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*Mult Scler* 2001 7: 269

DOI: 10.1177/135245850100700410

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## Case report

# Multiple sclerosis and oligodendroglioma

Ari J Green<sup>1</sup>, Andrew W Bollen<sup>2</sup>, Mitchel S Berger<sup>3</sup>, Jorge R Oksenberg<sup>1</sup>, and Stephen L Hauser<sup>\*,1</sup>

<sup>1</sup>Department of Neurology, University of California, San Francisco, California, CA 94143-0114, USA; <sup>2</sup>Department of Pathology, University of California, San Francisco, California, CA 94143-0506, USA; <sup>3</sup>Department of Neurological Surgery, University of California, San Francisco, California, CA 94143-0112, USA

Two cases of multiple sclerosis (MS) and oligodendroglioma are reviewed, increasing the total number of reported cases to 11. In this series, the clinical onset of MS preceded the discovery of the tumor by a mean of 15 years. No distinguishing features of oligodendroglioma were characteristic of MS-associated cases. However, there was an overrepresentation of benign MS. Although this could result from biased ascertainment, other possibilities, including effective remyelination mediated by mitotically active oligodendrocytes, or secretion of immunosuppressive cytokines by the tumor tissue, cannot be excluded. It is likely that the coexistence of MS and oligodendroglioma is due to chance alone, nonetheless the possibility that glioma derived factors can moderate the disease course in MS is deserving of further study. *Multiple Sclerosis* (2001) 7, 269–273

**Keywords:** multiple sclerosis; oligodendroglioma; glioma; oligodendrocyte

## Introduction

Although the patient with both multiple sclerosis (MS) and glioma is rare, some observers have proposed that a causal relationship might exist between these conditions. Scherer reported the first case of glioma in an MS patient in 1938, and currently more than 30 reported cases can be found in the literature.<sup>1–8</sup>

Oligodendrogliomas comprise between 4–7% of all gliomas and tend to have a less aggressive course than other glial cell malignancies. These are generally tumors of middle age, with a peak incidence during the fifth decade of life. Histologically, a substantial majority of these tumors are constituted by mature oligodendroglia and their precursors; the remaining 20%, termed mixed, contain admixtures of oligodendrocyte and astrocytic elements.<sup>9–11</sup> Malignant transformation to glioblastoma is unusual, but may occur. Oligodendrogliomas are believed to be derived from an O2A progenitor cell, which is also the precursor of certain astrocyte subtypes; their distinctive cytogenetic features are summarized elsewhere.<sup>12–15</sup>

In MS patients, four cases of ‘pure’ oligodendroglioma and five cases of mixed oligodendroglioma have been reported. One noteworthy feature of these reports has been an apparently benign course for MS in most of the cases. Here we report two additional cases of oligodendroglioma in patients with demyelinating disease and discuss the mechanisms which might confer a possible relationship between the two conditions.

## Case 1

This left-handed woman experienced initial symptoms of MS at age 34 years, consisting of right upper extremity numbness and weakness brought on by exertion and fatigue. At age 41 years, she developed bilateral numbness in the thoracic region lasting several weeks before remitting. At age 50 years she noted sensory loss below the clavicle, a ‘tight constrictive’ feeling across her thorax, left monocular visual blurring, and a Lhermitte phenomenon. Brain MRI revealed multifocal and periventricular areas of T2 hyperintensity, typical for MS; in addition, a nonenhancing mass lesion was present in the superficial white matter of the right temporal-parietal area with some sulcal effacement of the overlying cortex. Cervical MRI showed an intramedullary enhancing lesion at C2–3. A course of oral glucocorticoids was administered, followed by complete remission of her symptoms. The following year she developed diplopia and paresthesia which remitted without treatment. At age 54 years, follow-up MRI showed enlargement of the right temporo-parietal mass to 3 cm which now appeared partially necrotic. Total resection was performed; pathology revealed a low grade microcystic oligodendroglioma. Surgery was uncomplicated, with the exception of a transient postoperative visual field deficit. One year later she again developed numbness to the waist that remitted with oral glucocorticoids. Her current neurological exam reveals only minor abnormalities. Visual acuity is 20/25 OS, 20/20 OD with full visual fields and no loss of color perception. Extraocular muscles and cranial nerves are normal with the exception of a mild head tremor. She has mild hyperreflexia in the lower limbs, a left extensor plantar response, and an absent left superficial abdominal reflex. Motor and sensory exam and gait

\*Correspondence: SL Hauser

Received 26 March 2001; accepted 3 April 2001

are all normal. The patient's family history is remarkable, for she has a brother with low grade glioma and a paternal uncle with MS.

