Patients with Persistent Pain after Enucleation Studied by MRI Dynamic Color Mapping and Histopathology

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Purpose. To study possible causes of persistent pain in patients who underwent enucleation of the globe and in whom all other noninvasively detectable causes of pain had been ruled out.

Methods. Twenty patients were studied, 10 with intractable pain (score >5 on a 0-to-9 self-reporting pain scale) persisting for more than 6 months after enucleation (for various reasons) and 10 without pain (score <4) at least 6 months after enucleation. Magnetic resonance imaging (MRI) with dynamic color mapping (MRI-DCM) was used to quantify the motion of the optic nerve in millimeters per degree of gaze, 2 to 3 mm behind the implant. Histopathologic study of biopsy specimens was used to verify imaging findings.

Results. The optic nerve was attached to the implant in almost all (19/20) patients. On average, the motion was significantly less in patients with persistent intractable pain (0.04 mm/deg) than in patients without pain (0.08 mm/deg; normal orbit, 0.13 mm/deg). A biopsy specimen was available in 5 of 10 patients with persistent pain, and in 4 of those 5, microscopic neuroma was found close to the optic nerve–implant junction.

Conclusions. In the enucleated orbit, the optic nerve is usually attached to the implant and soft tissue motion is decreased. In patients who have persistent pain after enucleation, motion is decreased even more, and a high percentage of microscopic amputation neuromas are found. Increased stiffness of orbital soft tissue and optic nerve attachment after enucleation are detectable using MRI-DCM, and may play a role in susceptible patients in the development of microscopic amputation neuroma and pain. (*Invest Ophthalmol Vis Sci.* 2001;42: 2188–2192)

The main indications for removal of an eye are intraocular tumors, persistent ocular pain, and cosmesis. Enucleation is usually effective in resolving pain,[1,2] but, in rare cases, pain may persist.[3–5] The following causes of persistent pain after enucleation (or anophthalmic socket pain) are detectable by noninvasive means: nonoptimal fit of prosthesis, migration of the implant, lacrimal insufficiency, inflammatory conditions, space-occupying lesions, and psychiatric disorders.[5] However, another cause, painful microscopic amputation neuroma, is only diagnosable by removal of the implant and adherent tissues and subsequent histologic analysis.[5] Neuromas are thought to be the result of tractional or compression forces on the nerve, which are also thought to cause increased stiffness of the nerves and surrounding tissues.[6–8] The motion of soft tissues in the enucleated orbit can be assessed by a variety of means.[9] It can be measured noninvasively and objectively by magnetic resonance imaging with dynamic color mapping (MRI-DCM), consisting of fast cinematic MRI and optical flow motion analysis.[10,11] The purpose of this study was to determine possible causes of persistent pain in patients who underwent enucleation of the globe and in whom all the noninvasively detectable causes just listed had been ruled out.

Methods

The study involved an observational case–control design with 20 subjects: 10 patients with intractable persistent pain and 10 who served as control subjects. Patient data are summarized in Table 1. Patients were included in the pain group if they had undergone enucleation at least 6 months before inclusion, persistent pain had been present for at least 6 months, and detectable causes of pain according to the criteria put forward by Glatt et al.[5] had been excluded. The pain was scored during an interview on a 0-to-9 pain-scoring scale (see Table 2). Patients were included only if they scored 6 or more on this scale. Control patients were selected for the no-pain group by random selection from the outpatient clinic records of our hospital (a tertiary care center). Patients were included as control subjects if they had undergone enucleation at least 6 months before inclusion and scored 3 or less on the pain-scoring scale. In addition to these criteria, all subjects had to be more than 18 years of age and eligible for MRI-DCM examination.[10] All subjects were treated in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained after the nature of the study had been explained. The approval of the institutional review board of our hospital was obtained for the research protocol and the informed consent form.

MRI-DCM was performed according to a protocol published previously.[10,11] Transverse sequences of gradient-echo T_1-weighted images are acquired while the patient sequentially fixates on a row of nine horizontal marks placed at 8° intervals on the inside of the scanner bore. The motion in these sequences is estimated by first-order optical flow computation of motion estimates. All motion vectors are converted (from pixels per frame) to ratios of millimeters per degree change in gaze. The conversion from pixels to millimeters is performed by the MR scanner software, and the motion is converted from millimeters per frame (of 8° each) to millimeters per degree by division. The error of the motion measurement (direction and magnitude combined) was found to be less than 15%, and the error in magnitude by itself less than 8% in validation studies.[11] An experimental version of the DCM and optical flow software is available at no charge from The Image Sciences Institute, Utrecht, The Netherlands, at www.isi.uu.nl/people/michael/index.htm (please observe copyright and disclaimer requirements).

