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ABSTRACT

Background: Fisher syndrome (FS) is characterised by a triad of ophthalmoplegia, ataxia and areflexia. The lesion sites responsible for ataxia and ophthalmoplegia in FS require further exploration. The aim of this study was to determine the involvement of the central nervous system in FS using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET).

Methods: Cerebral glucose metabolism in 10 patients with FS was compared with that of 60 age and sex matched normal controls using PET. For individual analyses, 15 age and sex matched controls were selected from the control group. Patients also underwent MRI of the brain and measurement of serum anti-GQ1b antibody.

Results: Group analyses revealed increased metabolism in the cerebellar vermis and hemispheres, pontine tegmentum, midbrain tectum, left thalamus and right inferior frontal cortex ($p<0.001$, uncorrected). In contrast, the visual association cortices (Brodmann areas 18 and 19) showed decreased metabolism bilaterally. Individual analyses disclosed hypermetabolism in the cerebellar vermis or hemispheres ($n = 7$), inferior frontal cortex ($n = 5$) and brainstem ($n = 4$, $p<0.005$, uncorrected). A negative correlation between the cerebellar hypermetabolism and the interval from symptom onset to PET ($r = -0.745$, $p = 0.013$) was also found. Hypermetabolism was normalised on follow-up PET with an improvement in ophthalmoplegia and ataxia in one patient.

Conclusions: These findings indicate involvement of the central nervous system in FS, and the hypermetabolism in the cerebellum and brainstem suggests an antibody associated acute inflammatory process as a mechanism of this autoimmune disorder.

Fisher syndrome (FS) is characterised by a clinical triad of ophthalmoplegia, ataxia and areflexia.[1] The ocular signs range from isolated iridoplegia to complete ophthalmoplegia.[2] The antibody to ganglioside GQ1b is often present in the serum of patients with FS.[3–5] Patients may have antecedent *Campylobactor jejuni* infection and the anti-GQ1b antibody may show cross reactivity with surface epitopes on *C jejuni*.[6] The pathogenic role of anti-GQ1b antibody remains to be elucidated. However, ganglioside GQ1b is present in the paranodal portion of human ocular motor nerves and may be a target molecule in anti-GQ1b IgG antibody associated ophthalmoplegia.[4 7] In addition, the antibody activity also reflects the severity of the ophthalmoplegia.[8]

The lesion sites responsible for ataxia and ophthalmoplegia in FS require further exploration.[9–11] Although FS has been considered a variant of Guillain–Barré syndrome, some authors reported a cerebellar type of ataxia and supranuclear ophthalmoplegia in FS and suggested additional involvement of the central nervous system.[12 13] In view of a recent study on paraneoplastic cerebellar degeneration, another immune mediated neurological disorder, which demonstrated cerebellar hypermetabolism on positron emission tomography (PET) during the acute phase,[14] we performed ^{18}F-fluorodeoxyglucose (FDG) PET in 10 patients with FS and anti-GQ1b antibodies to determine the involvement of the central nervous system and to elucidate a pathogenic role of anti-GQ1b antibody in FS.

METHODS

Subjects

Ten patients (seven men) with a diagnosis of FS were recruited in the neuro-ophthalmological clinic and ward of Seoul National University Bundang Hospital from December 2005 to May 2007 (table 1). Patient age ranged from 19 to 71 years (mean 47.8 (SD 18.7), median 50). The diagnosis of FS was based on acute ophthalmoplegia, ataxia and areflexia without other identifiable causes.

