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Retinoblastoma: Clinical Presentation and the Role of Neuroimaging

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“He Was Never Quite ‘Himself’ after that Accident”: Exploring the Long-term Consequences of Mild Traumatic Brain Injury

Patients seek medical care after traumatic brain injury (TBI) roughly 2 million times per year in the United States. Eighty percent of these injuries can be classified as “mild”. The real incidence of TBI is, however, unknown, because victims of mild TBI often do not see a physician. Having your “bell rung” or “seeing stars” is an experience that a high percentage of us could talk about from personal experience. During athletics, these are injuries that fall into the “shake it off” category. In this issue, Hofman et al (page 441) report their study of victims of mild TBI, which used MR imaging, single-photon emission CT (SPECT), and formal neurocognitive testing. Seventy-seven percent of these patients had abnormalities seen on MR or SPECT studies or both. The question is: can you “shake off” such abnormalities manifested by brain imaging and physiological changes?

One would think that we should know the answer to this question, but there is little science to support an adequate response. What we do know about the clinical consequences of mild TBI is that a poorly defined subset of patients will have persistent symptoms that often are referred to as the “postconcussive syndrome”. In some cases, headaches, difficulties with memory or concentration, and behavioral changes can be quite debilitating. We also know that for people who carry the apolipoprotein-e4 allele, mild TBI is a risk factor for the development of Alzheimer disease (1). What are the implications of this when we learn that every high school football team in America averages almost two mild TBIs per season (2)? The annual national estimate of mild TBI among 10 high school sports (boys’ sports: baseball, basketball, football, soccer, wrestling; girls’ sports: basketball, field hockey, softball, soccer, volleyball) is 66,816 cases (2).

One difficulty with studying these patients is that they tend to “fall through the cracks” in clinical science. Head-injured patients are often cared for by neurosurgeons, because an early risk to these patients is the development of a delayed hematoma. Consequently, most studies of clinical management are focused on more severe TBI. Patients with mild TBI and few outward signs of injury often have difficulty finding an experienced physician interested in treating them after the risk of developing a delayed hematoma has passed. Therefore, those researchers who have an interest in mild TBI come from a wide range of backgrounds including psy-

chiatry, rehabilitation medicine, neurology, neuropsychology, neurosurgery, traumatology (general surgery), critical care (anesthesiology), and radiology. The result can be disjointed research efforts that are not well communicated to others studying the same problem. For example, neurosurgical research tends to document well the mechanism of injury and imaging findings, but long-term outcome information can be lacking. Alternatively, psychiatrists can have difficulty finding information on a patient’s mechanism of injury to correlate with poor outcomes.

The laboratory study of TBI has focused primarily on moderate and severe injuries. Only recently have studies been initiated that evaluate the effects of more mild injury. Provocative studies have shown ongoing cell death by apoptotic pathways in the days, weeks, and even months after experimental TBI. Do the abnormalities on MR and SPECT images that are seen in studies like Hofman et al’s signify the initiation of a long-term destructive process within the brains of these patients?

To study the effects of TBI better, we must define the disease process better. I believe that the treatment of cancer represents an appropriate analogy. Most of us learned about cancer as children by witnessing friends or family fighting this serious disease. To simplify the issue, adults taught us about cancer as a single disease. Most cancers share the attributes of causing pain and suffering, requiring aggressive treatment, and many types result in death. Few effective treatments for any cancer could have been discovered if the many different diseases that are called “cancer” were not defined as separate diseases. “Traumatic brain injury” must be viewed as a very nonspecific label for a group of pathophysiological events that share only their initiating event and require different treatments. TBI is many pathophysiological processes occurring at different times and in different patients. Some of the different mechanisms that contribute to damage in various models of TBI include: apoptotic cell death, calcium-mediated excitotoxicity, direct pressure from expanding hematomas, breakdown of the axonal cytoskeleton, cellular edema, mitochondrial dysfunction, and ischemia. In the study of a drug that prevents apoptotic cell death after TBI, efficacy cannot be demonstrated if many of the patients entered into the study do not have any apoptotic cell death. The analogy would be performing lung resections for cancer but not knowing if there was any tumor in the lung. Even if lung resections were ef-

fective for some patients, the study design could not answer the question.

MR imaging, spectroscopy, and other novel radiographic tests offer the power to provide data concerning both anatomic and biochemical changes in the brain after TBI noninvasively. I believe that radiologists working with other interested researchers will enable us to better classify TBI early after the injury, well within the therapeutic window for many types of secondary injury. This information will permit more appropriate evaluation of new treatment paradigms and improve our ability to provide important prognostic information to patients. Additionally, if we confirm that some mild TBI can have long-term cognitive consequences in certain people, the manner in which we permit our-

selves or our loved ones to be exposed to the risk of mild TBI could be altered significantly.

