Miller-Fisher Syndrome at King Chulalongkorn Memorial Hospital

Praween Lolekha MD*,
Kammant Phanthumchinda MD**

** Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Thammasart University Hospital, Pathum Thani, Thailand*
*** Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: *Miller-Fisher syndrome (MFS), a variant of Guillain-Barré syndrome (GBS) is a self-limiting demyelinating disease of the peripheral nervous system. Clinical spectrum, natural history, prognosis, and pathogenesis of MFS are not fully documented.*
Objective: *Probe the clinical features of MFS in a tertiary center in Thailand and compare its pattern with other Asian countries.*
Material and Method: *The clinical recordings were searched from databases at King Chulalongkorn Memorial Hospital (KCMH) between 2002 and 2007. Keywords were "Miller-Fisher syndrome" and "Guillain-Barré syndrome". Cases with MFS were recruited. The data regarding clinical features, course, treatments, and investigations were reviewed. Comparisons with other large Asian series were demonstrated.*
Results: *Six patients (male: female; 3:3) with MFS were analyzed. The incident rate is 7.7% that of GBS. The median age was 54.3 years (range 28 to 73 years). MFS frequently started with diplopia followed by ophthalmoplegia and ataxia. Other clinical symptoms included limb dysesthesia and weakness, dysphagia, dysarthria, and diffuse headache. Spontaneous recovery occurred in three patients while two patients received plasmapheresis and one received intravenous immunoglobulin (IVIG). Six months after neurological deficits, all patients were almost free of symptoms and had returned to their normal activities.*
Conclusion: *The incidence, clinical features, and prognosis of MFS in KCMH were comparable with the previous studies in other Asian countries. High percentage of limb dysesthesia and optic neuropathy were detected in the present series. Headache was also common among Thai MFS. Immuno-pathogenesis of MFS is well documented but immunomodulatory therapy should be considered only in some cases.*

Keywords: *Miller-Fisher syndrome, Guillain-Barré syndrome*

J Med Assoc Thai 2009; 92 (4): 471-7
Full text. e-Journal: *http://www.mat.or.th/journal*

Miller-Fisher syndrome (MFS) was described in 1956 and it has been considered a variant of Guillain-Barré syndrome (GBS)[1]. The syndrome is characterized by a triad of acute gait ataxia, ophthalmoplegia, and areflexia[1]. MFS occurred approximately 1-5% that of GBS in Western countries[2,3]. The incidence of MFS as a proportion of GBS has been reported to be higher in East Asia[4,5]. Previous studies showed an incidence of MFS making up 25% of GBS patients in Japan and 18% in Taiwan[4,5]. The difference may be related to host and genetic factors[4]. Since MFS is rare, its clinical spectrum, natural history, and prognosis are not fully documented. The purpose of the present study was to review clinical features of MFS admitted to King Chulalongkorn Memorial Hospital (KCMH) and to ascertain whether a pattern of the MFS in Thailand is identical to MFS in other Asian countries.

Correspondence to: Phanthumchinda K, Division of Neurology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: fmedkpt@md2.md.chula.ac.th

Material and Method

The clinical recordings were searched from databases at KCMH between 2002 and 2007. Keywords were "Miller-Fisher syndrome" and "Guillain-Barré

syndrome". Clinical diagnosis of MFS was documented by the clinical trial of gait ataxia, ophthalmoplegia, and areflexia[1]. GBS was diagnosed according to Asbury and Cornblath's clinical criteria[6]. Data on age, sex, history of antecedent infection, presenting symptom, clinical manifestations, CSF analysis, electrodiagnostic tests, imaging of the brain, treatment, and clinical course of the syndrome were analyzed. Two large series of MFS in Asia were selected from Pub Med for comparison.