Measurements of anti-GQ1b antibody

Serum samples were obtained from nine patients during the acute phase. The samples were analysed for the presence of IgG antibodies against GQ1b with an enzyme linked immunosorbent assay (ELISA) at Specialty Laboratories Inc (Santa Monica, California, USA). Control and patient sera were incubated for 2 h in microtitre wells precoated with gangliosides GQ1b. After washing off any unbound substances, a horseradish peroxidase labelled antibody mixed against human antibody was added to the wells and incubated for another 2 h. Following a second wash, a substrate solution containing tetramethylbenzidine was added to the wells. A blue colour developed in proportion to the amount of antiganglioside autoantibodies bound in the initial step and the colour development was stopped by adding an acidic stop solution, which turned the blue solution to a yellow colour. The intensity of the colour absorbance was measured at 450 nm. The titres of antiganglioside autoantibodies were expressed as ratios of a reference control. The samples were considered positive when the antibody titre was above 20% of the reference value.[15]

Brain MRI

MRI was performed with a 1.5 T unit (Intera; Philips Medical Systems, Best, The Netherlands) using our imaging protocol (axial turbo spin echo T2 weighted imaging and axial/sagittal spin echo T1 weighted imaging) in all patients.[16] The imaging parameters were 4800/100 (repetition time (ms)/echo time (ms)) for T2 weighted imaging and 500/11 for T1 weighted imaging with a section

Table 1 Clinical profiles and position emission tomography (PET) findings in the patients

Patient/age/sex	Preceding illness	Ocular motor abnormalities: Ophthalmoplegia	Ptosis	Iridoplegia	Ataxia	Areflexia	Laboratory findings: CSF protein (mg/dl)	NCS	Anti-GQ1b antibody	PET: Interval*	Increased metabolism	Decreased metabolism
1/51/M	URI, diarrhoea	Bilateral	−	+	+	+	57.7	Normal	+	3	Cerebellum (bilateral hemisphere, tonsil, vermis), pontine tegmentum	Inferior temporal cortex
2/71/F	URI	Bilateral	+	+	+	+	50.4	Normal	−	7	Cerebellum (vermis), left inferior frontal cortex, bilateral medial temporal area, midbrain	Bilateral occipital cortices
3/30/M	Myalgia	Right	+	−	+	+	56.6	Normal	+	35	Cerebellum (vermis)	−
4/49/F	URI, diarrhoea	Bilateral	+	+	+	+	63.7	Normal	+	25	Cerebellum (bilateral hemisphere, vermis), right parietal cortex (precuneus)	Bilateral occipital cortices
5/65/M	URI	Bilateral	+	+	+	+	58.7	Abnormal (SMPN)	+	8	Cerebellum (bilateral hemisphere, vermis), right inferior and left anterior frontal cortices	Bilateral occipital cortices
6/47/M	Oral herpes	Bilateral	−	−	+	+	45.5	Normal	+	12	Cerebellum (left inferior lobe), bilateral inferior and anterior frontal cortices, right temporal areas	Bilateral occipital cortices
7/61/M	Myalgia	Bilateral	+	+	+	+	55.8	Normal	−	87	−	Left occipital cortex
8/19/M	URI, diarrhoea	Bilateral	−	−	−	+	NA	NA	−	30	Left inferior frontal and temporal cortices, midbrain, pons, medulla oblongata	−
9/21/M	Diarrhoea	Bilateral	−	+	+	+	92.5	Normal	+	14	Cerebellar hemisphere ($p<0.01$), inferior frontal cortex, bilateral insula	−
10/64/F	URI	Bilateral	+	+	+	+	50.0	Normal	+	2	Cerebellum (tonsil) pontine tegmentum, parahippocampal area	−

*Interval indicates the days from symptom onset to PET studies.
NA, not applicable; NCS, nerve conduction studies; PET, positron emission tomography; SMPN, sensorimotor polyneuropathy; URI, upper respiratory infection.

Table 2 Brain regions showing increased or decreased metabolism in patients with Fisher syndrome

Side	Region	Coordinate*	T value	max-Z	Cluster size (k)†
Increased metabolism					
Rt	Cerebellum (posterior lobe)	(22, −84, −32)	4.79	4.43	2474
	Cerebellum (tonsil)	(2,−58,−40)	3.73	3.53	
	Pons	(8,−44,−36)	3.80	3.50	
Lt	Cerebellum (posterior lobe)	(−32,−80,−34)	4.30	4.03	1055
Lt	Cerebellum (anterior lobe)	(−18,−34,−22)	3.96	3.74	219
	Cerebellum (vermis)	(0,−56,−16)	3.33	3.19	
	Midbrain	(−2,−36,−8)	3.49	3.34	
Lt	Thalamus	(−12,−14,10)	4.06	3.82	130
Rt	Inferior frontal cortex (BA 47)	(44,34,−20)	4.02	3.79	122
Decreased metabolism					
Lt	Occipital cortex (BA 18/19)	(−30, −90,−4)	5.32	4.84	1169
Rt	Occipital cortex (BA 18/19)	(50,−70,−10)	5.25	4.79	461