## Case 2

A 44-year-old right-handed woman developed painless partial left monocular visual loss upon awakening. She also reported a history of uncinat seizures ('hazy feeling' followed by the smell of oil) on three previous occasions. Examination revealed an inferior left scotoma OS. VEPs were consistent with a diagnosis of optic neuritis. Lumbar puncture was normal; there was a single oligoclonal band. MRI revealed three T2 hyperintense white matter lesions: one in the cerebellar peduncle, a second adjacent to the right lateral ventricle in the splenium and a third in the centrum semiovale on the left. In addition a large T2 bright, T1 dark right temporal lobe lesion with some mass effect was noted in the right temporal lobe. Biopsy was nondiagnostic. Her visual symptoms subsequently resolved over the following few weeks. Three years later follow-up MRI revealed growth of the temporal lobe mass, and a partial resection was performed at an outside hospital. Pathology revealed a grade 2 oligodendroglioma. She remained asymptomatic, but underwent complete resection at age 51 years. Pathology at that time indicated a mixed oligoastrocytoma. The patient then underwent conformal external beam radiation at 5400 cGy in 30 treatments over a 2-month period. In the subsequent 2 years she had been largely symptom-free. She noted mild intermittent short term memory loss and infrequent seizure aura for which she takes phenytoin. She has had no further symptoms of demyelinating disease. Her neurological examination was normal except for a small left superior field deficit.

## Discussion

A summary of the two current and nine previously reported cases of MS and oligodendroglioma can be found in Table 1. The demographic characteristics of this group are typical of both MS and oligodendroglioma, including the mean age of onset for MS (34 years excluding one case diagnosed at autopsy) and age at presentation of oligodendroglioma (44 years). The gender parity of this series (1:1) likely reflects a combination of female predominance in MS (2–2.5:1) and male predominance in oligodendroglioma (1.5–2:1). The clinical form of MS was relapsing remitting in 58%, secondary progressive in 25%, and primary progressive in 17%, a distribution similar to that of the general MS population.<sup>16</sup>

MRI and autopsy findings are also typical for both conditions. The distribution of the tumors are equally divided between temporal and frontal lobes, with a few cases crossing over the midline or found in the parietal region. This is very similar to the distribution reported by Chin *et al*<sup>17</sup> for oligodendroglioma in general. Our cases and those reported by Khan *et al*<sup>18</sup>

and Scully *et al*<sup>19</sup> all had typical MRI findings for MS, consisting of multifocal T2 bright signal abnormalities located predominantly in periventricular and corpus callosum white matter, some of which enhanced after the administration of gadolinium. The other cases studied at autopsy displayed typical histopathologic features of MS.

A few of the cases should be considered with caution. Our second case experienced optic neuritis only, and brain MRI revealed three periventricular white matter lesions, insufficient for a diagnosis of laboratory-supported MS in a patient of this age (44 years). Still, this patient is worthy of inclusion in this series because any patient with a history of ON and an abnormal brain MRI suggestive of earlier subclinical demyelinating episodes is at high risk for progression to clinically definite MS.<sup>20</sup> The case reported by Rao *et al*<sup>21</sup> is atypical because the patient had no clinical record of neurological symptoms; although there are recorded cases of clinically silent MS and clinically silent oligodendroglioma, their coexistence must be highly unusual.

The first and most likely explanation for the concordance of these two conditions is chance alone. In the United States, MS has a prevalence of 00/100 000 and oligodendroglioma an incidence of 0.3–0.6/100 000. Absent a relationship between these two entities, probability alone predicts one to two cases of oligodendroglioma in an American MS patient each year. It is possible that an underrecognition of oligodendroglioma in MS patients could occur if a progressive neurologic deficit due to a slowly growing intracranial mass is incorrectly attributed to MS. On the other hand, the frequent clinical use of MRI to assess MS may overcome this diagnostic bias. It is now unclear how frequently oligodendrogliomas may remain subclinical, but because of their relatively indolent course they may be underreported.