Results

Six patients (male: female; 3:3) with MFS and 78 patients with GBS were recruited. The incident rate of MFS was 7.7% that of GBS. The mean age was 54.3 years (range 28 to 73 years). MFS was found throughout the year, predominantly in cool season (October to January: 4 patients). Respiratory tract infection symptoms occurred within 1 month before MFS onset was noted in five patients (83%). The interval between the onset of infection and neurological symptoms was 3.5 days (range 1-7 days). Acute onset of diplopia was a presenting symptom in all cases and four of them had mild gait ataxia on the same day. Total ophthalmoplegia was documented in all patients. Incomplete bilateral ptosis was noted in four patients and no ptosis was detected in two patients. All of the patients had no abnormal pupil light reflex due to third nerve palsy. The median duration of diplopia to total ophthalmoplegia was 4 days (range 2-7 days). Other neurological deficits were limb weakness (1 patient), dysesthesia in glove and stocking pattern (4 patients), dysarthria (2 patients), dysphagia (1 patient), unilateral peripheral-type facial weakness (2 patients), dyschromatopsia and bilateral optic neuropathies (1 patient), and diffuse headache (3 patients). All of these associated features except facial weakness simultaneously occurred within the clinical course of MFS triad. A patient with facial weakness developed the deficit on day 12 after the onset and during the recovery of MFS. None of the patients in the present series had impaired proprioception or autonomic disturbances. Nerve conduction studies were performed within the second week after the onset of the syndrome in four patients and revealed prolonged distal motor latencies as well as slow motor conduction velocities in three patients, prolonged F-wave in two patients. Lumbar puncture was done in five patients within 1 week after the onset and was not done in one patient due to previous laminectomy and lumbar fusion. The CSF profiles were normal in one patient and revealed albumino-cytologic dissociation in 4 patients. All patients had normal computer tomographic (CT) finding. Magnetic resonance imaging (MRI) was performed in three patients and no abnormality had been detected. The average duration of admission in hospital for all patients was 15.7 days (range 6 to 30 days). Immunomodulatory treatment was prescribed in three patients due to rapid progression of limbs and bulbar weakness: two received plasmapheresis and one received intravenous immunoglobulin (IVIG). Gait ataxia gradually improved in 10 days and fully recovered in 2 weeks while ophthalmoplegia gradually improved in10 days and fully recovered within 3 months. Areflexia recovered within 3 months in five patients and one patient still has areflexia after 1 year of follow up. Limb dysesthesia spontaneously recovered in 1 week. Limbs and bulbar weakness were gradually improved in 1 week after immunomodulatory treatment. Facial weakness was improved in 3 weeks. Bilateral optic neuropathies were spontaneously improved in 2 weeks and fully recovered in 6 weeks. Headache recovered within 1 week. All patients had normal activities of daily living at 6 months. The individual case in the present series and the comparison of this series with other two series from Japan and Taiwan are summarized in Table1 and Table 2 respectively.

Discussion

The high incident rate of MFS among GBS in KCMH as compared to the incident rate in the Western countries was parallel with the previous study in Japan and Taiwan[4,5]. Seasonal variations, associated with MFS was also documented in this series and other Asian countries[2-5]. Majority of MFS cases were associated with a non specific pathogen that causes upper respiratory tract infection[4,5,7-9]. The demographic data and clinical features of MFS in this series were comparable to other large series in Asian countries except for high percentage of limb dysesthesia as well as optic neuropathy in the present series and abnormal proprioception and autonomic involvement in other series[4, 5] (Table 2). The differences may be due to small sample size in the present series. Typical CSF albumino-cytologic dissociation, which is usually documented in MFS and GBS[9-11], was also detected in the present study. Diverse peripheral conduction abnormalities in this and other series[4,9,10], which was different from a more classical pattern in GBS, reflected a variation in the pathogenesis of the two syndromes.

