and MRI of the head and neck with contrast are performed and revealed no abnormality. Other laboratory studies including a complete blood count, electrolytes, renal function studies, urinalysis, transaminases, liver function studies, hepatitis panel, thyroid function studies, HIV-1, Anti GM-1 antibody, mycoplasma pneumoniae, cytomegalovirus, and Epstein Barr virus IgM are all normal. ESR is 41 mm/hour. Serum protein electrophoresis is normal. Cerebrospinal fluid analysis show clear and colorless fluid with normal glucose and protein. The CSF white blood



cells count is 14/ μ L with a differential count of 2% neutrophils, 90% lymphocytes, 5% monocytes, 1% basophils, 2% macrophages. The CSF red blood cells count is 3/ μ L. Angiotensin converting enzyme is negative, VDRL is non-reactive. Arboviruses, West Nile virus, St. Louis Encephalitis IgM are negative. Herpes simplex virus PCR is negative. Antibodies against ganglioside GQ1b is negative; Anti Hu and Purkinje cell antibodies are negative. Cerebrospinal fluid IgG synthesis rate is 19.7 mg/day (normal range is -9.9 to 3.3).

The normal brain and neck MRI make cerebral ischemia and neoplasm highly unlikely in explaining this patient's difficulties. The cerebrospinal fluid analysis is only revealing for abnormal IgG studies. In an otherwise normal cerebrospinal fluid study, this suggests the presence of an inflammatory process in the nervous system. Given the whole clinical picture, the diagnostic impression is Miller Fisher syndrome.

- What other diagnostic procedures (laboratory tests, etc.), if any, are needed?
- What treatment would you recommend?

Commentary V

The course of this patient's illness represents an interesting diagnostic dilemma. His initial evaluation is concerning for an acute infectious process affecting the oropharynx and upper respiratory tract. His initial therapy with high dose corticosteroid for presumed epiglottitis may have altered some laboratory findings. Despite the unusual initial presentation, the clinical findings along with some supportive evidence from diagnostic testing suggest that an inflammatory neuropathy is the most likely etiology.

Guillain Barre syndrome (GBS) is the most common cause of acute neuromuscular paralysis and acquired immune mediate neuropathy. This syndrome is heterogeneous in its clinical manifestations. This syndrome is commonly divided into three subgroups: acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. Variants of GBS include the Miller Fisher syndrome and bulbar variant. While it is convenient to classify these subtypes, it is unclear whether these subgroups truly exist or merely represent a spectrum of a disease with varying severity. The diagnostic criterion proposed by the World Health Organization is based upon clinical factors. The major criteria are: the occurrence of symmetrical weakness, decrease or disappearance of the myotatic reflexes, a nadir within 4 weeks and exclusion of other diagnoses.

The Miller Fisher variant of GBS represents 1-5% of all cases of GBS in Western countries. The incidence appears to be significantly higher in Asian countries ranging from 19% of all GBS cases in Taiwan to 25% of all GBS cases in Japan. It is characterized by ophthalmoplegia, ataxia, areflexia and a variable degree of limb muscle involvement. Recently proposed diagnostic criteria for definite Miller Fisher syndrome require clinical and electrophysiologic evidence of GBS plus ophthalmoplegia and ataxia or ophthalmoplegia and findings of IgG antibodies against ganglioside GQ1b. In over half of the cases, there is involvement of the lower cranial nerves. Involvement of the muscles of the trunk and extremities also occurs in half of the patients. Only a small proportion of patients fit the triad originally described by Fisher with the vast majority of patients having a generalized GBS. Other patients also complain of gastrointestinal symptoms and fevers. The first



symptoms are diplopia or ataxia or both. Other initial symptoms may include dysesthesia in the limbs, dysphagia, blepharoptosis, and photophobia.

Other laboratory studies to support the diagnosis Miller Fisher syndrome include albuminocytologic dissociation in the cerebral spinal fluid. Spinal fluid analysis for GBS is not very sensitive, especially during the first week of onset of symptoms. The specificity is variable depending on the differential diagnosis. The overall sensitivity is 85% at admission and 93% at the nadir with a specificity of 100% in patients who are paretic. Electrophysiologic studies in Miller Fisher syndrome can reveal abnormalities in distal latency, motor and sensory conduction velocities, F wave latency, and H reflexes. There are published reports of brainstem and cerebellar lesions on the MRI examinations, however, these are not universal findings. The presence of abnormal brain imaging may suggest the possibility of an alternative diagnosis.

Miller Fisher syndrome is frequently preceded by respiratory symptoms. However, the most common association is with *Campylobacter jejuni*. Several studies have found a correlation between serum antibodies against ganglioside GQ1b with Miller Fisher syndrome. Anti GQ1b antibodies are present in 86% of cases. It is also seen in classical GBS patient with extraocular involvement. GQ1b ganglioside is found in the paranodal regions of the extramedullary portions of oculomotor, trochlear, and abducens nerves. Immunostaining with anti GQ1b also reveal weak staining in deep cerebellar nuclei, gray matter of the brainstem, and dorsal root ganglia. The distribution of these epitopes may represent specific immunologic targets in causing the clinical findings in Miller Fisher syndrome. Anti GQ1b antibodies have also been found to cross react with lipopolysaccharide on the bacterial coat of *Campylobacter jejuni*. This raises a possible mechanism for the etiology of these antibodies in Miller Fisher syndrome.

Miller Fisher syndrome generally has a good prognosis for neurologic recovery. Improvement usually occurs in the order of ataxia, ophthalmoplegia, then areflexia. Chances for recovery is not affected by sex, age, prior infection, disability at nadir, or latency to nadir of neurologic deficits. In one study, all patients were nearly free of ataxia and ophthalmoplegia and had returned to regular activities by 6 months. The treatment for Miller Fisher syndrome is same as that for GBS, plasmapheresis or intravenous gamma globulin. There are no double blind, controlled trials to date.

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