We considered the possibility that shared genetic factors might underlie susceptibility to both conditions. The influence of genetic susceptibility on MS risk is well-known.<sup>22</sup> Genetic predisposition to glioma is suggested by its occurrence in our first patient and her sibling. To our knowledge only one sibling pair concordant for oligodendroglioma has been previously reported and this occurred in monozygotic twins.<sup>23</sup> Studies of families with multiple MS-affected members – in which common susceptibility genes would be expected to be present – have not reported cases of oligodendroglioma.<sup>24–26</sup> Large series of intracranial neoplasms from high prevalence MS populations (Scandinavia and northern Europe) are inconclusive but have raised the possibility that these regions also have a higher than expected incidence of oligodendroglioma.<sup>9</sup> Oligodendrogliomas are frequently characterized by deletions of 1p and 19q; chromosomal regions that have been associated with MS through dense microsatellite screens of the full genome in MS families.<sup>21</sup> Each of these large chromosomal regions contains many hundreds of genes, and such 'genomic convergence' could be easily explained by chance.

**Table 1** Reported cases of MS and oligodendroglioma concurrences

Patient	Oligo type	Age at MS onset	Age at Oligo Dx	MS status/course	MRI findings	EDSS at 10 years	Oligo location	Histology/pathology
Case 1	Pure	34	50	CDMS/RR	Focal non-enhancing T2 hyperintensities superior to LV and posterior to splenium of CC/distinct from tumor mass	1.5	R temporo-parietal junction	Microcystic low grade
Case 2	Pure/mixed	44?	44?	CPMS	Nodular areas of T2 bright white matter lesions up to 1 cm in diameter close to LV and in CC/distinct from tumor	1.0	R temporal lobe	Single mass grade 2/mixed oligoastrocytoma
Scully <i>et al.</i> <sup>19</sup>	Mixed	35	50	CDMS/RR	Multiple T2 bright lesions in periventricular white matter/distinct from tumor	~0.0	R frontal lobe	Diffusely infiltrating+focal anaplasia/sharply demarcated from MS plaques/<10% low grade astrocytoma
Khan <i>et al.</i> <sup>18</sup>	Pure	43	51	CDMS/RR	Multiple T2 bright periventricular and infratentorial white matter lesions/distinct from tumor	2.0 (8 years)	R posterior parietal lobe	Low grade (biopsy)
Giordana <i>et al.</i> <sup>35</sup>	Pure	34	42	CDMS/PP	N/A	N/A	Anterior CC, bilateral frontal lobes	Grade unclear/honeycombed and 'isomorphic'/not contiguous with MS lesions
Rao <i>et al.</i> <sup>21</sup>	Pure?	N/A	65	N/A	N/A	0.0	Diffuse R>L across CC	'Neoplastic' oligodendroglioma with spotty calcification, ring lesions in right frontal white matter/contiguous with plaques
Matthews and Moosy <sup>36</sup>	Mixed	26	44	CDMS/RR	N/A	1.0	L fronto-parietal lobes	High grade with neoplastic infiltration into surrounding white matter/two distinct cell types (1) pure oligodendroglioma with calcification (2) mixed tumor with anaplasia and microcavitary degeneration
Barnard and Jellinek <sup>37</sup>	Pure	28	43	CDMS/RR or CP	N/A	6.5	R temporal lobe+ metastasis to R cerebellar hemisphere	'Polymorphic' oligodendroglioma with mitotic figures and central necrosis/features resembling ependymoma
Anderson <i>et al.</i> <sup>38</sup>	Astrocytoma predominant mixed	39	47	CDMS/PP	N/A	N/A (7.0 at 8 years)		Pleomorphic astrocytoma with areas of oligodendroglioma and glioblastoma multiforme/prominent calcification/confluence of tumor and MS plaques
Anderson <i>et al.</i> <sup>38</sup>	Astrocytoma predominant mixed	~34	45	CPMS (autopsy confirmed)/RR	N/A	~0	L posterior frontal lobe	Large anaplastic astrocytoma with areas of oligodendroastrocytoma/confluence of tumor and MS lesions

Abbreviations: CDMS=clinically definite MS; RR=Relapsing–remitting; LV=Left ventricle; CPMS=Clinically probable MS; CC=Corpus callosum; PP=Primary progressive; CP=Chronic progressive

Therefore, the likelihood that common genetic factors underlie MS and oligodendroglioma appears low.