*Location of peak expressed as x, y, z coordinates in the Montreal Neurological Institute space.
†Cluster size k represents the number of contiguous voxels ($2\times2\times2$ mm^3) at a height threshold of $p<0.001$ (uncorrected).
BA, Brodmann area; Lt, left; Rt, right.

thickness of 6 mm, a matrix size of 256×256 (interpolated to 512×512) and a field of view of 200–220 mm. MRIs were assessed by two neuroradiologists who were blinded to the purposes of this study.

Image acquisition and analyses of PET

Brain PET studies were done using an Allegro PET scanner (Phillips Medical System, Cleveland, Ohio, USA).[14] The intervals from symptom onset to PET studies ranged from 2 to 87 days (median 13) (table 1). One patient underwent initial PET 3 days after symptom onset and follow-up PET 4 months later. Patients had fasted for at least 4 h before the studies and were administrated 185 MBq (5 mCi) of ^{18}F-FDG intravenously. Image preprocessing and statistical analysis were done using SPM2 (Statistical parametric mapping 2, Institute of Neurology, University College London, UK). All images were spatially normalised to the standard template provided by SPM2 and then smoothed using isotrophic Gaussian Kernel (FWHW 12 mm) to minimise noise and improve between subject spatial alignment. Appropriate voxel by voxel statistical tests were used to evaluate differences in glucose metabolism. Detailed methods on data acquisition and processing have been reported previously.[14]

Firstly, the metabolic abnormality in patients with FS was tested as a group. For comparison, 60 healthy subjects (43 men, mean age 50.1 (SD 14.9), range 24–71 years) without a previous history of neurological disorders or major illnesses served as normal controls. Regional glucose metabolism, which was proportionally scaled to global uptake, was compared between the patient and control groups after considering age as a covariate. Then, metabolic abnormality in each patient was individually assessed by comparing the patient's scan with that of 15 age and sex matched healthy subjects selected from the control group. The difference was considered significant when a cluster consisting of at least 100 contiguous voxels exceeded a threshold height of $p<0.001$ (uncorrected for multiple comparison) in group comparison and $p<0.005$ for individual analyses. We did not perform the correction of partial volume effect.[17]

We also determined a possible correlation between metabolic abnormalities and the interval from symptom onset to PET study. Furthermore, after calculating mean uptake in the brain regions which showed a significant correlation based on SPM analyses using marsbar (http://marsbar.sourceforge.net), the correlation between regional metabolism and intervals from symptom onset was retested as a region of interest using Spearman's rank correlation in SPSS 13.0 (SPSS Inc., Chicago, Illinois, USA).

All experiments followed the tenets of the Declaration of Helsinki and informed consent was obtained after the nature and possible consequences of the study had been explained to the participants. This study was reviewed and approved by the institutional review board.

