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Gilles Lecture: Ocular Motility in a Time of Paradigm Shift

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Abstract

Recent progress in understanding of the structure and function of extraocular muscles, and our ability to image them clinically, allows prediction of revolutionary progress in diagnosis and treatment of strabismus in the coming decades. This perspective memorializes a lecture given in honor of Dr. William Gilles, who has for decades been the paternal leader of strabismology in southern Australia.

Keywords

extra-ocular muscle; magnetic resonance imaging; pulley; strabismus

Introduction

The noted philosopher of science, Thomas Kuhn, has lucidly described how all science is conducted within frameworks called "paradigms(1)." Paradigms provide the means for thinking logically about problems, and for determining what sorts of information might or might not constitute evidence for the resolution of scientific controversies. Although it has perhaps not been explicit, ocular motility and strabismus have developed in the last centuries within a paradigm that no longer may be the most appropriate one for further progress within the field. I hope that in my earlier lectures at the Australia and New Zealand Squint Club I have been able to present a number of observations and arguments that a more specific and mechanistic paradigm for understanding the actions of extraocular muscles (EOMs) can be clinically advantageous(2,3). The future of the field of ocular motility and strabismus is likely to be influenced strongly by this paradigm shift. In describing it, is as also an opportunity to honor Dr. William Gilles for his leadership in Australian and international strabismology.

Fundamental Anatomical Discovery

New technologies, such as magnetic resonance imaging (MRI), have produced reliable observations that are inconsistent with the fundamental underpinning of the traditional theory of EOM action. For instance, Miller has reviewed the prevailing belief that EOMs follow the shortest path over the globe from their origins in the annulus of Zinn to their scleral insertion points(4). The shortest, or "great circle," path would require that rectus EOMs side slip over the globe in gaze positions transverse to their paths. Thus, in upward gaze the medial (MR) and lateral rectus (LR) muscles would slide slip superiorly, and in lateral gaze the vertical rectus muscles would side slip laterally. The geometrically expected effect is large, both on the position of the rectus EOMs relative to the globe, and on their pulling directions. Numerous

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MRI studies indicate that this side slip simply does not occur(4–7). Instead, rectus EOM paths can be demonstrated by MRI to be fixed in the orbit, rather than freely slipping over the globe.

The reason that EOMs are stabilized in this manner relative to the orbit is that they pass through structures known as the rectus "pulleys of Miller." The pulleys of Miller function as effective mechanical origins of the rectus EOMs, and cause their paths to change systematically with gaze.

Prior Beliefs Incorrect

Many implicit or explicit beliefs about the EOMs are now known to be fundamentally incorrect. As practitioners of ocular motility and strabismus, we presumed, for example, that EOM anatomy is basically the same in all patients. We presumed that EOM insertions determine essentially everything important about EOM pulling direction, which we presumed could always can be predicted based on the name of the EOM in question. Thus we believed that the "lateral rectus muscle" always moved the eye laterally into abduction, without any serious likelihood of other actions). We believed that the only mechanically important features of EOMs are their strength and "tightness." We incorrectly believed that everything important about ocular motility can be learned by a good clinical motility examination, including alignment measurements in diagnostic gaze positions. We also believed, perhaps self-servingly, that bad post-surgical alignment results following EOM surgery were the fault of the patient rather than the fault of the diagnostician or the surgeon.

New Fundamentals

Recognition of the existence of the pulleys of Miller fundamentally changes many beliefs about ocular motility. Since the pulleys constitute the functional origins of the EOMs, we cannot escape the implication that pulleys are strong determinants of EOM function. Every rectus EOM can have horizontal, vertical, and torsional actions that depend on the location and behavior of that EOM's pulley(3). Normal rectus pulleys move dynamically under the influence of the oblique EOMs(3,8–11). Pulleys, and not the brain, control some important aspects of ocular motility, such as ocular torsion. Pulleys can have very different properties in different patients. The internal complexity of the eye socket and its connective and muscular tissues makes it intrinsically impossible to resolve ambiguities concerning mechanisms by clinical examination alone in many cases. Additional functional anatomic information is required. All of this has important clinical indications because it is now recognized that diseases of the pulleys can be causes of strabismus, and that we can operate on the pulleys to correct strabismus.