The magnitude of the motion of the optic nerve 2 to 4 mm behind the implant was used as an indicator of soft tissue motion and recorded

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Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida, May 1997.

Submitted for publication February 12, 2001; revised May 2, 2001; accepted May 15, 2001.

Commercial relationships policy: N.

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Investigative Ophthalmology & Visual Science, September 2001, Vol. 42, No. 10

TABLE 1. Data of No Pain and Pain Groups

Patient	Age	Gender	Reason for Enucleation	Painful Atrophy	Type of Implant	Years Since Enucleation	Pain Score	Optic Nerve Motion (mm/deg)	Biopsy Specimen	Microscopic Neuroma
No pain										
1	59	F	Melanoma	N	Baseball	5	0	0.03		
2	86	M	Melanoma	N	Baseball	6	0	0.15		
3	93	F	Melanoma	N	Baseball	5	0	0.06		
4	43	M	Painful atrophy (detachment)	Y	Baseball	5	0	0.14		
5	65	F	Tumor	N	Baseball	35	0	0.11		
6	59	M	Painful atrophy (dislocated lens)	Y	Allen	35	1	0.05		
7	66	M	Trauma	N	Baseball	32	1	0.09		
8	38	F	Painful atrophy (endophthalmitis)	Y	Baseball	33	1	0.08		
9	93	F	Melanoma	N	Allen	22	1	0.03		
10	25	M	Painful atrophy (detachment)	Y	Baseball	7	2	0.06		
Pain										
11	57	M	Painful atrophy (glaucoma)	Y	Allen	11	8	0.04	Y	N
12	50	F	Melanoma	N	Allen	1	7	0.06	N	
13	46	F	Painful atrophy (keratoplasty)	Y	Baseball	6	8	0.01	Y	Y
14	52	F	Trauma	N	Baseball	18	8	0.04	N	
15	52	F	Painful atrophy (detachment)	Y	Baseball	8	6	0.01	Y	Y
16	22	M	Painful atrophy (detachment)	Y	Baseball	5	8	0.03	Y	Y
17	47	M	Trauma	N	Baseball	5	7	0.03	N	
18	30	F	Painful atrophy (endophthalmitis)	Y	Baseball	20	9	0.05	Y	Y
19	23	F	Trauma	N	Allen	1	8	0.04	N	
20	56	M	Melanoma	N	Allen	8	7	0.08	N	

in millimeters per degree. The motion of the outside of the implant, next to the stump of the optic nerve, was also recorded in millimeters per degree. Normal motion of the contralateral healthy eye was verified by checking the motion of the lens of that eye. To determine the attachment of the optic nerve to the implant, the orientation of the motion of the optic nerve and of the implant during left and right gaze were compared. If the orientation of the motion of these structures differed from each other less than 45°, the optic nerve was recorded as attached to the implant; otherwise, the optic nerve was recorded as not attached. With rigid attachment, the motion of the optic nerve and the implant are expected to be exactly the same (in other words, the difference should not be larger than 0°). The 45° limit was chosen

TABLE 2. English Version of the Anophthalmic Socket Pain Scoring Scale Developed for This Study

Score	Examples
0	No pain
1	Occasional tenderness (less than once weekly)
2	Occasional stab of pain (less than once weekly)
3	Frequent tenderness (less than once a day)
4	Frequent stabs of pain (less than once a day)
5	Pain occasionally distracting (more than once a day)
6	Pain frequently distracting, but work and relaxation are possible
7	Always in pain, occasionally disturbs sleep
8	Pain frequently disturbs sleep
9	Pain makes concentrating on any task difficult

In using this scale, the use of nonopiate analgesics is disregarded.

