

Progressive Subcortical Gliosis of Neumann: Does MRI/MRS Permit Ante Mortem Diagnosis?



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Abstract

The clinical, neuropsychological, and neuroradiological features of a patient with an early-onset dementia are presented. The clinical and neuropsychological profile suggested a diagnosis of frontotemporal dementia. Magnetic resonance imaging showed symmetrical frontotemporal atrophy and confluent symmetrical high signal intensity changes in frontal subcortical white matter. Proton magnetic resonance spectroscopy of this region showed a huge myoinositol peak, increased myoinositol:creatinine ratio, and reduced N-acetyl aspartate, features consistent with extensive gliotic change in the subcortical white matter, suggesting a diagnosis of progressive subcortical gliosis of Neumann. Magnetic resonance imaging and spectroscopy may be helpful in establishing the diagnosis of progressive subcortical gliosis ante mortem without recourse to cerebral biopsy.

Keywords: dementia; diagnosis; MR imaging; progressive subcortical gliosis of Neumann; spectroscopy

The term progressive subcortical gliosis (PSG) was first suggested by Neumann and Cohn in 1967 to describe a rare dementing disorder with typical histopathological findings, namely frontotemporal atrophy with a distinctive distribution of fibrillary astroglia in the superficial and deep cerebral cortical layers, as well as in the subcortical white matter, the latter sometimes extending to the basal ganglia, thalamus, brainstem, and even to the ventral horns of the spinal cord. Amyloid plaques, neurofibrillary tangles, Pick cells and Pick bodies were not seen.¹ Neumann had previously labelled cases with similar pathological findings as "Pick's disease type II" because of the similarity of the brain at the macroscopic level to Pick's disease (i.e. frontal atrophy).²

Occasional cases of PSG have been described subsequently, most with insidious onset occurring in the fifth or sixth decades,³ although some cases occur in later life.⁴ Disease duration is typically ten years or more. Most cases are sporadic, but occasional familial cases have been

described.^{1,3,5,6} In one of these families,⁶ PSG was reported to be linked to chromosome 17 and subsequently shown to be associated with a mutation in the gene encoding the microtubule-associated protein tau,⁷ indicating that this condition is a tauopathy, despite the absence of neurofibrillary pathology. Two reports have claimed immunostaining for prion protein in PSG brain,^{6,8} but one of these claims⁶ was subsequently retracted.⁹

The clinical phenotype of PSG is variable. Some patients have a presentation suggesting frontotemporal dementia (FTD),^{1,10} others resemble Alzheimer's disease (AD)^{1,3} and indeed may fulfil diagnostic criteria for AD.⁴ Occasional cases have been reported with clinical phenotypes which overlap with Creutzfeldt-Jakob disease (CJD)^{11,12} and progressive supranuclear palsy (PSP).¹³ Few reports contain details of neuroradiological investigations, but generally these seem not to have proven helpful, with diagnosis remaining dependent on neuropathological findings. Hence, with the exception of familial cases with a deterministic tau gene mutation,^{6,7} premortem diagnosis of PSG has not been possible.

We present a patient with cognitive decline suggestive of FTD, whose structural imaging showed marked frontotemporal atrophy with extensive high signal change in subcortical white matter seen on magnetic resonance imaging (MRI), consistent with gliosis, and confirmed with proton magnetic resonance spectroscopy (1H-MRS). We suggest these changes may represent a noninvasive way to diagnose PSG ante mortem.

Case Report

A 62-year-old woman was referred to the Cognitive Function Clinic with behavioural change. She denied any problems, but the history from her husband was of 18 months of odd behaviour, such as putting things in inappropriate places, forgetting the location of familiar household objects, and neglect of household chores. She struggled with the household accounts and sometimes bought large quantities of inappropriate goods. She had lost interest in her various hobbies. A longstanding phobia for cats was replaced by a tolerance of them sitting

on her lap, and she became indifferent to motorway driving which had previously provoked anxiety. Language skills were preserved and she could still help her husband with crossword puzzles. Her inability to plan or prepare meals necessitated her husband taking over kitchen duties. She had to be encouraged to wash her hair and change her clothes; often she would dress inappropriately for the weather conditions. She had a fixed routine, taking a long morning walk each day, always following the same route and never getting lost. There was no predilection for sweet or sticky foods, clockwatching, or ritual behaviour. She seemed to laugh off the various problems as they were enumerated, and reported her mood to be cheerful. Past medical history and family history were unremarkable.