Nosology Influences Our Thinking

Nosology, the discipline of naming, can be fundamentally important in molding our thinking. It is important to recognize that many assumptions and erroneous concepts in the traditional paradigm of EOM actions are deeply imbedded in the traditional paradigm's nosology. Much of our current terminology strongly directs our thinking to an outmoded paradigm for understanding ocular motility(12). Traditional terms used for describing ocular versions are a good example. Traditionally we have used terms such as inferior oblique (IO) overaction and underaction, which imply mechanistic causes that really should better be described as overelevation in adduction and underelevation in adduction, respectively. The terms "superior oblique (SO) overaction" and "SO underaction" make potentially erroneous assumptions about the mechanisms of abnormal versions, which should better be termed descriptively as "overdepression in adduction" and "underdepression in adduction," respectively.

Predictions

With these concepts in mind, one can, with some trepidation, make the following sorts of predictions about how the field of ocular motility is likely to evolve over the next decade. With openness to the new paradigm, strabismologists will begin to think about common clinical entities in novel ways.

Magnetic resonance imaging of the EOMs and orbits has now been refined to the level of near microscopic resolution. This means that strabismologists will no longer have to speculate about structural and neurologic lesions affecting the EOMs, but will have the opportunity to directly verify their presence or absence, and possible internal lesions. High resolution MRI techniques are now available clinically in some centers, and this availability is likely to become widespread within the next decade.

Application of these techniques to even normal anatomy has led to the discovery of the pulleys of Miller, and is likely to result in additional fundamental gross anatomic discoveries concerning the EOMs. One example is Duane retraction syndrome, where the previously presumed misinnervation of the LR by a branch of the oculomotor nerve can now be demonstrated where it is present. Furthermore, a common finding in Duane's syndrome is a double-headed LR muscle whose superior and inferior divisions of the global layer are typically separated and act at scleral insertion points separated by several mm vertically(13). What might this mean to the LR's action on the globe? If a double headed LR is limited only to Duane's syndrome, it probably does not have broad biologic significance. However, there is evidence that segregation of the LR into superior and inferior divisions occurs even in normal people (14). If this is the case, differences in tension between the superior and inferior bellies of the LR could produce appreciable vertical and torsional effects not heretofore considered. This possibility may or may not turn out to be correct. However, strabismologists should be open to the possibility that individual EOMs may be capable of actions not previously believed possible.

Extraocular muscles have numerous fiber types(15), and contain a plethora of variations in biological characteristics(16). It is inconceivable that such a diverse repertoire of biological features would be maintained throughout evolution and across species if it served no purpose. Each EOM has two layers" the orbital layer (OL) and the global layer (GL). Differing mechanical loads on the OL and GL are associated with corresponding structural, vascular, genomic, and metabolic specializations. Within individual humans, GLs of each of the four rectus EOMs contain similar numbers of fibers, in the range of 8,000 – 16,000. This similarity is appropriate, since all rectus GLs act to rotate the same essentially symmetrical load, the globe. The number of OL fibers varies more widely within individuals in the range of 7,000 – 14,000, in rough proportion to the amount of connective tissue suspending each pulley(17). Most fibers in the OL are fast, twitch-generating, singly-innervated fibers (SIFs), while the others are multiply-innervated fibers (MIFs) that either do not conduct action potentials, or do so only in their central portions(15). Orbital SIFs are specialized for intense oxidative metabolism and fatigue resistance(15). Vascular supply in the OL so greatly exceeds that in the GL that intravenous MRI contrast can be seen to perfuse the OL first(18). The high metabolism, fatigue-resistance, and generous blood supply of the numerous OL SIFs are suited to their continuous elastic loading by the pulley suspensions. Expression of unique myosin isoforms in OL SIFs may also be related to the requirements of fast twitch capability against continuous loading, since alterations in EOM activity patterns can change EOM-specific myosin heavy chain gene expression(19). About 90% of GL fibers are fast, twitch-generating SIFs, while 10% are slow, non-twitch MIFs having a broad range of fatigue resistance(15). The motor nerve arborization for the OL is distinct from that of the GL for all four human rectus EOMs(14).

