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Sir,

Mifepristone treatment in patients with surgically incurable sphenoid-ridge meningioma: a long-term follow-up

Sphenoid-ridge meningiomas are slow-growing benign tumours that may reach massive proportions, invading bone and/or encasing major blood vessels. Although the importance of surgery is well established, meningiomas often recur after incomplete resection, 'subtotal' or even 'total' extirpation. After subtotal resection, most frequently used in sphenoid-ridge meningioma surgery, 69% of patients are still recurrence-free, with the probability of recurrence as high as 91% after 15 years.[1,2] After a second resection; the probability that more surgery will be needed is 56% after 10 years. Although the survival rate is high after 15 years, there is a serious threat that, after one or more operations, the patient will become functionally disabled by impaired vision, even blindness, and suffer motor deficits having cosmetic and social implications.[2]

Therefore, other therapies such as gamma-knife and stereotactic radiotherapy have been developed,[3] although conventional radiosurgery remains beneficial. Recurrence and cerebral and/or visual radio-complications are frequently found at 10-year follow-up.[1] Hormone treatment is possible because most meningiomas contain progesterone-specific receptors.[4,5] Epidemiological data (preponderance in women, tumour growth during pregnancy, coexistence with breast cancer) suggests that progesterone receptors may play a role. Therefore, investigating how progesterone antagonists' function may prove advantageous. The progesterone-receptor antagonist Mifepristone (MIF; 17-β-hydroxy-β(4-dimenthyl-aminophenyl)-17α-(1-propynyl)estra-4,9-dien-one) binds to and blocks both this as well as cortisol receptors in meningiomas.

Several pilot studies suggest that progression of sphenoid-ridge meningiomas can be halted using progesterone-receptor antagonists.[4,6,7] In most cases, tumour growth and visual functions could be stabilized. Slight improvements in visual function, motility disturbances, and orbital symptoms were occasionally observed, as in the prospective study with 1-year follow-up[6] (see Table 1) in Rotterdam[4] and Leiden including 10 patients (five from Rotterdam, two from Leiden) with

Table 1 Unresectable meningiomas in two women treated with MIF

	Patient 1	*Patient 2*
Age (years) starting MIF	51	53
Diagnosis	Borderline vasc. meningioma	Meningo-theliomatous
Location	Sphenoid, cavernous sinus	Skull base, chiasm, Iin
Neurosurgery	1985 and 1987	1980 and 1987
MIF protocol study	1988–1989	1988–1989
Open study	1990–2003	1990–2003
Dosage MIF (mg)	200–400	200–400
Dosage DEX (mg)	1.5	1.5
Positive receptor progesterone	+	+
Amenorrhoa?	Yes	Yes
Total follow-up (years)	14	14
VA (RE/LE)	LE 1 year: FC 1 month	—
Before MIF	1.0, 0	0.1, 0
After MIF	1.0, 0	0.3, 0
VF		
Before MIF	Small defect nasal	Small central island
During MIF	Conform	Conform
Oculomotor disturbances	CS syndrome/>	—
Before	IIIn paresis	—
After	Improved	
Tumor growth During MIF	None	None
Complications	None	Uterus extirpation after 5 years

recurrent primary inoperable sphenoid-ridge and/or cavernous-sinus meningiomas. In Leiden, disease continued in two cases after stopping MIF treatment by protocol; visual functions recovered after renewing treatment. As to date, no long-term results can be found in the literature, the two Leiden cases showing initially favourable results will receive a $\geqslant$14-year follow-up.