An oligodendroglioma could theoretically stimulate an immune response to oligodendrocyte surface proteins or to myelin antigens that leads to auto-immune demyelination. Were this the case, a later age of onset for MS would be expected in this series but was not found. Clinical evidence of MS preceded oligodendroglioma in 10/12 cases and on average MS symptoms began 15 years prior to the identification of tumor. Thus, this hypothesis also appears unlikely to be true.

Perhaps damage induced by the MS disease process may directly increase susceptibility to oligodendroglioma by inducing oligodendrocyte precursors to proliferate and rendering them susceptible to neoplastic transformation. Recent histological studies of MS lesions have emphasized the considerable variability in oligodendrocyte pathology that may occur between cases.<sup>27-29</sup> Remyelination, which is commonly observed in MS lesions, requires oligodendrocytes to undergo at least one cellular division.<sup>30</sup> Were this indeed the mechanism of tumorigenesis, the tumors would be expected to arise within MS plaques. This does not appear to be true of the cases reviewed here. Sharp demarcation was noted between tumor and MS lesions in all the autopsy cases except the one described by Rao *et al.*<sup>21</sup> This distinction may be difficult to make with confidence, however, because the enlarging tumor mass may obscure or obliterate small MS lesions in its path.

The most notable feature of this series is the high prevalence of benign MS. A benign course, generally defined as an EDSS < 3.0 at 10 years after onset, has been estimated to occur in approximately 40% of all MS cases.<sup>31</sup> In the MS/oligodendroglioma series 83% (10/12) patients appear to satisfy a diagnosis of benign MS ( $z=5.745$ ,  $P=0.000$ ). As noted above, these cases might share in common a proliferative response by mitotically active oligodendrocyte precursors inducing neoplasia but also resulting in functionally effective remyelination. Alternatively, proliferating oligodendrocytes might secrete regulatory factors such as nerve growth factor,<sup>32</sup> or induce production of regulatory cytokines such as interleukin-10 by astrocytes or microglia,<sup>33,34</sup> contributing to an immunosuppressive milieu protective against further MS mediated injury. This latter hypothesis, although speculative, can be tested in laboratory models.

## References

- 1 Ho KL, Wolfe DE. (1981) Concurrence of multiple sclerosis and primary intracranial neoplasms. *Cancer* **47**: 2913–2919.
- 2 Nahser HC *et al.* (1986) Coincidence of multiple sclerosis and glioma: clinical and radiological remarks on two cases. *Surg Neurol* **26**: 45–51.