On the Mini-Mental State Examination,¹⁴ her score was initially 28/30 but dropped to 21/30 over six months with points lost for orientation in time and place and five minute recall. Using the Queen Square Screening Test for Cognitive Deficits,¹⁵ picture description was perfunctory, but object naming was preserved (8/10). Picture and object recall were both impaired. Fragmented letters and pictures were identified correctly. Verbal fluency was impaired for both letter and category (six words beginning with C, 4 animals in 60 seconds, respectively). Proverb interpretation was concrete. Formal neuropsychological assessment showed unequivocal intellectual loss (full scale IQ 77; predicted IQ on NART 116). Memory was weak on both immediate and delayed recall of verbal and visual material. Language was relatively preserved (Graded Naming Test 14/30) as were visuospatial skills (copying Rey figure). Verbal fluency was impaired (1st to 3rd centile) as was performance on the Stroop test (2nd centile). Using the Hospital Anxiety and Depression Scale,¹⁶ there was no evidence of anxiety or depression.

Neurological examination was unremarkable, specifically there were no frontal release signs (primitive reflexes), echophenomena (imitation behaviour), or muscle fasciculation around the shoulder girdle. She did demonstrate induced utilisation behaviour: when handed the examiner's glasses, she put them on without being told to do so.

Routine blood tests of haematology and biochemistry were within normal limits. EEG was within normal limits with reactive alpha rhythm. EMG showed no evidence of an anterior horn cell disorder.

Structural brain imaging with computed tomography (CT) showed pronounced enlargement of the cerebral cortical sulci in the frontal and temporal regions with symmetrical enlargement of the lateral ventricles (Figure 1). Homogenous low attenuation was seen in the white matter (Figure 1), on the basis of which a radiological diagnosis of subcortical arteriosclerotic encephalopathy (Binswanger's disease) was suggested, although there were no lacunar infarcts. MRI confirmed symmetrical frontal and temporal



Figure 1: Unenhanced CT brain scan showing frontotemporal atrophy, symmetrical enlargement of the lateral ventricles, and homogenous low attenuation of frontal white matter.

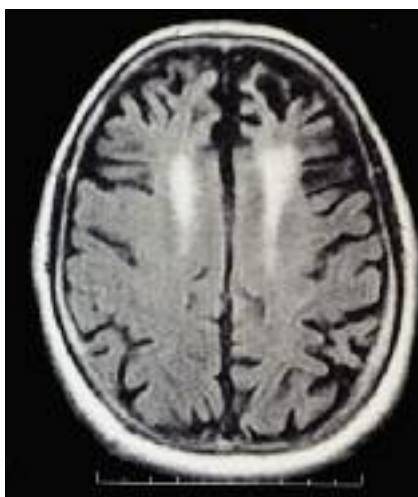


Figure 2: FLAIR MRI showing frontotemporal atrophy with confluent symmetrical high signal intensity change in frontal subcortical white matter.

lobe atrophy (Figure 2). In addition, on T2-weighted and FLAIR images, confluent and symmetrical high signal intensity changes were seen in frontal subcortical white matter (Figure 2). Single voxel 1H-MRS (GE Signa 1.5T Scanner; TE = 35 ms; TR = 1500 ms) showed a huge myoinositol (mI) peak in frontal white matter (Figure 3). Metabolite ratios using creatine (Cr) as a reference showed elevated mI:Cr and reduced N-acetyl aspartate (NAA):Cr ratio. These ratios were

reversed in occipital lobe (Figure 3). The MRI/MRS findings were interpreted as consistent with extensive gliotic change in frontal subcortical white matter, with neuronal loss,¹⁷ supporting a diagnosis of PSG, and not consistent with vascular change.¹⁸ The patient declined brain biopsy for diagnostic purposes.