Case reports

Case 1

In 1985, a 48-year-old woman with diplopia, caused by VI nerve palsy, and trigeminal problems and proptosis was diagnosed in our clinic with sphenoid-ridge meningioma (Table 1). Visual acuity (VA) was 1.0 for right (RE) and left (LE) eyes. Her menstrual cycle subsided in 1981. After craniotomy with tumour-block excision, III nerve palsy persisted. She appeared to develop diabetes insipidus for which DDAVP (anti-diuretic hormone) was prescribed. In 1986, LE-VA deteriorated to 0.5 with a slightly pale optic disc. Homonym visual-field (VF) defects together with cavernous-sinus syndrome and hypopituitarism, probably resulting from tumor progression, were diagnosed and treated with hydrocortisone and thyroxin. In 1987, LE visual functions rapidly decreased to hand movements with more homonym impairment and RE nasal VF loss but improved to 1.0 and 0.6 after a second neurosurgical decompression of the opticochiasmal system. In 1988, LE-VA decreased to light perception and her general condition deteriorated. As surgery and radiotherapy were undesirable, hormone therapy using 200 mg MIF was chosen with permission according to the Rotterdam protocol. Since MIF blocks the cortisol receptor, 0.5 mg doses of dexamethasone (DEX) were given three times daily. Tumour growth was halted and all visual functions improved (RE-VA 1.0, LE LP and less VF defects). After 1 year, MIF therapy was stopped according to protocol. However, all signs and symptoms showed that her condition was deteriorating again (VA 1.0, VF 0, more VF defects on both sides). Our pituitary-tumour group decided to renew MIF treatment. Visual functions improved. In 1990, RE-VA was 1.0 while LE-VA improved to finger counting at 2 m. During the 12-year follow-up, LE vision deteriorated slowly to zero, while RE visual functions stabilized during the next 2 years, with a normal nasal VF and small ventral island on the temporal side. In 1993, VA and VF decreased slightly, and MIF was increased successfully to 400 mg daily. During the next 2 years, slight improvement was followed by stabilization over the next 7 years (Figure 1, special VF bar). Neither CT scan nor MRI showed any tumour growth during that period: a large meningioma of the sphenoid and cavernous sinus was found with carotid-artery encasement, extension in the sphenoidal sinus and clivus with slight impression of the III ventricle and close relation to the optic nerve in the apex of the orbit on both sides.

Case 2

In 1987, a 52-year-old woman was referred to our clinic (Table 1) with a medical history including headache in 1978 and amenorrhoea at the age of 41 years. Craniotomy was performed in 1980 for a skull-based meningioma. In 1986, she suffered from persistent headache and progressive impairment of visual functions. CT scan showed no recurring meningioma. In our outpatient department, CT scan revealed a large recurrent *en plaque* skull-based tuberculum sellae meningioma causing LE blindness and decreased RE visual functions. Lung embolus developed after a second craniotomy. Her visual functions improved until they failed again severely in September 1988. Only a small island of vision remained (RE-VA 0.16; Figure 2a). Using Lamberts *et al*.[4] protocol with permission, 200 mg MIF was given once daily that blocked the cortisol receptor, increasing levels of plasma cortisol and ACTH. To prevent hypocortisolism, DEX therapy (0.5 mg, 3 $\times$ daily) was initiated. All endocrinological and systemic functions and ultrasound of the intra-abdominal sex organs were normal. After 5 months, headache vanished and visual functions stabilized. CT scan of the skull base and orbit showed no tumour growth. Thereafter, following some changes in visual function together with malaise, the dosages of MIF (to 2×200 mg) and DEX (to 4×0.5 mg) were increased.

Hormone therapy was discontinued after 1 year, following treatment protocol. However, VA decreased again (to FC 4 m) after 1 month. As only a small island of vision remained, MIF treatment was renewed using the same treatment protocol. After 4 months of treatment, visual functions (RE-VA 0.2, fewer VF defects) improved to the levels found during the first year of treatment. In 1991, visual functions stabilized, CT scan revealed no tumour growth, and DEX was reduced to 3×0.5 mg.