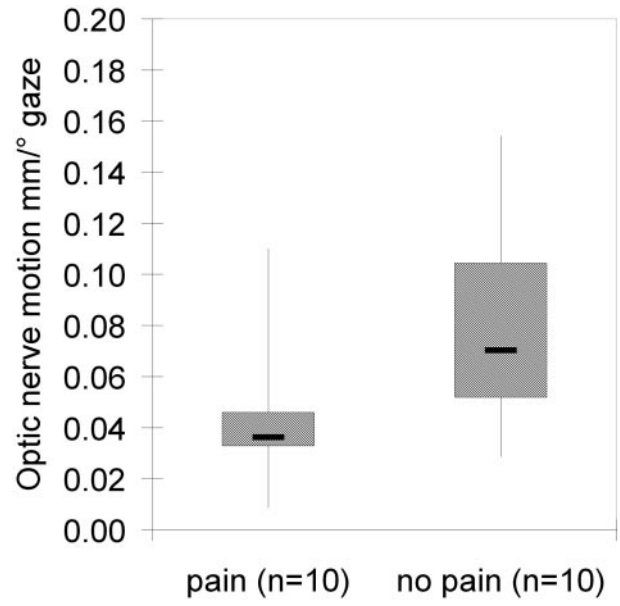

FIGURE 1. Optic nerve motion in patients with and without persistent intractable pain after enucleation. The lower and upper edges of the *box* indicate the lower and upper quartiles of the motion (in millimeters per degree) in the groups. The extent of the lower and upper *whiskers* indicate the minimum and maximum motion. The *line* within the box indicates the mean motion.

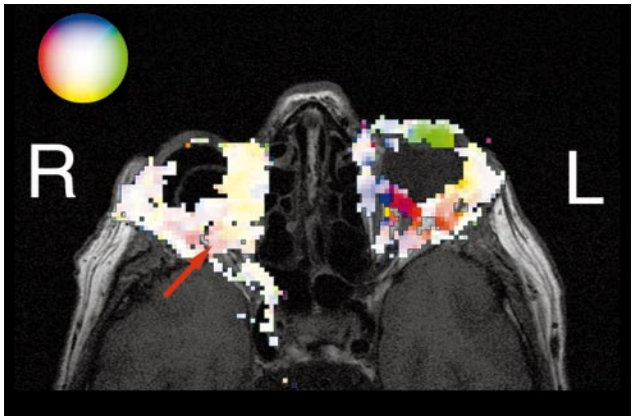

FIGURE 2. Visualization of soft tissue motion in patient 15 (*pain* group). Baseball implant in the right orbit, with patient gazing to his left. The optic nerve and surrounding tissues in the enucleated orbit moved less than the normal tissues in the normal orbit (more saturated colors). The back of the implant moved less than the optic nerve, and the optic nerves and the other soft tissues had motion of similar magnitude (similar saturation). The motion of the optic nerve was coupled to that of the back of the implant. The index in the *upper left* of the figure helps in understanding the orientation and magnitude of motion in relation to a color (saturated *green* is fast to the left, i.e., to the *right* in the figure; *pale yellow* is slow posteriorly). *Red arrow:* position at which optic nerve motion was measured.

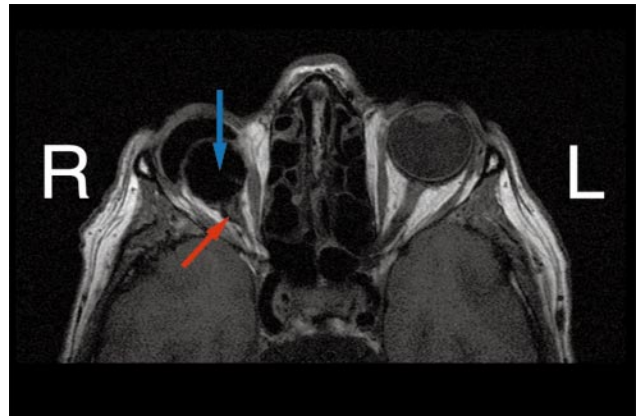

FIGURE 3. Static MRI for patient 15. *Blue arrow*: baseball implant attached to the optic nerve in the right orbit, with the prosthesis in front of it. *Red arrow*: junction of the optic nerve to the back of the sclera-covered implant.

before the study so that more loosely coupled attachments could also be diagnosed. Averages are presented as mean and 95% confidence interval. Patient data across groups were analyzed with Pearson's χ^2 test. Data were averaged for the pain and no-pain groups, and compared with the unpaired Student's *t*-test. For the significance test, a two-tailed $P < 0.01$ was used. Analysis was performed by computer (Excel 7.0; Microsoft Corp., Seattle, WA).