Table 1. Miller-Fisher syndrome at King Chulalongkorn Memorial Hospital between 2002-2007

Case	Date	Age (years)/ Sex	Antecedent infection	Time to total ophthalmoplegia	Clinical symptoms	Electrodiagnostic test	Imaging of the brain	CSF examination	Treatment	Outcome Improvement after onset Complete recovery time
1	Jan 2003	59/M	Non specific URI	4 days	Diplopia, ptosis, headache	Prolonged Normal DML, DSL, NCV	Normal	Not done	Conservative	Improved in 14 days Complete recovery at 4 weeks
2	April 2005	44/F	Non specific URI 7 days PTA	2 days	Diplopia, ataxia, ptosis, headache, dysesthesia, mild weakness	Prolonged DML, DSL, NCV	Normal	WBC2 (L) Protein 23.5 Sugar 52/79	Plasmaphresis 5 days	Improved in 22 days Complete recovery at 8 weeks
3	Aug 2006	62/F	Non specific URI	7 days	Diplopia, ptosis, headache, bilateral visual loss	Prolonged DML, NCV, DSL, F-wave	Normal	Acellular Protein 66 Sugar 76/120	Conservative	Improved in 21 days Complete recovery at 7 weeks
4	Oct 2006	60/M	Non specific URI 5 days PTA	5 days	Diplopia, ataxia, dysesthesia	Not done	Normal	WBC 2 (L) Protein 40 Sugar 81/168	Plasmapheresis 4 days	Improved in 21 days Complete recovery at 12 weeks
5	Nov 2006	73/F	-	2 days	Diplopia, ptosis, dysesthesia, dysarthria	Prolonged DML, DSL, NCV	Normal	WBC4 (L) Protein 25 Sugar 51/121	IVIG x 5 days	Improved in 12 days Develop Lt. facial palsy (LMN) day 12 Complete recovery at 12 weeks
6	Dec 2007	28/M	Non specific URI 4 days PTA	4 days	Diplopia, ataxia, ataxia, dysphagia, dysarthria, dysesthesia	Normal	Normal	Acellular Protein 76 Sugar 60/90	Conservative	Improved in 14 days Develop Lt. facial palsy (LMN) day 11 Complete recovery at 3 weeks

Table 2. Comparison of clinical series of MFS in Asia

Clinical series	Mori et al[4] (n = 50)	Lyu et al[5] (n = 32)	MFS in KCMH (n = 6)
Incident rate	25% of GBS	18% of GBS	7.7% of GBS
Mean age	N M	45 years	54 years
Sex	Male	No difference	No difference
Season/Temperature	Spring/15-23°C	Spring/15-23°C	Winter/23-28°C
Upper respiratory track infection	76%	56%	83%
Acute gastroenteritis	4%	0%	0%
Clinical features (%)			
Ataxia	100%	100%	100%
Areflexia	100%	100%	100%
Ophthalmoplegia	100%	100%	100%
Ptosis	58%	59%	67%
Pupillary abnormalities	42%	N M	0%
Limb weakness	20%	25%	17%
Limb dysesthesia	24%	34%	67%
Abnormal proprioception	18%	N M	0%
Autonomic involvement	8%	3%	0%
Optic neuropathy	0%	0%	17%
Facial palsy	32%	50%	33%
Bulbar palsy	26%	59%	33%
Headache	N M	40%	50%

NM: not mentioned

MFS and GBS are postulated to be a peripheral demyelinating autoimmune disease[1,9,10]. However, there are occasional reports of central nervous system involvement such as supranuclear gaze palsy and optic neuropathy[12]. Imaging of the brain usually was normal but occasionally showed lesions in the brainstem, cerebral white matter, spinocerebellar tract, and cerebellum providing evidence supporting central nervous involvement[13-15].