In 1993, after blood loss, gynaecological ultrasound examination showed an irregular uterus and endometrial polyp. Serum levels of oestradiol, LH, and FSH did not verify the assumption that the patient was menopausal. After hysterectomy, pathology revealed endometrial hyperplasia. It was concluded that the irregular cycle probably resulted from the antiprogestagenic effect of MIF. Based on hormone studies, DEX was changed to prednisone in decreasing doses and MIF was reduced to 200 mg. From July 1992 to May 2002, VA measured

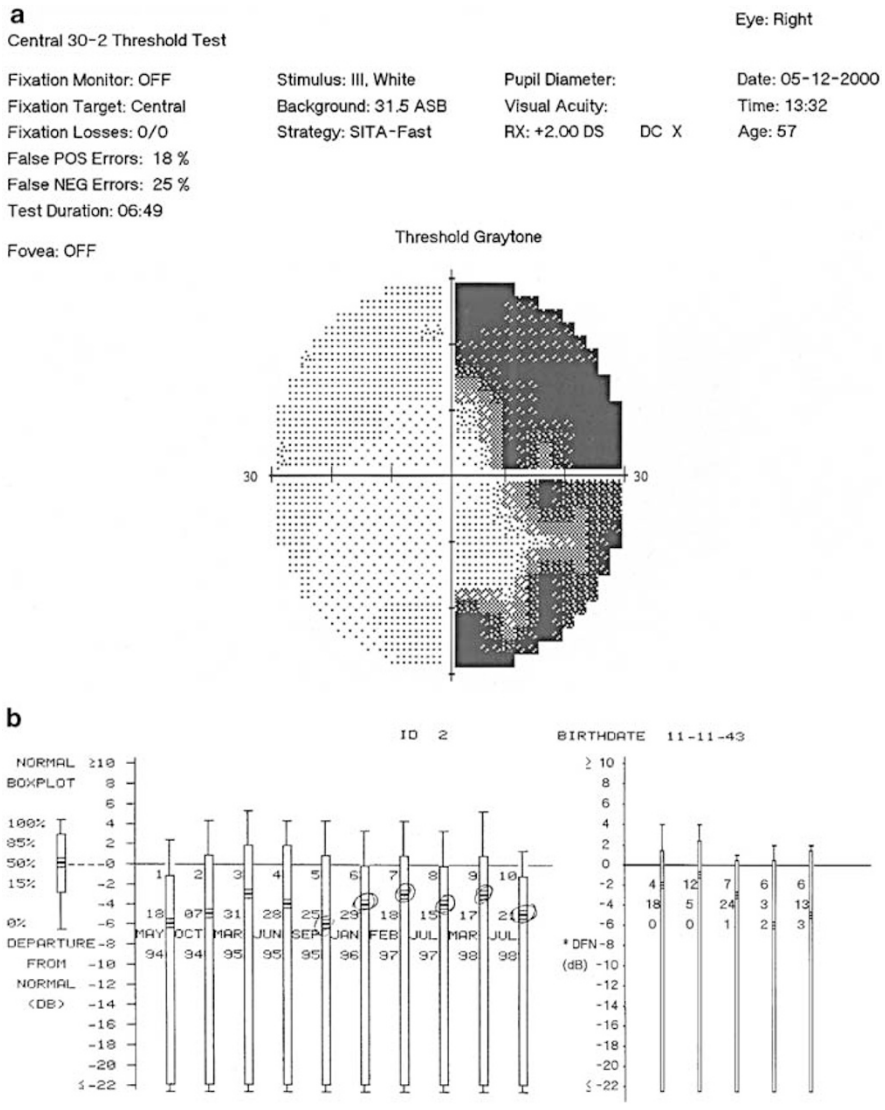

Figure 1 (a) Humphrey visual field analyses one example of the stationary 14 years of the RE. (b) Change analysis for Case 1 who had no significant progression of the visual fields/visual defects in 14 years. The box plot summarize the range of sensitivities in each test result relative to what is normal for the patient's age. The highest and the lowest points of each box plot show the extreme values for each test result, 45% of test points have deviations from normal falling within the middle box.

