Progressive dementia and gait disorder in a 78 year old woman

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Case presentation
This 78 year old right handed white woman had a medical history significant for a cerebellar tumour, removed at age 12 by Dr Harvey Cushing. Reportedly, this was an astrocytoma and the removal was successful. Her balance was never perfect, but she was able to walk unassisted. She lived at home with her husband and had two children who are in good health.

The patient was essentially well until November 1995 when on a trip to Israel she became rather tired and had increased difficulty in walking. On her return from this trip, she complained of fatigue, lethargy, dizziness, and progressive memory loss. In January 1996 she developed bilateral hand tremor, evident both at rest and during action. Her primary care physician made a diagnosis of Parkinson’s disease and treated her with levodopa and amantadine, with only temporary benefit. After an increase in the dose of levodopa, she experienced visual hallucinations and worsening tremor, which resolved on discontinuation of the drug.

At the end of March 1996, she had a transient episode in which she suddenly raised her right leg while seated and collapsed on the chair soon after. According to a witness, she lost consciousness for a few seconds. She was admitted to a community hospital where a neurological evaluation was unremarkable, aside from mild dilatation of the lateral ventricles and prominence of the cerebral sulci and Sylvian fissures.

By December 1996, she was unable to write, read, or initiate conversation. Gait was unsteady and the left side was described as slightly weaker than the right. A mild intention tremor was noted bilaterally. A repeat MRI of the brain, with and without contrast infusion, showed dilation of the ventricular system, sulcal prominence without evidence of midline shift or mass effect, and post-surgical changes of the cerebellar hemispheres. Signal hyperintensity on T2 images involving the left temporal lobe, and both thalami was also evident. A diagnostic impression of early Alzheimer’s disease superimposed on chronic cerebellar dysfunction.

Her clinical condition gradually worsened and on May 1997 she was sleeping most of the day. Mini mental state evaluation gave a score of 8/30. She had frontal release signs, bilateral Babinski’s sign, unsteady gait, and intermittent sphincter incontinence. She was able to take only one small step with assistance and was
wheelchair bound. Medications included Inderal for tremor, ritalin for hypersonnia, zoloft for depression, and aspirin for CVA prophylaxis. On 14 May 1997, she experienced an episode of sudden “collapse” with incontinence of urine and stool. An EEG showed a poorly organised, symmetric theta rhythm with additional delta slowing, without evidence of epileptic activity. She gradually deteriorated and died at home in June 1997. A necropsy was obtained.

Differential diagnosis
Dr C Warren Olanow
Let me go through some of the features that characterise this rather complicated case. The patient was a 78 year old woman with a clinical course that seems to have been dominated by dementia. I don’t think that the tumour that she was operated on for over 60 years ago has anything to do with the current illness. She had some slight residual disturbance of balance, but she was otherwise intact.

The current problem began in November 1995 with non-specific weakness and fatigue, and progressive memory loss. In a 78 year old person who presents with progressive memory loss, the first cause one would consider is Alzheimer’s disease. Vascular dementia is also relatively common, but a vast majority of patients with vascular dementia also have Alzheimer’s disease changes. In January of 1996, she was diagnosed with Parkinson’s disease. She had resting and action tremor, worsening gait dysfunction, and probably some rigidity. At that point, one may consider that there was involvement of the basal ganglia and the cerebral hemispheres, at least the hippocampal region, and that we might be dealing with a combination of Alzheimer’s disease and Parkinsonism or Lewy body disease.

In March 1996, added to the problem is an episode in which she experienced a sudden movement of the right leg followed by transient loss of consciousness. Despite a provisional diagnosis of transient ischaemic attack, this episode should probably be considered a seizure and suggests the involvement of the cerebral cortex. Patients with Parkinson’s disease not only do not have seizures, but are relatively protected from having seizures. This may be due to the fact that the globus pallidus and the substantia nigra pars reticulata flood the brainstem with inhibitory stimuli and tend to turn off the structures that promote seizures.

We did a study several years ago and noticed that in patients with epilepsy who develop Parkinson’s disease or Lewy body disease, the dementia also manifests with profound in comparison to what you would expect to see with conventional Alzheimer’s disease. This raises the notion of other CNS structures, prion disease has the capacity to affect a larger number of structures and to rapidly evolve—in fact even more rapidly than we see in this case. In addition to all of the above, she developed a bilateral Babinski’s response suggesting the involvement of the corticospinal tracts. She rapidly continued to deteriorate in all capacities and eventually died in June 1997, after a total clinical course of 18 months.
At this point it is opportune to review the brain MRIs, because they show some interesting findings. Dr Drayer, can we review the neuroradiologic studies?

Dr Burton Drayer

In the initial brain MRI study, performed in May 1996, there are clearly signal abnormalities on the T1 and T2 images in the left medial temporal lobe (fig 1), although this study was reported as normal. In addition, there are high signal abnormalities in the midbrain (fig 1 C) and thalamus bilaterally (fig 1 D). Some gyral swelling and subtle signal abnormality in the gyral region as well seem to suggest a more generalised process (fig 1 E), and can explain the clinical occurrence of seizures. All these areas of abnormal signal do not enhance. The cerebellum shows the old postsurgical abnormality (fig 1 F) and the ventricles are enlarged.

