THE MILLER FISHER SYNDROME

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INTRODUCTION

Although variants of the Guillain-Barre' syndrome (GBS) with ataxia, areflexia, and ophthalmoplegia were reported prior to 1956, Fisher, first described three cases with this distinct triad, without concomitant peripheral neuropathy, as a separate entity.1,2

According to Berlit and Rakicky, there are 223 cases of the Miller Fisher syndrome reported between 1956 and 1992.1 Controversy still continues regarding the nature of the disease as a peripheral or central nervous system (CNS) disorder, or a combination of both. Although I will attempt to explore that more completely, it appears, at least in my experience, the disorder is one of a peripheral neuropathy. As with all syndromes, overlap signs and symptoms are seen, and in some cases an actual transition from the "benign Fisher variant" to the more "sinister GBS" occurs.

Smith and Walsh coined the eponym bearing Fisher's name, attacking it to a syndrome outside his field of interest, stroke.1

The incidence of Fisher's syndrome is approximately 5% of all cases reported with GBS. The male/female ratio is about 2:1, and the mean age is said to be 43.6 years.1 Of the 223 cases reported prior to 1993, 14.3% were children, the youngest being 14 months, and the oldest 80 years of age. In the 12 personal cases I could pull from my files the youngest was 2 1/2 years and the oldest 76 years old.

CLINICAL SYNDROME

The majority of patients have a preceding viral illness 1-3 weeks prior to the onset of the neurological syndrome, which has been my clinical experience. Diplopia and ataxia are the most commonly reported initial symptoms. Most of my patients reported an unsteadiness or even a shaking sensation preventing them from ambulating. Some have had to hold on to a wall or the furniture in the acute phase to keep from falling. There are varying degrees of unsteadiness, some found only on examination where in others there is a frank stumbling ataxia, eventually requiring a wheelchair to get around. One patient, I recall, reported a peculiar "disequilibrium", associated with any sudden loud noise. As luck, or in this case bad luck, would have it, this woman lived near a rock quarry where a lot of dynamite blasting occurred. On one particular occasion, a loud blast caused her to jerk and fall breaking her nose and contusing her face. An EEG showed a peculiar generalized single discharge just before a clinical myoclonic jerk in response to a loud noise in the room. This resolved, fortunately, over the next several months. She died within the year from a myocardial infarction and the autopsy failed to reveal any CNS lesion. This case left me wondering again, about a possible, at least, electrophysiological CNS disturbance. In several patients I have observed a peculiar shaking or trembling at the height of the neurological symptoms. It is unlike cerebellar titubation. The appendicular dysmetria is not the side-to-side or "snake-like" incoordination on finger-to-nose testing, but a rapid jerking. This may be a product of sensory denervation, that will be discussed later. In the literature over 90% of unsteady patients were felt to have "cerebellar ataxia".1

About one-half of all patients with the Miller Fisher syndrome will have a complete ophthalmoplegia, including pupillary paralysis, sometime in the course of the disease. Most patients will reach their maximum neurological deficit within a week of the onset. A number begin to complain of a vague blurring of their vision, which unless total bilateral ptosis intervenes, progresses to frank diplopia within several days. Variable degrees of ophthalmoplegia occur. I've seen isolated complete bilateral ptosis in one case, and isolated bilateral internal ophthalmoplegia in another. Within a month both pupils, in this latter case, were denervated and supersensitive to dilute solutions of Pilocarpine. The latter is fairly easily explained as a peripheral disturbance in both ciliary ganglia, but the former is more difficult because isolated fibers to both levator palpebral alone would have to be affected, again raising the question about CNS disease. This patient, however, was the same one who had the "dynamite-induced-myoclonus", and her mesencephalic oculomotor complex appeared normal at autopsy. I've observed isolated abduction deficits, but I have not seen isolated third nerve palsies. Over the telephone, I've obtained the history of an isolated trochlear nerve palsy in a physician friend of mine who called from out of state. This was later confirmed by a Neuro-Ophthalmologist who felt the patient had a mild case of the Miller Fisher syndrome. Most of the times I've observed combinations of both vertical and horizontal gaze palsies. I've not had the same experience others have had with intact Bell's phenomena or other supranuclear signs. It would appear that most of the denervation is occurring at or near the orbital apex, especially in the patients I've observed with pupillary involvement. At least two showed signs of supersensitivity to dilute solutions of Pilocarpine. Keane reported two patients with tonic pupils that he felt was secondary to intraorbital disease, but he also found signs of supranuclear gaze dysfunction, leading him to consider a concomitant brainstem lesion.4 These cases were reported before MRI was available, and in the one patient that had a cranial CT, it was normal.