0.2–0.3 (sometimes 0.4) with a small island of vision especially located at the nasal side 10° field (Figure 2b). MRI demonstrated no tumour growth of the tuberculum sellae meningioma, a large tumour process located anterior to the sella and extending to the clivus, pineal body, with erosion of the anterior clinoid process, sella bottom, and dorsum sellae.

Comment

From 1988 to 1990, two women with skull-based meningiomas containing progesterone-positive receptors were treated for 1 year with 200 mg MIF according to protocol to stabilize both tumour and visual functions. After a period without MIF, all VFs decreased again with increasing blindness. In an open study (second part), hormone treatment using either 200 or 400 mg MIF was given during 12.5 years. (The drug was not available for treating more cases between the original study and 1998.) During the first 2-year observation period, ophthalmic and neuro-ophthalmic screening were performed every 3 months and CT scans were made twice. Thereafter, the eyes were examined every 3 months and VFs measured every 6 months. Later, MRI was performed every 1 and 2 years.

Endocrinal tests, including determination of plasma ACTH, cortisol, and progesterone levels, were run

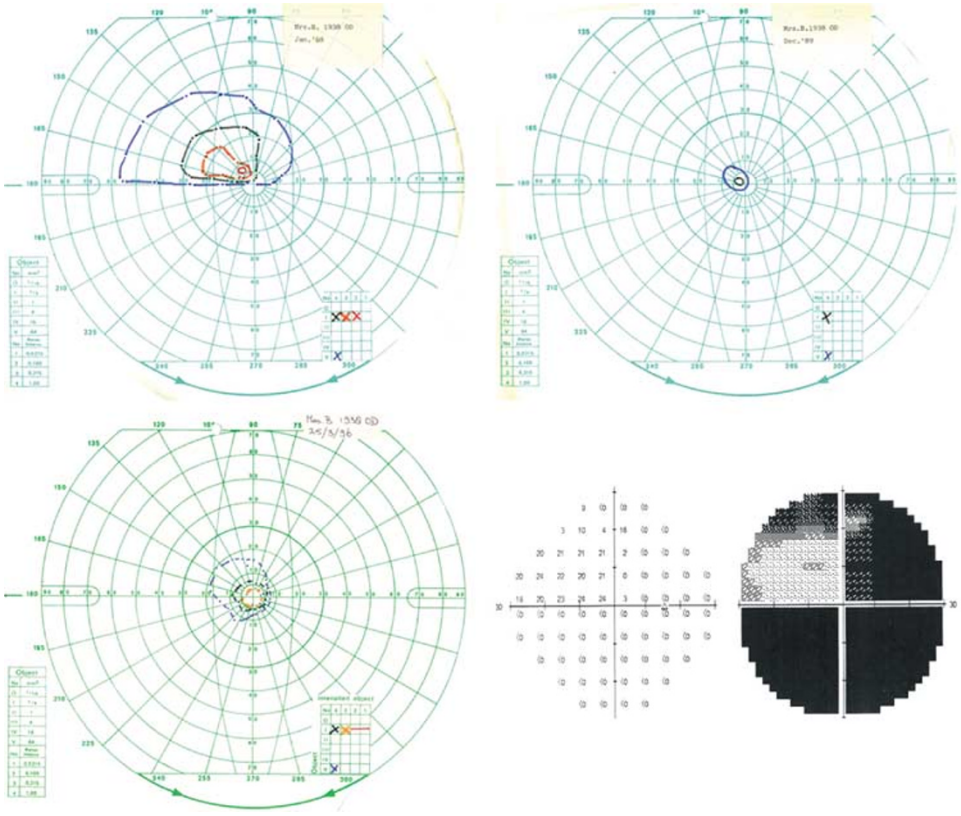

Figure 2 VF of Case 2. upper part: VF during the first period of observation, after surgery, and again progression. Lower part: Goldmann and Humphrey analyzer after 12 years (total) treatment period.

every 6 weeks during the first year of treatment. The women were examined gynaecologically at regular intervals. After 12 years, all visual functions were still at the level achieved after 1 year of MIF treatment. Our second patient who deteriorated severely and had been threatened with imminent blindness (Table 1), even showed slight improvement after treatment. One patient underwent hysterectomy for endometrial hyperplasia.