RESULTS

The mean age in the pain group was 43 ± 13.4 years (SD) and in the no-pain group, 63 ± 23.2 years. There was a significant difference in age ($P = 0.015$), partly because of biased patient selection. Of the 16 subjects originally eligible for inclusion in the no-pain group 3 could not be reached, and 3 refused participation (these usually stated that they would have had to take time off from their jobs for research of no benefit to themselves). The mean age of these 16 subjects was 57.1 years, not different from the mean age in the pain group ($P = 0.08$). There was no statistical difference in gender ($\chi^2 = 0.689$, $P = 0.41$) and side of surgery ($\chi^2 = 1.0$, $P = 0.32$) between the two groups. Reasons for enucleation varied, but there was no significant difference in the frequency of painful atrophy ($\chi^2 = 0.84$, $P = 0.36$). No patients reported an increase or a change in character of the pain on ocular motion, all subjects were cooperative and underwent MRI-DCM uneventfully, and all subjects were able to follow all gaze positions.

Optic nerve motion, motion of the implant, and attachment of the optic nerve to the implant are summarized in Table 1. The optic nerve was always attached to the implant in the pain group and in all except one patient in the no-pain group. In the

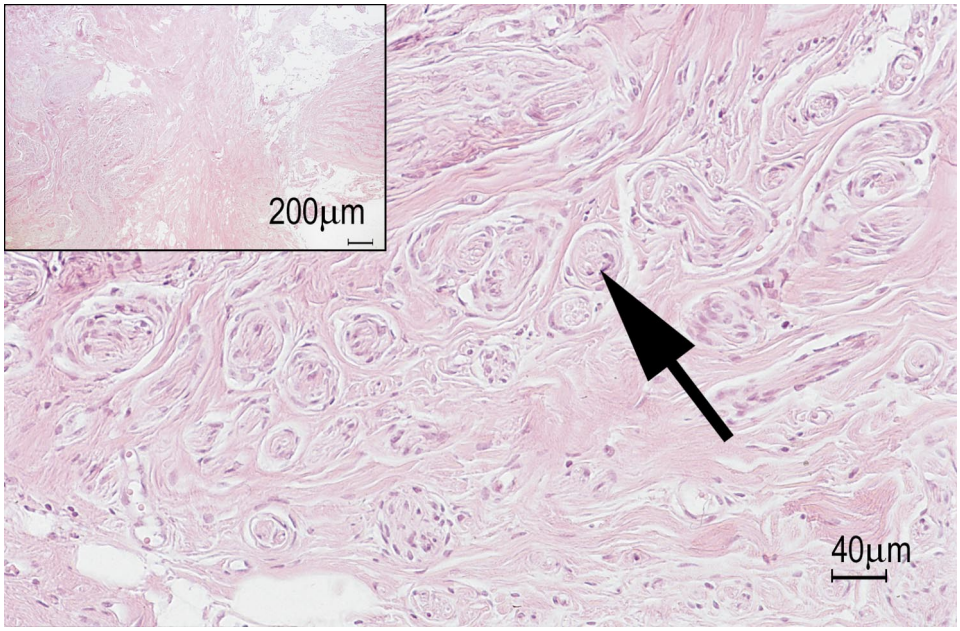

FIGURE 4. Biopsy specimen from patient 16 showing a microscopic amputation neuroma located close to the optic nerve–implant junction. *Black arrow*: small nerve fiber bundle. *Inset*: low-magnification overview with optic nerve stump on the *right* and fibrous tissue near its junction with the implant, showing an amputation neuroma on the *left*. Hematoxylin-eosin stain; magnification, 40 µm; *inset*, 200 µm.

normal contralateral eye, all subjects had normal gaze motion (average, 0.13 mm/deg; 95% confidence interval [CI] 0.122–0.148 mm/deg) and could fixate all marks. Figure 1 shows the mean and upper and lower quartiles of the motion in the pain and no-pain groups. The frequency distributions of the motion in both groups approximately followed a normal distribution. The average optic nerve motion was decreased ($P < 0.01$) in the pain group (average 0.04 mm/deg; 95% CI 0.026–0.050 mm/deg) in comparison with the no-pain group (0.08 mm/deg; 95% CI 0.053–0.108 mm/deg). This difference in soft tissue motion between groups could be entirely attributed to the difference between patients with baseball-type implants, with and without pain, as shown by segregation of the groups according to implant type. Between patients with baseball implants ($n = 14$) with and without pain there was a significant average difference of 0.06 mm/deg ($P = 0.005$), whereas between patients with Allen implants ($n = 6$) there was no difference ($P = 0.41$). There was no correlation of the soft tissue motion with age in either the no-pain or pain groups. Figure 2 shows a visualization of soft tissue motion in the enucleated orbit in patient 15 from the pain group. Figure 3 shows the anatomy and the attachment of the optic nerve to the implant for this patient in more detail.