In the next decades, I predict that at least some of this complexity of EOM structure and function will become understood, and that this complexity may help us to understand the diagnosis and treatment of strabismus.

Threshold of The Molecular Era

The field of ocular motility stands at the threshold of the molecular era in therapy. Already, knowledge of the biology of angiogenesis is being exploited to treat retinal vascular diseases. Skeletal muscles generally, and EOMs in particular, are exquisitely responsive to their mechanical loads and patterns of innervation. Growth factors can already be applied to strengthen the EOMs of experimental animals(20). In the next decade or two, it is likely that the molecular switches that implement these changes will become understood, giving us the opportunities to manipulate the size and contractile properties of EOMs in beneficial ways. This opens the doorway to therapies that strengthen EOMs, rather than merely repositioning or weakening them.

Future Clinical Use of Imaging

The new capabilities of MRI will in the next decades be able to directly demonstrate neuropathies of EOMs. It is now routinely possible to demonstrate the motor nerve entries into EOMs(13,21). Magnetic resonance imaging in multiple gaze positions routinely demonstrates the size, paths and contractile states of EOMs(22–24). In the next decade, such multipositional imaging of the orbits will be routine preoperative evaluation tools in the management of complex strabismus.

Extraocular muscle imaging seems clinically useful, and can provide unique functional anatomical information that can be clinically useful to guide treatment(22,23). Imaging should, and will, increasingly be performed in appropriate clinical situations. Through an embrace of preoperative imaging, strabismologists will eventually catch up with other surgical specialties in the use of preoperative imaging.

Cutting The Gordian Knot of Superior Oblique Palsy

No cranial neuropathy could be more prototypic than SO palsy as a cause for cyclovertical strabismus. Nevertheless, a recent basic re-examination of SO function and the consequences of SO palsy illustrates that our clinical understanding of this entity are thoroughly snarled and may be fundamentally incorrect. Theoretical, experimental, and much clinical evidence support the idea that acute, unilateral SO palsy produces a small ipsilateral hypertropia that increases with contralateral gaze, and with head tilt to the ipsilateral shoulder(25,26). The basis of this “3-step test” is traditionally believed related to ocular counter-rolling, so that the eye ipsilateral to head tilt is normally intorted by the SO and superior rectus (SR) muscles whose vertical actions cancel(27). However, ipsilateral to a palsied SO, unopposed SR elevating action is supposed to create hypertropia. The 3-step test has been the cornerstone of diagnosis and classification cyclovertical strabismus for generations of clinicians(28,29). Much evidence, however, indicate that the 3-step test’s mechanism is misunderstood. Kushner has pointed out that were traditional teaching true, then inferior oblique (IO) weakening, the most common surgery for SO palsy, should increase the head tilt-dependent change in hypertropia; the opposite is observed(30). Among numerous inconsistencies with common clinical observations(30), bilateral should cause greater head tilt-dependent change in hypertropia than unilateral SO palsy; however, the opposite is found(31). Modeling and simulation of putative effects head tilt in SO palsy suggest that SO weakness alone cannot account for typical 3-step test findings(32,33).

Multiple conditions can simulate the “SO palsy” pattern of incomitant hypertropia(34). Vestibular lesions produce head-tilt dependent hypertropia, also known as skew deviation (35) that can mimic SO palsy by the 3-step test(36). Pulley heterotopy can simulate SO palsy (37), and is probably not its result, since SO atrophy is not associated with significant alterations in pulley position in central gaze(38). Although the 3-step test has long been a lynchpin of clinical strabismology, neither the test’s mechanism nor implications for EOM pathology are understood.