A repeat study in October 1996 shows the same signal abnormalities in the thalami, midbrain, and cerebral grey matter with very little change compared with the study performed 6 months earlier. Incidentally, MRA shows a very small right vertebral artery that formed 6 months earlier. Incidentally, MRA does not show the typical variants of the vertebral artery that would be expected on the left and right sides. The normal vertebral arteries are not seen on the left side. In addition, there are high signal abnormalities in the basal ganglia (17/22), corpus callosum (12/22), brainstem (3/22), and cerebellum (2/22). Changes are only noted in T2 weighted scans and do not tend to enhance. The diagnosis usually cannot be made clinically but can be suspected based on the progression of symptoms and signs and the MRI pattern. Ultimately, a brain biopsy or necropsy is needed to confirm the diagnosis of gliomatosis cerebri. Total radiation may improve the median survival, which ranges from 6 to 9 months in untreated cases.

In summary, the diffuse involvement of multiple CNS regions including the cortex, hemispheres, basal ganglia, thalamus, brainstem, and possibly the cerebellum with evidence of diffuse swelling on MRI are most consistent with the diagnosis of gliomatosis cerebri. Whereas parkinsonism is a most unusual presentation of gliomatosis cerebri, dementia is a common manifestation, and I think that the diagnosis of gliomatosis cerebri is what best explains what happened to this patient.

Clinical diagnosis
Alzheimer’s disease; parkinsonism; possible prion disease

Dr Olanow’s diagnosis
Gliomatosis cerebri
Progressive dementia and gait disorder in a 78 year old woman

Figure 1  Initial brain MRI study, performed in May 1996.  (A, B) Non-enhanced and enhanced T1 coronal images with decreased signal and swelling of the left temporal lobe and no abnormal enhancement.  (C, D, E) Signal hyperintensity in the left temporal, midbrain, bilaterally in the thalamus, and subtle changes in the cortex on T2 axial images.  (F) Surgical changes in the cerebellum and signal hyperintensity in left temporal lobe on T2 axial images.
Pathological discussion
Dr Daniel Perl

We received this brain from an outside hospital. This patient was enrolled in our Alzheimer’s disease brain bank programme, and following our standard dissection protocol, only the right side of the brain was analysed. The external aspect of the brain showed no abnormality. The medial aspect disclosed only non-specific dilatation of the lateral ventricle and some changes in the cerebellar area where Dr. Cushing had done his surgery. There was scarring in the midline cerebellar vermis. There was no residual tumour in the fourth ventricle. Sixty nine years after surgery, this area looked remarkably clean. The substantia nigra and locus coeruleus looked normally pigmented, without gross abnormalities. Similarly, no obvious gross abnormality could be seen on coronal sections of the cerebral hemispheres. A Bielschowsky stain of the hippocampus showed no neurofibrillary tangles and no senile plaques. There were diffuse plaques in the cortex, consistent with age related changes in a 78 year old woman, but there was no evidence of Alzheimer’s disease. Further, there were no spongiform changes indicative of a prion related disease.

In the pons, there was a suggestion of hypercellularity even at low power. The cerebellar peduncles were remarkably hypercellular, with diffuse infiltration of cells. At higher power, these cells had very variable appearance with small pyknotic nuclei alternating with large atypical and frankly neoplastic nuclei scattered all through the tissue. The locus coeruleus was normally pigmented but diffusely infiltrated by numerous, pleomorphic astrocytes that had the appearance of neoplastic astrocytes.

In the midbrain, the substantia nigra was normally pigmented. No Lewy bodies were seen, therefore excluding the diagnosis of Parkinson’s disease. However, the extensive cellularity was again evident throughout. The oculomotor nuclei and the raphe neurons were surrounded by the same extensive cellularity, with atypical, neoplastic features at higher power (fig 2).

The thalamus was also quite hypercellular, without evidence of abnormal vasculature. The hippocampus did not show diffuse infiltration, although at higher power we were able to see individual atypical astrocytes, likely part of the same neoplastic process. Atypical astrocytic cells, with clear neoplastic features diffusely infiltrated the amygdala and inferior temporal lobe. The cerebral cortex looked normal at low power, but looking with care it was possible to see individual atypical astrocytic nuclei scattered throughout this tissue. The cortex was therefore involved, but not as extensively as we have seen in some other areas. The putamen looked similarly infiltrated. The abnormal cells were astrocytes; they stained positively with glial fibrillary acidic protein, and the pattern of diffuse infiltration was consistent with the diagnosis of gliomatosis cerebri.

Gliomatosis cerebri is a disorder that was first described by Samuel Nevin in 1938 as a diffuse proliferation of pleomorphic, neoplastic glial cells widely distributed throughout the CNS.14 Two types of gliomatosis cerebri are recognised15; one in which there is no underlying glioblastoma epicentre and the other in which there is an identifiable focal neoplastic nidus with extensive dissemination of neoplastic astrocytes throughout the CNS, far exceeding what is typically seen in glioblastoma. This case seems to belong to the first type.

Pathological diagnosis
Gliomatosis cerebri
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