Several studies showed evidence supported molecular mimicry between ganglioside GQ1b, a major composition of myelin in peripheral nerve and lipopolysaccharide in some infectious agents especially *Campylobacter jejuni*[8,11,16-22]. Ganglioside GQ1b is abundantly detected in cranial nerve III, IV, VI, optic nerve, dorsal root ganglia, presynaptic neuromuscular junction[23] and anti-GQ1b antibody has been detected in MFS and GBS patients who had ophthalmoplegia as well as optic neuropathy[17,20-25]. The role of this antibody and pathogenesis of these cranial neuropathies has been strongly suggested[16,19,25]. The ophthalmoplegia and ptosis, which are the cardinal features of MFS, are interesting neurological signs and had been documented in other series as well as the present series. Ophthalmoplegia without ptosis may occur in MFS, a variant of GBS while ptosis without other signs of occulomotor weakness may occur in GBS[2,5]. Immunologic abnormalities affected occulomotor nerve in both GBS and MFS can be localized and selective. Peripheral type facial weakness also occurred in about 30-50% of MFS[4,5,26]. However, ganglioside GQ1b is not abundant in cranial VII[23]. The pathomechanism of facial palsy in these syndromes may be different and other unknown antibodies may be contributing factors[27]. Mechanism of ataxia in MFS has not been fully explained[9]. It is possible that the anti-GQ1b antibodies against dorsal root ganglion and neuromuscular terminal in muscle spindle afferents[28] will contribute to the ataxia and proprioceptive sensation impairment[28]. Interestingly, headache is not uncommon in MFS and has been detected in 7-40% of MFS cases[5,29]. The pathogenesis of the headache in patients with MFS is debated[30]. Some authors suggested that headache in MFS may be related to the central nervous system involvement[12,13] but neuroimaging, which have been usually normal, did not support this hypothesis. Mild increased intracranial pressure from CSF outflow obstruction at arachnoid granulations caused by the effect of increased CSF protein is another theory[30]. However, the headache in

MFS usually started days before the elevation of CSF protein. Headache from demyelination of the cervical and cranial sensory nerves caused by antibodies to gangliosides and resulting in activation of the trigeminovascular pain pathway, may be the most challenging suggestion[30,31]. MFS is usually a self-limiting syndrome but about 5% of cases may have a progressive course and have clinical features of full-blown GBS[4,5,32]. Immunomodulatory treatments included plasmapheresis and IVIG used in GBS have been applied in MFS[33,34]. It is reasonable to advocate these specific treatments in an MFS patient who has associated clinical features of rapid progression of limb, bulbar, or respiratory weakness[9,35,36]. The overall natural history of MFS is benign and most of the patients have a full recovery[9].

References

1. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956; 255: 57-65.
2. Arnason G. Acute inflammatory demyelinating polyneuropathy. In: Dyck PJ, Griffin JW, Low PA, Poduslo JF, editors. Peripheral neuropathy. 3rd ed. Philadelphia: Saunders; 1993: 1437-97.
3. Bogliun G, Beghi E. Incidence and clinical features of acute inflammatory polyradiculoneuropathy in Lombardy, Italy, 1996. Acta Neurol Scand 2004; 110: 100-6.
4. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. Neurology 2001; 56: 1104-6.
5. Lyu RK, Tang LM, Cheng SY, Hsu WC, Chen ST. Guillain-Barré syndrome in Taiwan: a clinical study of 167 patients. J Neurol Neurosurg Psychiatry 1997; 63: 494-500.
6. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltimore) 1969; 48: 173-215.
7. Henderson RD, Ohlrich GD, Pender MP. Guillain-Barre syndrome and optic neuritis after Mycoplasma pneumoniae infection. Aust N Z J Med 1998; 28: 481-2.
8. Koga M, Gilbert M, Li J, Koike S, Takahashi M, Furukawa K, et al. Antecedent infections in Fisher syndrome: a common pathogenesis of molecular mimicry. Neurology 2005; 64: 1605-11.
9. Lo YL. Clinical and immunological spectrum of the Miller Fisher syndrome. Muscle Nerve 2007; 36: 615-27.
10. Li H, Yuan J. Miller Fisher syndrome: toward a more comprehensive understanding. Chin Med J (Engl) 2001; 114: 235-9.
11. Yuki N, Wakabayashi K, Yamada M, Seki K. Overlap of Guillain-Barrésyndrome and Bickerstaff's brainstem encephalitis. J Neurol Sci 1997; 145: 119-21.
12. Toshniwal P. Demyelinating optic neuropathy with Miller-Fisher syndrome. The case for overlap syndromes with central and peripheral demyelination. J Neurol 1987; 234: 353-8.
13. Urushitani M, Udaka F, Kameyama M. Miller Fisher-Guillain-Barré overlap syndrome with enhancing lesions in the spinocerebellar tracts. J Neurol Neurosurg Psychiatry 1995; 58: 241-3.
14. Ouhabi H, Bourazza A, Rouimi A, Boutaleb N, Mosseddaq R. Bilateral optic neuritis and ponto-mesencephalic involvement shown by MRI in Miller-Fisher syndrome. Rev Neurol (Paris) 1998; 154: 780-2.
15. Inoue N, Ichimura H, Goto S, Hashimoto Y, Ushio Y. MR imaging findings of spinal posterior column involvement in a case of Miller Fisher syndrome. AJNR Am J Neuroradiol 2004; 25: 645-8.
16. Williams MH. The spectrum of IgG GQ1(b) syndrome: an unusual cluster. J Clin Neurosci 2001; 8: 315-8.
17. Suzuki T, Chiba A, Kusunoki S, Chikuda M, Fujita T, Misu K. Anti-GQ1b ganglioside antibody and ophthalmoplegia of undetermined cause. Br J Ophthalmol 1998; 82: 916-8.
18. Overell JR, Willison HJ. Recent developments in Miller Fisher syndrome and related disorders. Curr Opin Neurol 2005; 18: 562-6.
19. Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. Ann Neurol 1992; 31: 677-9.
20. Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. Neurology 1993; 43: 1911-7.
21. Colding-Jorgensen E, Vissing J. Visual impairment in anti-GQ1b positive Miller Fisher syndrome. Acta Neurol Scand 2001; 103: 259-60.
22. Chan JW. Optic neuritis in anti-GQ1b positive recurrent Miller Fisher syndrome. Br J Ophthalmol 2003; 87: 1185-6.
23. Chiba A, Kusunoki S, Obata H, Machinami R,