RESULTS

Clinical characteristics

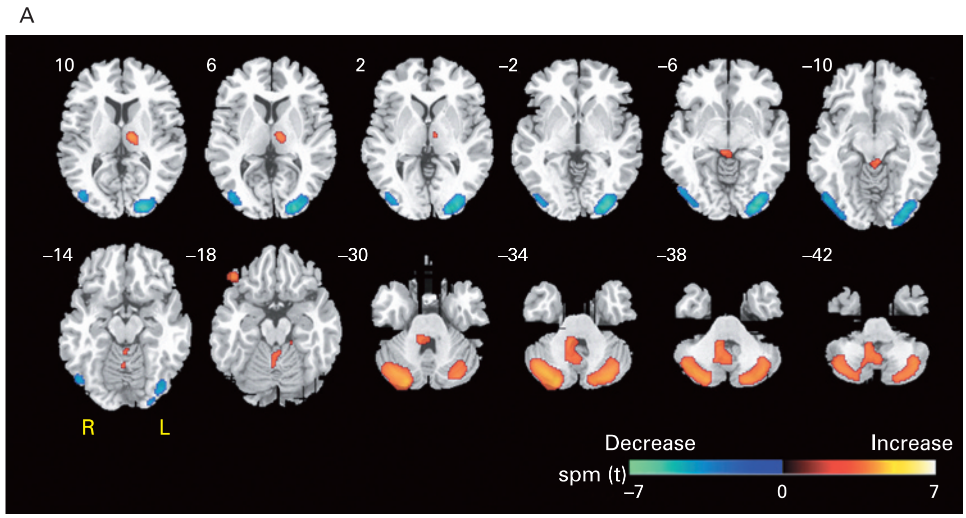
Most patients developed ophthalmoplegia along with ataxia and areflexia several days after upper respiratory infection or diarrhoea (table 1). The symptoms and signs usually progressed over several days to weeks. Ophthalmoplegia involved both eyes in all patients but one (patient No 3) who showed limitations of adduction, depression and elevation, and ptosis without pupillary abnormality in the right eye, which mimicked pupil sparing third cranial nerve palsy. Extraocular movements were limited both horizontally and vertically in all patients but one (patient No 8) who showed only limited abduction in both eyes. Ptosis was observed in six and the pupils were involved in seven patients (table 1).

Serum IgG anti-GQ1b antibodies were found in seven patients (table 1). CSF examination was normal except for mildly elevated protein (table 1). In spite of generalised areflexia, nerve conduction studies were normal in all patients but one (patient No 5) who had also suffered from diabetes. Brain MRI did not show any abnormality which could explain the patients' symptoms and signs. In all patients, symptoms and signs improved markedly within 6 months after symptom onset.

PET findings

Group analyses revealed increased metabolism in the cerebellar vermis, bilateral cerebellar hemispheres, pontine tegmentum, midbrain tectum, right inferior frontal cortex (Brodmann area 47) and left thalamus ($p<0.001$, uncorrected) (table 2, fig 1A). In contrast, the bilateral occipital cortices (Brodmann areas 18 and 19) showed decreased metabolism (fig 1A).

Individual analyses disclosed hypermetabolism in the cerebellar vermis or hemispheres in seven of the 10 patients



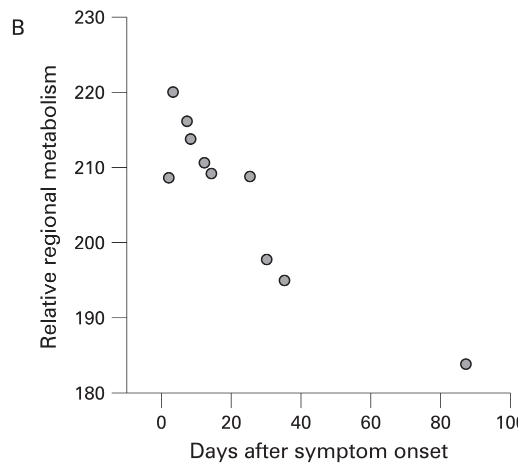


Figure 1 (A) Brain ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) of patients with Fisher syndrome showed increased glucose metabolism in the cerebellum (posterior cerebellar hemisphere, vermis, tonsil), pontine tegmentum, midbrain tectum, left thalamus and right inferior frontal cortex. In contrast, both occipital cortices (Brodmann areas 18 and 19) exhibited hypometabolism. Brain metabolism in patients was compared with 60 age and sex matched healthy controls. Significant voxels ($p<0.001$, uncorrected, cluster $k>100$) in statistical T maps were superimposed on the standard MRI templates spatially normalised into Montreal Neurological Institute space. The number in the left upper corner of each image indicates the distance (mm) of each axial plane from the bicommissural plane, and the colour coding bar represents T scores. R, right; L, left. (B) Hypermetabolism in the cerebellar vermis (max-Z $=4.10$ at x, y, z $=$ (16, −74, −48)) shows a negative correlation with the interval from symptom onset to FDG-PET study. The correlation rho is $=-0.746$ ($p=0.013$) at two tailed test. Each point represents an individual subject.