- 3 Aarli JA *et al.* (1989) Glioblastoma associated with multiple sclerosis: coincidence or induction? *Eur Neurol* **29**: 312–316.
- 4 Reagan TJ, Freiman IS. (1973) Multiple cerebral gliomas in MS. *J Neurol, Neurosurg Psychiat* **36**: 523–528.
- 5 Lahl R. (1980) Combination of multiple sclerosis and cerebral glioblastoma. *Eur Neurol* **19**: 192–197.
- 6 Roytta M, Latvala M. (1986) Diagnostic problems in MS: Two cases with clinical diagnosis of MS showing only a diffusely growing malignant astrocytoma. *Eur Neurol* **25**: 197–207.
- 7 Viergege P *et al.* (1984) Multiple sclerosis and cerebral tumor. *Clin Neuropathol* **3**: 10–21.
- 8 Scherer H. (1938) La 'glioblastomatose en plaques': sur les limites anatomiques de la gliomatose et des processus sclerotiques progressifs. *J Belg Neurol Psychiat* **38**: 1–17.
- 9 Zulch K. (1986) *Brain Tumors*, ed 3. Berlin: Springer-Verlag, pp 240–258.
- 10 Couldwell WT. *Oligodendroglioma*, in *Brain Tumors*. pp 479–491.
- 11 Vandenberg SR, Lopes MBS. (1999) Classification. In: *The Gliomas*, Berger MS and Wilson CB (eds.). Philadelphia: WB Saunders, pp 181–184.
- 12 Cairncross JG *et al.* (1998) Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* **90**: 1473–1479.
- 13 Jenkins RB *et al.* (1989) A cytogenetic study of 53 gliomas. *Cancer Genet Cytogenet* **39**: 253–279.
- 14 Kraus JA *et al.* (1995) Shared allelic losses on chromosomes 1p and 19q suggest a common origin of oligodendroglioma and oligoastrocytoma. *J Neuropathol Exp Neurol* **54**: 91–95.
- 15 Reifenberger J *et al.* (1994) Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol* **145**: 1175–1190.
- 16 Hauser S, Goodkin D. (2001) Multiple Sclerosis. In: *Harrison's Principles of Internal Medicine*, Braunwald E *et al.* (eds.). New York: McGraw Hill.
- 17 Thomas DGT, Graham London DI, eds. (1980) *Brain tumours: scientific basis, clinical investigation and current therapy*. Boston: Butterworths.
- 18 Khan OA *et al.* (1997) Concurrence of multiple sclerosis and brain tumor: clinical considerations. *Neurology* **48**: 1330–1333.
- 19 Scully RE *et al.* (1997) Weekly clinicopathological conference: case records of the Massachusetts General Hospital. Case 12-1997. *NEJM* **336**: 1163–1171.
- 20 Optic Neuritis Study Group. (1997) The 5-year risk of MS after optic neuritis: experience of the Optic Neuritis Treatment Trial. *Neurology* **49**: 1404–1413.
- 21 Rao TV *et al.* (1986) Multiple sclerosis with an associated diffuse oligodendroglioma. *NIMHANS* **4**: 105–110.
- 22 Oksenberg J, Baranzini S, Barcellos L, Hauser S. (2001) Multiple sclerosis. Genomic rewards. *J Neuroimmunol* **171**–184.
- 23 Roelvink NC *et al.* (1986) Concordant cerebral oligodendroglioma in identical twins. *J Neurol Neurosurg Psychiatry* **49**: 706–708.
- 24 Robertson NP *et al.* (1996) Clinical concordance in sibling pairs with multiple sclerosis. *Neurology* **47**: 347–352.
- 25 Multiple Sclerosis Genetics Group. (1998) Clinical demographics of multiplex families with multiple sclerosis. *Ann Neurol* **43**: 530–534.

- 26 Brassat D *et al.* (1999) Familial factors influence disability in MS multiplex families. French Multiple Sclerosis Genetics Group. *Neurology* **52**: 1632–1636.
- 27 Ozawa K *et al.* (1994) Patterns of oligodendroglia pathology in multiple sclerosis. *Brain* **117**: 1311–1322.
- 28 Bruck W *et al.* (1994) Oligodendrocytes in the early course of multiple sclerosis. *Ann Neurol* **35**: 65–73.
- 29 Lucchinetti C *et al.* (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* **47**: 707–717.
- 30 Kerstead HS, Blakemore WF. (1997) Identification of post-mitotic oligodendrocytes incapable of remyelination within the demyelinated adult spinal cord. *J Neuropathol Exp Neurol* **56**: 1191–1201.
- 31 Goodkin DE, Hertsgaard D, Rudick RA. (1989) Exacerbation rates and adherence to disease type in a prospectively followed-up population with multiple sclerosis: implications for clinical trials. *Arch Neurol* **46**: 1107–1112.
- 32 Villoslada P *et al.* (2000) Human nerve growth factor protects common marmosets against autoimmune encephalomyelitis by switching the balance of T helper cell type 1 and 2 cytokines within the central nervous system. *J Exp Med* **191**: 1799–1806.
- 33 Cannella B *et al.* (1998) The neuregulin, glial growth factor 2, diminishes autoimmune demyelination and enhances remyelination in a chronic relapsing model for multiple sclerosis. *Proc Natl Acad Sci USA* **95**: 10100–10105.
- 34 Williams K *et al.* (1996) IL-10 production by adult human derived micro-glial cells. *Neurochem Int* **29**: 55–64.
- 35 Giordana MT *et al.* (1981) Association between multiple sclerosis and oligodendroglioma: Case report. *Ital J Neurol Sci* **4**: 403–410.
- 36 Mathews T, Moosy J. (1972) Mixed glioma, multiple sclerosis, and Charcot-Marie tooth disease. *Arch Neurol* **27**: 263–269.
- 37 Barnard RO, Jellinek EH. (1967) Multiple sclerosis with amyotrophy complicated by oligodendroglioma. History of recurrent herpes zoster. *J Neurol Sci* **5**: 441–455.
- 38 Anderson M *et al.* (1980) Gliomatous transformation and demyelinating diseases. *Brain* **103**: 603–622.