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Retinoblastoma: Clinical Presentation and the Role of Neuroimaging

Retinoblastoma is the most common intraocular tumor of childhood, but it remains a rare disease. Retinoblastoma occurs in one of 15,000 to 20,000 live births (1). Approximately 200 new cases a year are diagnosed in the United States. The disease presents in infancy or early childhood, with the majority of cases diagnosed before the age of 4 years (2). The disease rarely occurs in older children or in adulthood. Unilateral disease occurs in approximately two thirds of all patients, whereas bilateral retinoblastoma comprises approximately one third of the total (2).

The most frequent presenting sign of retinoblastoma is leukocoria, a white pupillary reflex. Other presentations include strabismus (crossed or deviating eyes), decreased vision (particularly in bilateral cases), appearance of inflammation, retinal detachment, glaucoma, hypopyon (tumor cells anterior to the iris), or ocular pain (3).

The genetics of retinoblastoma follow Knudson's two-hit hypothesis. Patients who have unilateral, unifocal disease have mutations at the retinoblastoma locus in both alleles within a single retinal cell. This is an unlikely event; therefore these tumors are unifocal and unilateral. In contrast, patients who harbor an underlying germline mutation develop tumors that are characteristically multifocal and bilateral. These patients carry a mutant Rb gene in every cell of their bodies. Loss of heterozygosity tends to occur in the tumors of patients with germline mutations, and the normal allele is preferentially lost (4-6). These patients with germline mutation are predisposed to midline brain tumors (primitive neuroectodermal tumors [PNETs]) and to the development of second nonocular tumors (7).

Unfortunately, the patient's phenotype at presentation does not always correlate with the underlying genetic predisposition. Twelve percent of patients with unilateral disease have underlying germline

mutations and are at risk to develop disease in the uninvolved eye (8). These patients are also prone to develop PNETs and second nonocular tumors, particularly sarcomas. When patients present with unilateral retinoblastoma, the tumor frequently fills 50% or more of the ocular volume; when the tumor is confluent, the ophthalmologist cannot determine whether it was unifocal or multifocal in origin.

Mosaicism exists in this disease as it does in other tumor suppressor syndromes such as neurofibromatosis. Mosaic carrier parents may not manifest the disease themselves, but may still transmit the mutation in a percentage of their gametes. Siblings of patients with retinoblastoma are therefore at risk to develop the disease and should be screened from birth (9).

Despite its low incidence, retinoblastoma has contributed greatly to our understanding of cancer. The retinoblastoma gene (Rb) was the first ocular disease gene to be cloned and also the first representative of a class of genes called tumor suppressors. These genes predispose individuals to neoplasia by their deletion. It is the function of the protein products of tumor suppressor genes to regulate cellular division. The retinoblastoma gene product exerts its regulatory role in the cell cycle at the G1 stop point. This stop allows repair of DNA to occur prior to replication. The under-phosphorylated form of the retinoblastoma gene product binds to numerous transcription factors and sequesters them, preventing transcription. Phosphorylation of the Rb gene is regulated by complex formation between cyclins and CDKs, an event that in turn is regulated by signals that extend from the outermost boundary of the cell. With the phosphorylation of the Rb gene product, transcription factors are synchronously available to exert their actions. An especially important binding partner of Rb is elongation factor (E2F). This transcription factor binds to consensus sequences across the genome to activate

transcription and to allow the cell to proceed through the cell cycle. In the absence of a normal retinoblastoma gene product, cells divide without a regulated G1 checkpoint. This results in replication of DNA without repair and a predisposition to the development of multiple neoplasias over a lifetime (10).

Children with retinoblastoma develop ocular cancers from birth into their sixth year of life. They also develop midline primitive neuroectodermal brain tumors at a rate of 7% to 11% of germline cases. By the teen years, these patients develop sarcomas, particularly within the orbital radiation treatment field, as well as outside that field. Throughout their lives, retinoblastoma patients have a predisposition to many cancers with a 59% 35-year mortality for patients with underlying germline mutation (2).

Retinoblastoma in its diffuse form is particularly difficult to diagnose. As Brissé et al (page 499) describe in this issue of *AJNR*, diffuse retinoblastoma may mimic Coats disease, an exudative retinopathy that can produce massive yellow white lipid deposits within the retina. Although infrequent, misdiagnoses of patients with retinoblastoma can occur, sometimes leading to unnecessary surgical procedures that have the potential to disseminate neoplastic cells. We have never performed a fine-needle aspiration biopsy in a patient with retinoblastoma, and we believe strongly that there is never an indication to perform an intraocular procedure in these children. Intraocular procedures can result in mortality from tumor dissemination in this patient population, and even transcorneal approaches are not without risk (11).

We agree with the authors that, because biopsy is precluded, indirect approaches are required to make an accurate diagnosis of retinoblastoma. We believe that each imaging technique contributes different information to the management of this disease.