($p<0.005$, uncorrected) (table 1). Another patient (patient No 9) showed a tendency towards increased metabolism in the cerebellar hemisphere ($p<0.01$), and cerebellar metabolism was normal in the remaining two patients (patient Nos 7 and 8) (table 1). Five patients also showed hypermetabolism in the inferior frontal cortex (patient Nos 2, 5, 6, 8, and 9) and four (patient Nos 1, 2, 8 and 10) in the brainstem. In addition, the medial temporal lobe and precuneus were the infrequent sites of hypermetabolism in individual patients. In contrast, five patients (patient Nos 2, 4, 5, 6 and 7) exhibited hypometabolism in the occipital cortices (table 1).

We also determined the effect of interval from symptom onset to PET on regional metabolism, which exhibited a negative correlation between the interval and cerebellar hypermetabolism (max-Z $=4.10$ at x, y, z $=$ (16, −74, −48), cluster $k=789$ at $p<0.005$) (fig 1B). Spearman rank correlation coefficient of the region based analysis was −0.746 ($p=0.013$, two tailed test).

One patient (patient No 1) performed the follow-up PET study 4 months later when the ophthalmoplegia almost resolved, and the follow-up PET showed normalisation of the initial cerebellar hypermetabolism (fig 2).

DISCUSSION

In patients with FS, we found cerebellar and brainstem hypermetabolism using PET. Patients also showed hypermetabolism in the right inferior prefrontal cortex and left thalamus while the occipital cortex exhibited decreased metabolism. Interestingly, the initial cerebellar hypermetabolism decreased markedly on follow-up PET in one patient, and analyses disclosed a negative correlation between the cerebellar hypermetabolism and the intervals from symptom onset to PET studies.

Anti-GQ1b antibody is present in up to 90% of patients with FS.[4 18] The GQ1b ganglioside is enriched in the paranodal regions of the extramedullary oculomotor, trochlear and abducens nerves, and anti-GQ1b activity reflects the severity of ophthalmoplegia and cerebellar-type ataxia in FS,[5 8] explaining the close association with acute ophthalmoplegia.[7 8] However, GQ1b ganglioside is also found in the cerebellum, and serum anti-GQ1b IgG antibodies from patients with FS or Guillain–Barré with ophthalmoplegia and ataxia selectively stain the cerebellar molecular layer.[19] Furthermore, GQ1 ganglioside expression is also found in the brainstem.

Previous reports have debated on whether the ataxia in FS is due to a central or peripheral process (sensory ataxic neuropathy).[9 13 19] The hypermetabolic areas (cerebellar vermis, cerebellar hemispheres, pontine tegmentum and midbrain tectum) observed in our patients are well correlated with the clinical features of ataxia and ophthalmoplegia, and suggest that the ataxia and ophthalmoplegia in FS may be of central origin, at least in part. Previously, MRI also documented central lesions in FS.[20 21]

Patients with anti-GQ1b antibody may present with varying combinations of ophthalmoparesis, ataxia, areflexia or altered