Internuclear ophthalmoplegia, one-and-a-half syndromes, and dorsal midbrain syndromes have all been reported.5,8

The third "cardinal sign" of areflexia has been present in all of my patients, and is reported in greater than 80% in the literature.
As with any other disease relegated to a "syndrome", we
tend to group symptoms and signs together to help recognize
patterns for easier diagnosis. We then allow other signs to be
included until we stretch the disorder and add a plus(+) to the
end of the eponym. The literature reports involvement of other
cranial nerves in over 50% of cases. FACIAL nerve involvement
is the most frequent one reported, and that has been my
experience as well. Occasionally involvement of cranial nerves
9,10, and 12 are observed. Fifth and eighth nerve dysfunction
are quite rare.

Some papers began to include limb paralysis, but it would
appear in these cases a transition from Fisher's syndrome
to a true GBS.

Sensory symptoms without paralysis are not uncommon in
my patients, and accounts for about half of those reported. A
typical case from my clinical practice follows.

This 52 y.o woman developed a cold with some headache
two weeks prior to admission. Shortly after the infection
completely resolved, she complained of blurred vision and then
horizontal and vertical diplopia. Bilateral ptosis developed
making it difficult to see. After several days of the visual
symptoms she complained of loss of balance and numbness in
the fingers on both hands. There were no bulbar symptoms
and no respiratory problems. Neurological examination
showed an awake, fluent, oriented patient with normal speech
and swallowing. There was a total external ophthalmoplegia
with significant ptosis to obscure vision. No Bell's phenomena
was evident. The pupils reacted normally and the fundi were
benign. She was areflexic and walked with some assistance to
steady her. There was no motor weakness and no discernable
sensory loss. No Babinski signs were present. CT scan of the
brain was normal. CSF showed a normal opening pressure
with no cells, a protein of 48mg%, and a glucose of 68mg%.
She refused an EMG. Although she was symptom free within
three months, her deep tendon reflexes failed to recover.

LABORATORY INVESTIGATIONS

The cerebrospinal fluid (CSF) is abnormal in most cases if
the lumbar puncture is done late enough (2-3 weeks) into the
neurological course. Earlier, the CSF is usually normal. Two-
thirds of patients are reported to have mild elevations in
protein, but I've not seen protein elevations often. About 1%
of the cases in the literature show WBC's in the CSF but over
half of mine show a mild degree of lymphocytosis (between 10
and 20 lymphs/hpf).

As with some of my patients, quantitative electrophysiological studies are not always performed. Sauren,
et al. reported ten carefully selected patients with Fisher's
syndrome who underwent careful EMG. Almost all had
altered sensory nerve action potentials, more pronounced in the
lower than upper extremities. Distal motor nerve latencies and
F-wave latencies were normal. In the patients we've done in
our institution, the findings have been similar. These EMG
findings along with distal parasthesias led the authors to
conclude that the disease is one of peripheral sensory nerve
axon involvement. Blink reflexes were normal in all patients
without facial palsy. Ropper reports similar findings, and he
and Shahani feel that ataxia is on the basis of peripheral
neuropathy also. Evoked potential studies have also
suggested peripheral conduction delays. In a pathologically
studied case, brainstem auditory responses and visual evoked
responses were normal on the tenth day of the illness. Demyelination and inflammation of the oculomotor nerves
were seen, but no CNS lesions were found.

Abnormalities in neuroimaging have been reported, but all
of these patients had other obvious signs of brainstem
dysfunction, and not the lone clinical triad Fisher
described. A cross between a brainstem encephalitis and
a peripheral neuritis makes most sense in these cases. Ropper
believes the syndrome is useful diagnostically when it is not
confused with various incomplete midbrain lesions. I've
found no lesions in the brainstem on neuro-imaging.

PROGNOSIS

The prognosis, in my experience, parallels the literature.
Most patients recover completely. The mean recovery time
is reported to be about 10 weeks. The shortest recovery was 14
days, the longest 18 months. There are case reports of
recurrences between one and 29 years. Eight fatalities have
been recorded.

TREATMENT

Corticosteroids and plasmapheresis have been used but
there is no substantial evidence that either is needed or helps.

In conclusion, my experience with Miller Fisher syndrome
is one of a benign nature resolving inside of 2-3 months,
sometimes as quickly as one month. It appears to be one of
a peripheral inflammatory neuropathy, and involves cranial
nerves and sensory axons, as suggested by Ropper, due to
some common antigenic property. Patients reported with
brainstem signs have more extensive disease, causing
inflammatory changes in the CNS, and should not be classified
in the same category as the Miller Fisher syndrome. The
outlook in patients, strictly classified, is good, and these
patients should not have corticosteroids or plasmapheresis
with the presumption that a catastrophe will occur if they're not
treated immediately.

References

2. Fisher M. An unusual variant of the acute idiopathic polyneuritis (Syndrome of
5. Minuth TL, Barone J. Relation of multiple cranial nerve dysfunction to the Guillaum-Same
syndrome. J Neurol Neurosurg Psychiatry 1965; 28:115-120.