In 5 of 10 patients in the pain group, a biopsy specimen of tissue around the optic nerve–implant junction was obtained through a transconjunctival incision. The other five patients refused a biopsy for a variety of reasons. In four (80%) of the former five patients, one or more amputation neuromas were present in the biopsy specimen. In one patient, the only one of this group with an Allen implant, no neuromas were found. The neuromas were always located close to the junction of the optic nerve with the implant, either along the nerve or along the anterior part of an extraocular muscle. Figure 4 shows a histologic section with an amputation neuroma from patient 16. After the biopsy, three of the four patients with a neuroma showed resolution of pain (defined as a pain score of 3 or less, 6 months after biopsy).

Discussion

The results of this study indicate that, in the enucleated orbit, tissue motion is decreased in comparison with tissue motion in the normal orbit; the optic nerve stump is usually (19/20) attached to the implant; tissue motion is decreased even more in patients with persistent intractable pain (i.e., those in whom all noninvasively detectable causes of pain have been excluded), compared with patients who have undergone enucleation without subsequent pain, and this decrease is present only in patients with baseball implants; and amputation neuromas can often be found near the optic nerve–implant junction in these patients.

Possible sources of bias in this study may include the higher average age in the no-pain group than in the pain group. However, we found no correlation between tissue motion and age in our patients, and to our knowledge, there is no evidence in the literature for such an age-dependent effect. Another possible source of bias is potential inaccuracy in the optical flow motion estimation technique, but the optical flow algorithm has been shown to occasionally underestimate (but not overestimate) larger motion magnitudes in validation studies.[11] Motion in the enucleated socket may have been less because of the pain; however, motion in the contralateral healthy orbit was normal. The number of patients (five) in which a biopsy sample was available was too small to establish a relationship between decreased motion and presence or absence of painful microscopic neuroma. It is possible that, in most of the other patients with pain, no neuromas would have been found. Although neuromas often cause pain, especially if subject to pressure and/or motion, this is not always the case. It is possible that in patients without pain, neuromas are also present in the enucleated orbit.[8] However, the fact that three of four patients had resolution of pain suggests a causal relationship.

To our knowledge, this is the largest study of patients with persistent intractable pain after enucleation and the first to look at the role of tissue motion in the enucleated orbit. The decrease in motion in patients with persistent pain who have baseball implants may be related to tight attachments of the optic nerve to the intraconal fatty tissue or higher stiffness of the orbital contents due to fibrosis caused by the surgery. In combination with the movement of the optic nerve during gaze due to the nerve's attachment to the implant, this tightness or stiffness may subject the intraorbital nerves to increased, continuously changing pressure and traction and decreased motion. All these are favorable conditions for the development of painful amputation neuroma.[8] This mechanism may be the reason such a large proportion of the patients who had persistent intractable pain had microscopic amputation neuromas. In these patients, by definition, no macroscopic neuromas were present, and the neuromas that were found histologically were very small and thus would have easily escaped detection on MRI or computed tomography.

In conclusion, this study shows that MRI-DCM may be of use in the evaluation of persistent intractable pain after enucleation. This procedure is capable of showing that tissue motion is decreased in the enucleated orbit in comparison with the normal orbit, and that the optic nerve is usually attached to the implant. Of course, its sensitivity and specificity in diagnosing this condition remain to be established. Other methods, such as semiautomatic measurement from two- and three-position MRI, are just as capable of measuring the globe–optic nerve motion as the optical flow method used in MRI-DCM.[12] Globe–optic nerve motion was selected as a reproducible indicator of intraconal soft tissue motion. MRI-DCM is capable of measuring the motion of any orbital tissue, and we could also have chosen to measure any other region in the soft tissue, which is much more difficult with semiautomatic motion measurement from two- and three-position MRI.

In patients with persistent pain, motion is decreased even more, and in these patients, a high percentage of amputation neuromas are found close to the implant. Increased stiffness of orbital soft tissue and optic nerve attachment after enucleation are detectable using MRI-DCM. These circumstances and the consequent continuously changing pressure and motion in the enucleated orbit may play a role in some patients in the development of painful microscopic amputation neuroma and persistent intractable pain. Further study in a larger group is needed to verify these findings, and a postmortem study may be useful to evaluate enucleated orbits. Further study may also reveal what steps, if any, can be taken to ensure the removal of all amputation neuromas from the orbit to effect an improvement in the pain these patients experience.

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