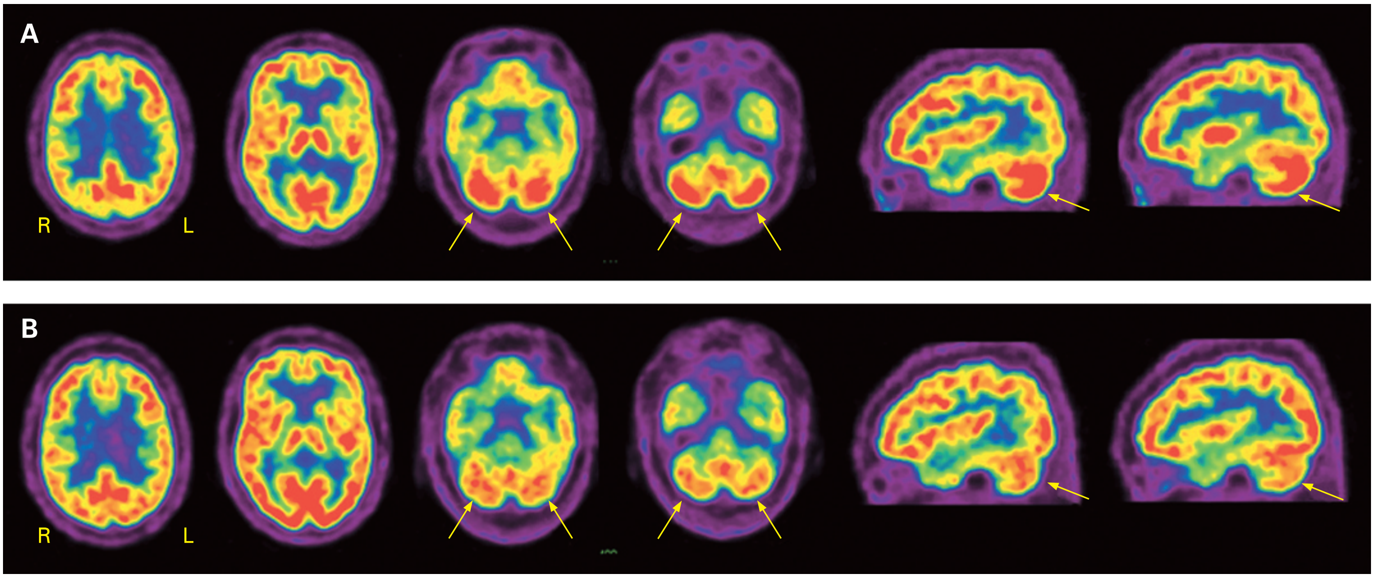


Figure 2 In patient No 1, cerebellar hypermetabolism during the acute phase (A) decreased markedly on follow-up ^{18}F-fluorodeoxyglucose-positron emission tomography (B) 4 months later. The colour scale indicates the regional uptake value normalised for whole brain. The same scale is used for (A) and (B). R, right; L, left.

sensorium.[22] Anti-GQ1b IgG antibody is also found in approximately 60% of patients with Bickerstaff's brainstem encephalitis which is characterised by consciousness disturbance and upper motor neuron signs.[23 24] These findings all support a spectrum of an immune mediated disease involving both the peripheral and central nervous system in anti-GQ1b antibody syndrome,[5 21 25–27] even though our patients did not show the features of Bickerstaff's brainstem encephalitis.

However, there has been no report on cerebellar hypermetabolism in FS while hypermetabolism of the central nervous system has been documented in limbic encephalitis and paraneoplastic cerebellar degeneration, another well known autoantibody mediated disorder.[14 28] The hypermetabolism in those disorders has been attributed to inflammatory changes, and stereotaxic biopsy in fact revealed inflammation with lymphocytic infiltrations and reactive gliosis in one patient.[28]

Our patients also showed a negative correlation between cerebellar hypermetabolism and intervals from symptom onset to PET studies. Furthermore, the initial cerebellar hypermetabolism was normalised on follow-up PET in one patient. The increased metabolism in the target brain areas is common during the acute stage of leukoencephalitis of autoimmune or infectious aetiologies.[14 29 30] Furthermore, the hypermetabolism may resolve or evolve into hypometabolism at a later stage,[14] which also indicates that the increased metabolism during the acute phase is related to an active inflammatory process.

Our patients also exhibited hypometabolism in the visual association cortices (Brodmann areas 18 and 19). In view of the diplopia which all patients suffered from because of ophthalmoplegia, the hypometabolism in the visual association area may indicate an adaptive functional suppression of the cortical responses to deranged visual inputs. Previously, occipital hypometabolism was also observed in patients with oculopalatal tremor, another disorder with impaired visual processing caused by pendular nystagmus.[31]