When a child is referred to us with retinoblastoma, we first examine the child, while awake, in the office. This allows us to take a careful family history, looking for near relatives with retinoblastoma, tumor predisposition syndromes, or eye loss. We also attempt to narrow the differential diagnosis by exploring the child's medical history (episodes of pica are correlated with toxocara canis exposure, low birth weight with retinopathy of prematurity, etc.). We evaluate the child, while awake, to determine the visual potential of each eye. We then schedule an examination under anesthesia. At that examination, we perform indirect ophthalmoscopy, fundus photography, and A- and B-scan ocular sonography. We check corneal dimensions and the axial length of the eye, because persistent hyperplastic primary vitreous is associated with a foreshortened globe and is important in the differential diagnosis of retinoblastoma. We check intraocular pressure and evaluate the anterior segment of the eye. Neovascular glaucoma can be diagnosed by these means, and children with this diagnosis are

unlikely to retain vision over the long term. We draw blood for toxocara titers and other uveitis laboratory analyses if intraocular inflammation is high in the differential diagnosis. We look for hyperechoic flecks on B-scan sonography, as these represent intrinsic tumor calcification and make a diagnosis of retinoblastoma very likely. We occasionally see fine flecks of calcium by use of sonography, which cannot be depicted by CT scanning. We schedule CT under the same anesthesia to confirm the presence of intraocular calcification and to exclude extraocular disease. We use MR imaging selectively to exclude the presence of orbital or optic nerve disease at diagnosis and to follow patients with germline retinoblastoma for the development of PNETs.

If midline PNETs present symptomatically, they respond poorly to therapy. We attempt to determine this diagnosis prior to symptoms with routine MR neuroimaging on a 6-month basis for children at risk. We also routinely perform MR studies in children who have histopathologic risk factors for local disease recurrence on an enucleation specimen. Such risk factors include invasion of the optic nerve posterior to the lamina cribrosa (where the meninges insert on the optic nerve) or massive chorioidal invasion. If we see evidence of invasion of the optic nerve posterior to the lamina cribrosa, we also offer the patient 6 months of adjuvant chemotherapy with carboplatin, vincristine, and etoposide. We believe that patients who manifest tumor at the cut-end of the optic nerve are at great risk for systemic relapse, and we offer these patients aggressive chemotherapeutic regimens, including bone marrow transplantation, as well as orbital or whole-brain radiation therapy (4). These patients are followed up very closely with sequential MR neuroimaging to diagnose orbital or intracranial relapse.

In recent years, treating physicians have moved away from radiation as the primary treatment for retinoblastoma toward chemoreduction with laser hyperthermia and cryotherapy. These latter therapies seek to avoid problems associated with radiation in children, especially the development of mid-face hypoplasia, cataracts, and the much-increased rate of sarcomas within the radiation field. These newer treatment regimens, however, require increased vigilance on the part of the ophthalmologist and the radiologist, because tumors require aggressive local control in conjunction with chemotherapy to prevent relapse. Because chemotherapy combined with local treatment has the advantage of not being associated with cataract formation, the ophthalmologist is able to survey the retina serially by indirect ophthalmoscopy. This diagnostic approach demonstrates greater sensitivity and specificity than any imaging technique can provide (12). Despite the trend toward chemotherapy combined with local treatment, many children with retinoblastoma still require radiation therapy. These children develop cataracts, and visualization of the retina becomes limited. In these children, neuroimaging and

Table: Differential diagnosis of leukocoria

Coats disease
Persistent hyperplastic primary vitreous
Toxocariasis
Idiopathic vitritis
Retinopathy of prematurity
Rhegmatogenous retinal detachment
Cataract
Ocular coloboma
Retinal dysgenesis
Astrocytic hamartoma (tuberous sclerosis)

sonography are the only methods available to diagnose disease relapse. We use a combination of A- and B-scan sonography, thin-section CT scanning, and MR imaging using 3D fast spin-echo sequences to follow intraocular disease in patients with cataracts.

We congratulate Brissé et al on their excellent discussion of the diffuse form of retinoblastoma. This is an entity that can be easily misdiagnosed. Inappropriate intraocular procedures can result in disease dissemination. Retinoblastoma should always be considered in the differential diagnosis of any intraocular pathologic process in a child (Table). Frequently children with retinoblastoma have histories of ocular or periorbital trauma, and retinoblastoma can present with hyphema, hypopyon, or glaucoma. The children with less characteristic presentations are those who are most frequently misdiagnosed. No child who presents to an ophthalmologist with a limited view to the back of the eye should undergo an intraocular procedure without appropriate preoperative imaging. We believe that sonography, CT, and MR imaging have complementary and important roles in the management of childhood ocular disease. Because retinoblastoma has such a high mortality once neoplastic cells are no longer confined to the eye, the ophthalmol-

ogist and radiologist should always keep this disease in mind when considering the differential diagnosis of childhood eye disease (11).