Discussion

Although the clinical and investigation findings were in keeping with suggested criteria for the diagnosis of frontotemporal dementia,¹⁹ the imaging findings were thought to be suggestive of subcortical gliosis, and hence in keeping with a diagnosis of PSG. PSG has a variable clinical presentation, with cases reported which resemble FTD, AD, PSP and CJD. Hence the differential diagnosis is broad, and paraclinical investigations which might assist in diagnosis would be desirable.

Although neuroimaging has proved helpful in the diagnosis of other dementing disorders, particularly sequential volumetric MRI in AD,²⁰ radiological investigation has seldom been reported in PSG. In their original paper, Neumann and Cohn reported symmetrical enlargement of the lateral ventricles and cortical atrophy on pneumoencephalography (cases 1 & 2).¹ CT has confirmed the presence of atrophy.^{3,4,6,12} SPECT scanning has been reported to show bilateral frontotemporal hypoperfusion.¹⁰

Few reports of MR imaging have appeared: case 2 of Lanska et al.⁴ had two MR scans six months apart, the first was "unremarkable" and the second showed "diffuse atrophy and nonspecific white matter change" (not illustrated). However, the biopsy-proven case of Vermersch et al. showed extensive periventricular and subcortical signal hyperintensity on T2-weighted MR scans; these changes were thought to be the imaging correlate of the neuropathologically confirmed gliosis.¹⁰

Gliosis is observed pathologically at the subcortical level in FTD and in frontal lobe dementia with motor neurone disease.²¹ Modest changes in signal intensity may be seen in the white matter on T2-weighted and proton density MR imaging in Pick's disease.²² Hence, it has been suggested on theoretical grounds that this technique may be useful in diagnosing disorders which cause white matter gliotic change, such as PSG.²² Although pathology was not available in our case to confirm or refute the diagnosis of PSG, the MRI

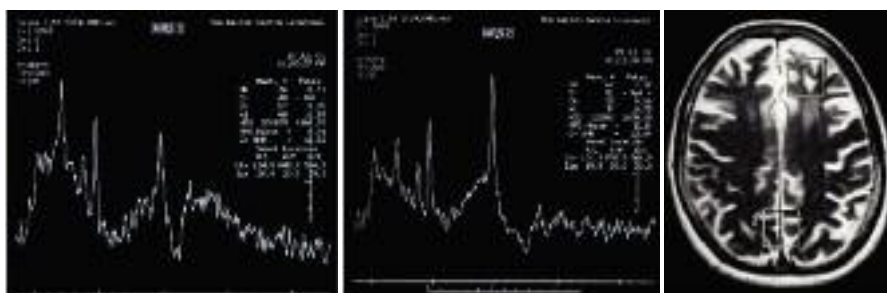


Figure 3: Single voxel 1H-MRS from frontal subcortical white matter (left) showing a large mI peak with raised mI:Cr ratio, and reduced NAA and low NAA:Cr ratio, consistent with extensive gliotic change, contrasting with normal MRS from occipital voxel (middle).

appearances closely resemble those in the case of Vermersch et al.,¹⁰ although less extensive, in which the diagnosis of PSG was proven histologically. The clinical picture and MRI/MRS findings were not suggestive of subcortical arteriosclerotic encephalopathy (Binswanger's disease).¹⁸

We have not identified any prior reports of IH-MRS in patients with PSG, but it has been used in FTD.¹⁷ Frontal lobe reductions in N-acetyl compounds (mean reduction 28%) and glutamate and glutamine (mean reduction 16%) were suggestive of neuronal loss, and increased myoinositol (19%) suggested increased glial content. The MRS results in our patient are qualitatively similar to those in FTD, but quantitatively different, the huge myoinositol peak and elevated ml:Cr ratio suggesting extensive gliosis, consistent with a diagnosis of PSG.

MRI has facilitated the diagnosis of certain neurodegenerative disorders, such as variant Creutzfeldt-Jakob disease²³ and neurodegeneration with brain accumulation of iron-1,²⁴ thus obviating the need for brain biopsy. We suggest that MRI and MRS may similarly be helpful in establishing the diagnosis of PSG ante mortem without recourse to invasive procedures for tissue diagnosis. We suspect that MRI/MRS with this type and distribution of signal change may be highly specific for PSG,¹⁰ but it is possible that the sensitivity may be lower (cf. ref 4, case 2). ◆

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