The hypermetabolism observed in the right prefrontal/frontal cortex and left thalamus requires comment. In view of the lack of corresponding symptoms/signs, negative MRI, only slight changes in CSF and inability of the antibody to access the brain parenchyma, antibody mediated inflammation of all of these regions seems unlikely as a mechanism of the hypermetabolism. The frontal cortices are known to adjust locomotor performance in response to altered environments.[32] In FS, the diplopia and ataxia may require more attention and intention in adjusting locomotion and limb movements. This, in turn, would give rise to hyperactivity in the frontal cortices. A similar finding of sustained prefrontal hyperactivity is also observed during ataxic gait in patients with infratentorial stroke,[33] which also suggests a compensatory mechanism for the impaired locomotor control. The mechanism of thalamic hypermetabolism is also unknown. As the thalamus serves as a relay station for the sensory processing or cerebello-cortical projection,[34] sensory deafferentiation or cerebellar hypermetabolism may affect thalamic metabolism. However, as sensory stimuli usually evoke thalamic activation,[35] the possible sensory deprivation in our patients with FS may not account for the thalamic hypermetabolism. The bilateral cerebellar hypermetabolism in our patients also does not readily explain the increased metabolism in the left side only. Instead, the thalamic hypermetabolism might be ascribed to a reciprocal interaction with the occipital cortices. The occipital hypometabolism, probably an adaptive response to deranged visual inputs, may have been achieved by modulation of multimodal sensory processing in the left thalamus.[34] The activation–deactivation pattern between the thalamus and occipital cortex has also been observed in oculopalatal tremor[31] and during the acute stage of vestibular neuritis.[36]

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Competing interests: None.