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Reporting Lumbar Disk Abnormalities: At Last, Consensus!

Residents and fellows in musculoskeletal radiology or neuroradiology, who are trying to learn how to interpret imaging studies of the spine, are generally flabbergasted when they realize they will have to use a different terminology every time they review and report films with a different staff radiologist. They also find it somewhat weird that their mentors, whom they admire for their understanding of sophisticated MR physics, are incapable of explaining with a straight face how to differentiate a *broad-based protrusion* from an *asymmetrical bulge*. The answer to such annoying questions is likely to be: "Don't worry, this comes with experience!" Those who try to gain a better understanding of these concepts by browsing through text-

books or pulling out the relevant literature soon realize that no national or international consensus has ever been reached regarding comprehensive classification or standardized definitions of common lesions affecting intervertebral disks. A few schemes have been proposed by individuals, groups of authors, or nomenclature committees of professional associations, but none has been widely recognized as authoritative. This absence of consensus is greatly related to the multiple controversial aspects of disk abnormalities. Not only is there lack of general agreement regarding etiology, pathophysiology, validity of diagnostic procedures, clinical relevance of imaging findings, and, of course, treatment, but we are still uncertain about the bio-

mechanics and even the anatomy of the intervertebral disk, especially in relation to spinal ligaments and membranes.

When the American Society of Spine Radiology (ASSR) was created in 1993, its founding members recognized the pressing need to deal with the lack of nomenclature standardization. Seventeen members enthusiastically volunteered to be part of the first ASSR ad hoc Nomenclature Committee and, in response to a preliminary survey, sent back to the chairperson so many conflicting opinions that efficient deliberations to reach a consensus appeared hopeless. In 1997, a smaller but well-balanced committee was formed, consisting of seven neuroradiologists from six different countries, with distinctive cultural backgrounds, perspectives, training, and, of course, inevitable biases. Rather than trying to devise a new system starting from scratch, it was agreed to scrutinize, modify, and improve previous work of a committee of the North American Spine Society (NASS), chaired by David Fardon, an orthopedic spine surgeon with extensive expertise in nomenclature and coding issues. Dr. Fardon graciously accepted to collaborate with us in this revision process, and formed a parallel clinical committee, including orthopedic surgeons, neurosurgeons, musculoskeletal radiologists, and one neurologist.

All participants in this revision process agreed to adhere to the following seven principles: 1) scope restricted to intervertebral disks and adjacent vertebral bodies; 2) focus limited to *lumbar* disks, although some concepts could eventually be extrapolated to other spinal segments; 3) use of the English language; 4) usefulness for interpretation of all types of imaging studies, and suitability for clinicians of various medical or surgical subspecialties; 5) simplicity, with the least possible number of categories, so that substantial interobserver agreement could be achieved; 6) consistency with macroscopic pathoanatomy: the postmortem study would be the optimal standard of reference to establish the validity of the model; and 7) freedom from legal and socioeconomic considerations, which are likely to differ anyway from state to state or from country to country.

After 20 months of tedious deliberations, mostly via e-mail, a consensus was reached at the level of

the imaging and clinical task forces. The project then underwent an extensive revision process after being circulated to all ASSR members in order to get additional input. The document has since been presented to, and endorsed by, the NASS Board of Directors, the ASSR and ASNR Executive Committees, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons. It has also been approved by the CPT and ICD Coding Committee of the American Academy of Orthopaedic Surgeons. Endorsement by other North American, European, and international societies is currently pending. This work is being simultaneously posted on the website of the journal *Spine*, and on the ASSR and ASNR websites (www.asnr.org), owing to special arrangements concluded between the Editors and Publishers of *Spine* and the *American Journal of Neuroradiology*.

The length of this extensive document should not turn you off. The essential *Recommendations* actually hold in two pages referring to very simple illustrations. With hope, you will find the *Discussion* section worth reading, because it provides justification and explanations for the recommendations, as well as additional guidelines for detailed descriptions of disk herniations. Of course, the *Glossary* is not intended to be read from A to Z, but is provided as a quick reference tool for definitions of commonly used terms. And, by all means, skip the chapter on *Coding* if your practice does not require you to deal with this boring issue. The proposed classification and some of the preferred definitions will very likely disappoint some of you. Standardized terminology is essential to ensure uniformity and reliability in the collection, analysis, communication, storage, and retrieval of data; but terminology is established by way of convention, and consensus does not mean unanimity: some degree of compromise is expected from all who are involved. And consider the bright side: next time residents or fellows bug you with embarrassing questions on “bulging disks” or “protrusions”, referring them to this document will get you elegantly off the hook.

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