Both the short-term studies of Haak *et al*[6] and Grunberg *et al*[7] as well as our study with a long-term follow-up have shown that the initial benefits of treatment persist. Although Grunberg *et al*[7] only prescribed 1 mg DEX during the first 14 days of therapy, we advise combining MIF with DEX to prevent cortisol deficiency. Apparently, there is no sign of tachyphylaxis. Although based on a small patient group, these results appear more favourable than those expected after radiotherapy, an alternative treatment associated with optic neuropathy, neurological impairment, or cerebral necrosis (3%) and death (4%).[3]

We conclude that MIF is an attractive option for treating patients with inoperable recurrent sphenoid-ridge and cavernous-sinus meningiomas and for preventing severe cranial nerve and general morbidity, even after long-term follow-up exceeding 14 years.

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Sir,

Hemorheological changes in patients undergoing haemodialysis for chronic renal failure and retinal ischaemia

I read with interest the article by Pahor 'Retinal Light Sensitivity in Haemodialysis Patients'.[1] The author has shown that there was a significant reduction in retinal light sensitivity in 36% of patients undergoing haemodialysis (HD) for chronic renal failure (CRF) as indicated by the significant reduction in their field global indices: mean deviation, pattern standard deviation, and corrected pattern standard deviation in comparison with the control group. In the discussion, the author explained that this may be the result of the retinal circulatory disturbance secondary to hypertensive retinopathy and atherosclerotic changes in the carotid arteries that cause chronic ischaemic retinopathy due to increased red cell aggregation and its reduced deformability and increased blood viscosity.

First, I would like to add that the above haemorheological changes, in addition to increased plasma fibrinogen, were reported in CRF patients undergoing HD and were found to increase the blood viscosity.[2,3] These changes are presumed to precede and conduce to the development of astherosclerosis[2] in HD patients and, together with the microcirculatory disturbance known to develop in association with increased blood viscosity,[4,5] could result in chronic retinal ischaemia. Erythrocyte abnormalities described in CRF patients seem to be particularly relevant in this context. In a review by Caimi,[6] alteration in erythrocytes' membrane properties, due to oxidative stress, was suggested to lead to their increased aggregability and reduced deformability and to explain their reduced survival that, in addition to reduced erythropoietin synthesis by the impaired kidneys, causes anaemia. Although anaemia may counterbalance the hyperviscosity in these patients, it indeed increases the ischaemic brunt on the retina.

Second, the questions that follow from the interesting findings of this study are whether we will need to keep these patients under review to detect these early deficits in retinal function and whether it will be necessary to treat them upon detection of such signs. Noninvasive functional assessment by visual field testing or alternatively electrophysiological tests, as suggested in the study, would be appropriate and would serve the first purpose. Since hyperviscosity-induced changes in retinal and choroidal circulation were proved to reverse,[7] one can only speculate that they could at least be partially reversed or slowed down with early treatment in HD patients. Maintaining good control of these patients' blood pressure, plasma cholesterol level and correction of anemia can certainly be paramount in that regard. Dipyridamole (Persantin) would be an additional therapeutic option that could improve the microcirculatory function through improving erythrocyte deformability.[8] Notably, giving aspirin to these patients could potentially be hazardous because of their increased tendency for bleeding due to platelet dysfunction. However, considering that there is no evidence thus far that any treatment will have any beneficial effect on retinal function, the decision to investigate or to treat, I believe, will remain up to the clinician's discretion.

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