High-resolution MRI has quantified normal changes in SO cross section with vertical gaze, and SO atrophy and loss of gaze-related contractility typical of SO palsy(39–42). Neurosurgical SO denervation rapidly produces neurogenic atrophy and ablates contractile thickening normally observed in infraduction. A striking and consistent MRI finding has been non-specificity of the 3-step test for structural abnormalities of the SO belly, tendon, and trochlea, found in only in ~50% of patients(43). Even in patients selected because MRI demonstrated profound SO atrophy, there was no correlation between clinical motility and IO size or contractility(42). Pathology of the pulleys of Miller may produce patterns of strabismus that mimic what has classically been considered to be that of SO palsy. On the other hand, denervation atrophy of palsy of the SO muscles is strikingly evident in MRI of the orbits, which also demonstrates in such cases the ablation of the normal contractile thickening of the SO belly in infraduction. It is predicted that the gold standard for the diagnosis of SO palsy will ultimately be a radiographic one, the demonstration of reduced SO size and contractility on an imaging study.

Additional Concepts of Extraocular Muscle and Nerve Pathophysiology

The classic differential diagnosis for a malfunctioning EOM has included essentially four entities: (1) weak; (2) overacting; (3) tight; and (4) misinnervated. To this list the new paradigm should add the following: (1) heterotopy of a pulley of Miller; (2) instability of a pulley of Miller; (3) hindrance to normal motion of a pulley of Miller; and (4) segmental anomaly of an EOM.

It has clinically been common to diagnose cranial motor neuropathies of the oculomotor system based on clinical motility findings. While in cases such as abducens palsy this seems to be a reliable technique unlikely to be replaced by anything better, longstanding and complex cases such as partial oculomotor palsy will in the future be better confirmed by direct radiographic evaluation of the oculomotor nerve and its pathway to its target EOM. In congenital disorders of the oculomotor nerve, it is already possible to make this diagnosis, and it has provided additional clarity as to the mechanisms of congenital oculomotor palsy in conditions such as congenital fibrosis of the EOMs(44). Congenital fibrosis of the EOMs is now no longer believed to be a myopathy, but is believed to be a primary motor neuropathy of the oculomotor nerve(45,46).

Novel Surgical Techniques

Recognition of the existence of the pulleys of Miller and the oblique EOM pulleys affords numerous opportunities for additional differential diagnoses, and additional surgical techniques. It is predicted that these techniques will make it possible to correct strabismus without so much resort to recession, resection, and other surgery aimed at the insertion point between rectus tendons and sclera. It is already possibly to surgically treat accommodative esotropia with excessive accommodative convergence by MR pulley surgery that does not require any tendon disinsertion or scleral suturing(47,48). An increase in our repertoire of surgical options should result in better surgical outcomes more appropriately tailored to individual patients.

Computational Modeling and Simulation

Over the past 30 years, many efforts have been made to apply computer modeling and simulation to the diagnosis and treatment of strabismus(49). As computers became faster and more capable, it became evident that computational speed was not the limiting factor in the utility of such computer models in strabismus. Rather, the limiting factor was our understanding of the structure and function of EOMs(3). As the orbital connective tissue system and the existence of the pulleys of Miller have been better clarified, we will have the opportunity to develop accurate and clinically useful computational models for the diagnosis and treatment of strabismus.

Conclusion

Prediction is always a hazardous endeavor, particularly when it involves the future. Nevertheless, many of the foregoing predictions seem like safe wagers. The field of ocular motility and strabismus is in a time of revolutionary paradigm shift. Understanding of the new functional anatomic paradigm of EOMs should empower ocular motility specialists with new and useful ways of analyzing complex problems in ocular motility, and in solving these problems surgically. Specialists in the field should be open to the concept that the anatomy and physiology learned in school is at best incomplete, and in many respects are fundamentally incorrect. We should be on the lookout for large improvements in fundamental knowledge that will benefit patients with strabismus.

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