Cerebral glucose metabolism in Fisher syndrome


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Cerebral glucose metabolism in Fisher syndrome

Y K Kim,1 J S Kim,2 S-H Jeong,1,3 K-S Park,2 S E Kim,1 S-H Park2

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 18F-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 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.3,4 Patients may have antecedent Campylobacter jejuni infection and the anti-GQ1b antibody may show cross reactivity with surface epitopes on C. jejuni.5 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 In addition, the antibody activity also reflects the severity of the ophthalmoplegia.2

The lesion sites responsible for ataxia and ophthalmoplegia in FS require further exploration.2–11 Although FS has been considered a variant of Guillain–Barre 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 18F-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 47.9 (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 mixture 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 anti-ganglioside 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 4000/100 (repetition time (ms)/ echo time (ms)) for T2 weighted imaging and 500/11 for T1 weighted imaging with a section...
<table>
<thead>
<tr>
<th>Patient/age/sex</th>
<th>Preceding illness</th>
<th>Ocular motor abnormalities</th>
<th>Laboratory findings</th>
<th>PET</th>
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<td>Ophthalmoplegia</td>
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*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.
thickness of 6 mm, a matrix size of 256x256 (interpolated to 512x512) 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). 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.

PET findings

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

<table>
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<th>T value</th>
<th>max-Z</th>
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<tr>
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<td>(44,34, −20)</td>
<td>4.02</td>
<td>3.79</td>
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</table>

| 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 (2x2x2 mm³) at a height threshold of p<0.001 (uncorrected).

BA, Brodmann area; Lt, left; Rt, right.

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 5) 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.
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 ($\text{max-Z} = 4.10$ at $x, y, z = (16, −74, −48)$, cluster $k = 789$ at $p < 0.005$, 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).

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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. 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, explaining the close association with acute ophthalmoplegia. 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. 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). 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.

Patients with anti-GQ1b antibody may present with varying combinations of ophthalmoparesis, ataxia, areflexia or altered
sensorium. 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. These findings all support a spectrum of an immune mediated disease involving both the peripheral and central nervous system in anti-GQ1b antibody syndrome, 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. 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.

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. Furthermore, the hypermetabolism may resolve or evolve into hypometabolism at a later stage, 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 oculopatatal tremor, another disorder with impaired visual processing caused by pendular nystagmus.

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. 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, 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, sensory deafferentiation or cerebellar hypermetabolism may affect thalamic metabolism. However, as sensory stimuli usually evoke thalamic activation, 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. The activation–deactivation pattern between the thalamus and occipital cortex has also been observed in oculopatatal tremor and during the acute stage of vestibular neuritis.

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Competing interests: None.

Ethics approval: This study was reviewed and approved by the institutional review board.
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