Kanazawa I. Ganglioside composition of the human cranial nerves, with special reference to pathophysiology of Miller Fisher syndrome. Brain Res 1997; 745: 32-6.
24. Willison HJ. Ganglioside complexes as targets for antibodies in Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 2006; 77: 1002-3.
25. Sawanyawisuth K, Tiamkao S, Jitpimolmard S, Vincent A. A case of Miller Fisher syndrome with anti GQ1b in Thailand. J Med Assoc Thai 2007; 90: 391-3.
26. Berlit P, Rakicky J. The Miller Fisher syndrome. Review of the literature. J Clin Neuroophthalmol 1992; 12: 57-63.
27. Chida K, Takase S, Itoyama Y. Development of facial palsy during immunoadsorption plasmapheresis in Miller Fisher syndrome: a clinical report of two cases. J Neurol Neurosurg Psychiatry 1998; 64: 399-401.
28. Kuwabara S, Asahina M, Nakajima M, Mori M, Fukutake T, Hattori T, et al. Special sensory ataxia in Miller Fisher syndrome detected by postural body sway analysis. Ann Neurol 1999; 45: 533-6.
29. Koga M, Yuki N, Hirata K. Pain in Miller Fisher syndrome. J Neurol 2000; 247: 720-1.
30. Friedman DI, Potts E. Headache associated with miller fisher syndrome. Headache 2007; 47: 1347-8.
31. Phillips MS, Stewart S, Anderson JR. Neuropathological findings in Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 1984; 47: 492-5.
32. Blau I, Casson I, Lieberman A, Weiss E. The not-so-benign Miller Fisher syndrome: a variant of the Guilain-Barre syndrome. Arch Neurol 1980; 37: 384-5.
33. Zifko U, Drlicek M, Senautka G, Grisold W. High dose immunoglobulin therapy is effective in the Miller Fisher syndrome. J Neurol 1994; 241: 178-9.
34. Yeh JH, Chen WH, Chen JR, Chiu HC. Miller Fisher syndrome with central involvement: successful treatment with plasmapheresis. Ther Apher 1999; 3: 69-71.
35. Bussin J. Miller Fisher syndrome in an elderly man. Age Ageing 2001; 30: 268-9.
36. Overell JR, Hsieh ST, Odaka M, Yuki N, Willison HJ. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. Cochrane Database Syst Rev 2007; (1): CD004761.