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REFERENCES

1. **Fisher CM.** An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med* 1956;**255**:57–65.
2. **Al–Din SN,** Anderson M, Eeg-Olofsson O, *et al*. Neuro-ophthalmic manifestations of the syndrome of ophthalmoplegia, ataxia and areflexia: a review. *Acta Neurol Scand* 1994;**89**:157–63.
3. **Chiba A,** Kusunoki S, Shimizu T, *et al*. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. *Ann Neurol* 1992;**31**:677–9.
4. **Chiba A,** Kusunoki S, Obata H, *et al*. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain–Barre syndrome: clinical and immunohistochemical studies. *Neurology* 1993;**43**:1911–17.
5. **Yuki N,** Sato S, Tsuji S, *et al*. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. *Neurology* 1993;**43**:414–17.
6. **Jacobs BC,** Endtz H, van der Meche FG, *et al*. Serum anti-GQ1b IgG antibodies recognize surface epitopes on Campylobacter jejuni from patients with Miller Fisher syndrome. *Ann Neurol* 1995;**37**:260–4.
7. **Chiba A,** Kusunoki S, Obata H, *et al*. Ganglioside composition of the human cranial nerves, with special reference to pathophysiology of Miller Fisher syndrome. *Brain Res* 1997;**745**:32–6.
8. **Mizoguchi K.** Anti-GQ1b IgG antibody activities related to the severity of Miller Fisher syndrome. *Neurol Res* 1998;**20**:617–24.
9. **Kuwabara S,** Asahina M, Nakajima M, *et al*. Special sensory ataxia in Miller Fisher syndrome detected by postural body sway analysis. *Ann Neurol* 1999;**45**:533–6.
10. **Jamal GA,** Ballantyne JP. The localization of the lesion in patients with acute ophthalmoplegia, ataxia and areflexia (Miller Fisher syndrome). A serial multimodal neurophysiological study. *Brain* 1988;**111**:95–114.
11. **Al-Din AN,** Anderson M, Bickerstaff ER, *et al*. Brainstem encephalitis and the syndrome of Miller Fisher: a clinical study. *Brain* 1982;**105**:481–95.
12. **Keane J,** Finstead B. Upward gaze paralyses as the initial sign of Fisher's syndrome. *Arch Neurol* 1982;**39**:781–2.
13. **Ropper AH,** Shahani B. Proposed mechanism of ataxia in Fisher's syndrome. *Arch Neurol* 1983;**40**:537–8.
14. **Choi KD,** Kim JS, Park SH, *et al*. Cerebellar hypermetabolism in paraneoplastic cerebellar degeneration. *J Neurol Neurosurg Psychiatry* 2006;**77**:525–8.
15. **Lee SH,** Lim GH, Kim JS, *et al*. Acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody. *Neurology* 2008;**71**:426–9.
16. **Choi KD,** Oh SY, Park SH, *et al*. Head-shaking nystagmus in lateral medullary infarction: patterns and possible mechanisms. *Neurology* 2007;**68**:1337–44.
17. **Quarantelli M,** Berkouk K, Prinster A, *et al*. Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction. *J Nucl Med* 2004;**45**:192–201.
18. **Odaka M,** Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. *J Neurol Neurosurg Psychiatry* 2001;**70**:50–5.
19. **Kornberg AJ,** Pestronk A, Blume GM, *et al*. Selective staining of the cerebellar molecular layer by serum IgG in Miller-Fisher and related syndromes. *Neurology* 1996;**47**:1317–20.
20. **Giroud M,** Mousson C, Chalopin JM, *et al*. Miller-Fisher syndrome and pontine abnormalities on MRI: a case report. *J Neurol* 1990;**237**:489–90.
21. **Petty RK,** Duncan R, Jamal GA, *et al*. Brainstem encephalitis and the Miller Fisher syndrome. *J Neurol Neurosurg Psychiatry* 1993;**56**:201–3.
22. **Kusunoki S,** Chiba A, Kanazawa I. Anti-GQ1b IgG antibody is associated with ataxia as well as ophthalmoplegia. *Muscle Nerve* 1999;**22**:1071–4.
23. **Bickerstaff ER.** Brainstem encephalitis. Further observations on a grave syndrome with a benign prognosis. *BMJ* 1957;**i**:1384–7.
24. **Odaka M,** Yuki N, Yamada M, *et al*. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Güillain–Barré syndrome. *Brain* 2003;**126**:2279–90.
25. **Ito M,** Kuwabara S, Odaka M, *et al*. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: Clinical analysis of 581 cases. *J Neurol* 2008;**255**:674–82.
26. **Winer JB.** Bickerstaff's encephalitis and the Miller Fisher syndrome. *J Neurol Neurosurg Psychiatry* 2001;**71**:433–5.
27. **Yuki N,** Sato S, Tsuji S, *et al*. An immunologic abnormality common to Bickerstaff's brain stem encephalitis and Fisher's syndrome. *J Neurol Sci* 1993;**118**:83–7.
28. **Scheid R,** Lincke T, Voltz R, *et al*. Serial 18F-fluoro-2-deoxy-D-glucose positron emission tomography and magnetic resonance imaging of paraneoplastic limbic encephalitis. *Arch Neurol* 2004;**61**:1785–9.
29. **Kassubek J,** Juengling FD, Nitzsche EU, *et al*. Limbic encephalitis investigated by 18FDG-PET and 3D MRI. *J Neuroimmaging* 2001;**11**:55–9.
30. **Hirayama K,** Sakazaki H, Murakami S, *et al*. Sequential MRI, SPECT, and PET in respiratory syncytial virus encephalitis. *Pediatr Radiol* 1999;**29**:282–6.
31. **Moon SY,** Cho SS, Kim YK, *et al*. Cerebral glucose metabolism in oculopalatal tremor. *Eur J Neurol* 2008;**15**:42–9.
32. **Suzuki M,** Miyai I, Ono T, *et al*. Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study. *NeuroImage* 2004;**23**:1020–6.
33. **Mihara M,** Miyai I, Hatakenaka M, Kubota K, Sakoda S. Sustained prefrontal activation during ataxic gait: a compensatory mechanism for ataxic stroke? *Neuroimage* 2007;**37**:1338–45.
34. **Haines DE.** *Fundamental neuroscience for basic and clinical applications*, 3rd Edn. Philadelphia: Churchill Livingstone, 2006.
35. **Davis KD,** Kwan CL, Crawley AP, *et al*. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 1998;**80**:1533–46.
36. **Bense S,** Bartenstein P, Lochmann M, *et al*. Metabolic changes in vestibular and visual cortices in acute vestibular neuritis. *Ann Neurol* 2004;**56**:624–30.