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Why Visual Function Does Not Correlate With Optic Glioma Size or Growth

It has long been known that little correlation exists between visual function and tumor size with respect to optic gliomas (World Health Organization grade I juvenile pilocytic astrocytomas).¹⁻³ Surprisingly, however, a deterioration in visual function in those harboring such masses is still often taken as clinical evidence of tumor progression and used to justify intervention for lesions that otherwise may have failed to demonstrate any growth.⁴

An understanding of why deterioration of clinical function may not be a sign of tumor progression but could actually indicate glioma regression may help to better resist physician and family impulses to intervene.⁵

Optic gliomas are congenital in origin. Masses formed within the central nervous system in utero may influence the subsequent apoptosis of excess axons,⁶ in effect molding themselves in relative harmony with remaining axons to allow maximal visual function despite the presence of what may otherwise appear to be an impressive tumor. Nonetheless, following the final organization of visual pathways, subsequent growth could alter such an in utero-established arrangement. Optic gliomas are also intrinsic to the optic nerve. Thus, the hamartomatous overgrowth of glial cells with supporting tissue elements that normally surround each axon, should it occur in uniform fashion, may not necessarily impede axoplasmic flow and neuronal signaling. Neurons remain functional and viable with elevated pressures uniformly distributed.^{7,8} Pressure applied focally, on the other hand, particularly from tumors arising extrinsic to a nerve, can easily create pressure gradients that pinch axons and block axoplasmic flow, thus producing subsequent atrophy.⁸ As an analogy, just as a human can withstand high pressure evenly distributed, such as is generated by several tons of water when near the bottom of a swimming pool, it could nonetheless poorly tolerate even a fraction of such pressure were it to be applied focally, such as by an elephant resting its foot on a person's torso (Alfredo A. Sadun, MD, PhD, oral communication, February 2009).

Hence, some optic gliomas can be large congenitally or noted to continue to grow to great extents along considerable lengths of the visual axonal pathways without causing any perceptible loss of visual acuity or function.¹⁻³ Others much smaller but with less uniform growth may compress or kink axons focally, causing considerable visual morbidity.¹⁻³

It should then be of no surprise that an intrinsic lesion shrinking in nonuniform fashion could also give rise to inhomogeneities and pressure gradients causing kinking of axons and loss of function,^{3,8} just as an enlarging tumor might do. Such an apparently paradoxical worsening of vision is acknowledged during the medical treatment of prolactinomas. While external compression of the chiasm may produce an

initial visual field loss, following successful medical involution of the pituitary tumor, the chiasm itself may herniate into an enlarged and relatively empty sella. In some cases, this may result in traction and kinking of axons with renewed loss of function.⁹ Likewise, although the intracranial pressure diminishes following cerebrospinal fluid leaks, deterioration of visual function can also be expected when the brain, no longer buoyed by fluid, settles onto the skull base and compresses the chiasm with pressure points between the brain and pituitary fossa.¹⁰ Keeping such alternative processes in mind, one can comprehend the futility of using functional testing such as visual evoked potentials to monitor the progression of optic gliomas.

To summarize, spontaneous regression of gliomas is not a rare occurrence and can be accompanied by loss of vision.³ Some medical practitioners misinterpret loss of function, either clinically or by means such as visual evoked potentials, as evidence of tumor progression. This can misguide them to initiate unproven treatment modalities for gliomas that are already beginning to shrink. They may subsequently attribute efficacy to a purported remedy for an eventually detected reduction of glioma size. Particularly when trying to assess the beneficial effects of future therapies in investigational trials, such errors should not be allowed to occur.

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Substance P Concentration in Human Amniotic Membrane

Amniotic membrane can act as a biological bandage contact lens to the ocular surface, with therapeutic anti-inflammatory properties. The analgesic benefits of this intervention are believed to be due to mechanical protection. Amniotic membrane is also used in the treatment of neurotrophic corneal disease. Substance P is a neurotransmitter released by C-terminal nerve endings. It mediates acute inflammation and is known to play a role in modulating pain sensation. Substance P is also known to promote proliferation of various cell types, including epithelial and nerve progenitor cells.^{1,2} In this in vitro pilot study, we investigated the relationship between amniotic membrane and substance P.

Methods. This study was approved to use surplus tissue from 6 previously harvested amniotic membranes. The original samples were washed, prepared, and stored using standard techniques to ensure no contamination from blood. Residual pieces were defrosted and washed 4 times in phosphate-buffered saline. Sections measuring 0.5 × 0.25 cm were used throughout. The tissue was sonicated for 1 minute in phosphate-buffered saline and 0.5% Triton X and spun in a Jouan microfuge for 10 minutes at 400 rpm. This was analyzed using a Parameter Substance P competitive enzyme immunoassay (R&D Systems).

Results. Substance P was present in amniotic membrane samples at a range between 4000 and 6000 pg/mL. (Samples were diluted 1:50 to enable analysis.) In comparison, substance P levels in independent saliva and serum samples from volunteers in the research team ranged between 8 and 200 pg/mL in saliva and between 1200 and 1300 pg/mL in serum. We were unable to demonstrate uptake of substance P following incubation with the saliva or serum by this method owing to the very high concentration of substance P in amniotic membrane.

Comment. This pilot study demonstrates that substance P is present in very high concentrations in amniotic membrane. This exceeded the concentrations in our control sources of serum or saliva and was found despite several months of storage. Substance P has been identified in amniotic fluid in mid to late gestation.³ Further investigation would be required to elucidate whether this is the source of amniotic membrane's substance P. Urine is known to be a rich source of substance P, and fetal urine is produced from 12 weeks after conception. We wonder whether protective absorption of substance P by amniotic