กลุ่มอาการมิลเลอร์ ฟิชเชอร์ ที่พบในโรงพยาบาลจุฬาลงกรณ์

ประวีณ โล่ห์เลขา, กัมมันต์ พันธุมจินดา

ภูมิหลัง: *กลุ่มอาการมิลเลอร์ ฟิชเชอร์ เป็นกลุ่มอาการผันแปรของกลุ่มอาการ กิแลงแบเร ซึ่งมีการทำลายของปลอกประสาทในระบบประสาทส่วนปลาย และสามารถหายได้เอง อาการทางคลินิก การดำเนินโรค การพยากรณ์โรค และพยาธิสภาพยังไม่เป็นที่ทราบแน่ชัด การศึกษาในครั้งนี้มีจุดประสงค์ เพื่อศึกษาถึงอาการทางคลินิกของกลุ่มอาการมิลเลอร์ ฟิชเชอร์ในประเทศไทยเปรียบเทียบกับประเทศอื่นๆในทวีปเอเชีย*

วัสดุและวิธีการ: *ได้ทำการรวบรวมบันทึกข้อมูลทางคลินิกจากฐานข้อมูลของโรงพยาบาลจุฬาลงการณ์ระหว่างปี พ.ศ. 2545-2550 รหัสคำคือ "กลุ่มอาการมิลเลอร์ ฟิชเชอร์" และ "กลุ่มอาการกิแลงแบเร" ผู้ป่วยที่วินิจฉัยว่าเป็นกลุ่มอาการมิลเลอร์ ฟิชเชอร์ ถูกนำมาศึกษา อาการทางคลินิก การดำเนินโรค ผลการรักษา และการตรวจทางห้องปฏิบัติการ ได้ถูกรวบรวม วิเคราะห์ และเปรียบเทียบกับการศึกษาอื่นในประเทศในทวีปเอเชีย*

ผลการศึกษา: *ได้วิเคราะห์ผู้ป่วยจำนวน 6 ราย (ผู้ชาย: ผู้หญิง, 3:3) ที่มีอาการของกลุ่มอาการมิลเลอร์ ฟิชเชอร์ อุบัติการณ์ของกลุ่มอาการนี้คิดเป็น 7.7% ของกลุ่มอาการกิแลงแบเร อายุระหว่าง 28-73 ปี (เฉลี่ย 54.3 ปี) อาการนำของกลุ่มอาการนี้มักเริ่มจากอาการมองเห็นภาพซ้อน กล้ามเนื้อควบคุมการเคลื่อนไหวของตาเป็นอัมพาต และอาการเดินเซ อาการอื่น ๆ ที่พบ ได้แก่ อาการชาและอ่อนแรงที่รยางค์ อาการกลืนลำบาก อาการพูดไม่ชัด และอาการปวดศีรษะ ผู้ป่วย 3 รายอาการดีขึ้นเองในขณะที่ผู้ป่วย 2 รายได้รับการรักษาโดยการล้างเลือด และผู้ป่วยอีก 1 รายได้รับการรักษาโดยอิมมูโนโกลบูลินทางหลอดเลือดดำ ผู้ป่วยทุกรายอาการดีขึ้น และใช้ชีวิตได้ตามปกติ 6 เดือน หลังจากเริ่มมีอาการทางระบบประสาท*

สรุป: *อุบัติการณ์ และอาการทางคลินิกของกลุ่มอาการมิลเลอร์ ฟิชเชอร์ที่พบในโรงพยาบาลจุฬาลงกรณ์ ใกล้เคียงกับการศึกษาอื่น ๆ ในประเทศในทวีปเอเชีย อาการชาที่รยางค์ที่พบมากขึ้น และอาการเส้นประสาทตาพิการพบได้จากการศึกษานี้ อาการปวดศีรษะพบได้บ่อยในกลุ่มอาการมิลเลอร์ ฟิชเชอร์ในคนไทย กลไกการเกิดกลุ่มอาการมิลเลอร์ ฟิชเชอร์ มีหลักฐานชัดเจนว่าเกิดจากพยาธิสภาพทางภูมิคุ้มกัน แต่การรักษาด้วยวิธีการปรับภูมิคุ้มกันควรพิจารณาใช้ในบางราย*