Overhaul of TBI Classification Is Explored

BY DOUG BRUNK

SAN DIEGO — The way Dr. Geoffrey T. Manley sees it, the classification of traumatic brain injury needs an extreme makeover.

For the past 35 years, clinicians have relied on symptomatology from the Glasgow Coma Scale (GCS) to classify traumatic brain injuries (TBIs) as mild, moderate, or severe, but such emphasis on symptoms "misses the point," Dr. Manley, chief of neurotrauma and vice chairman of the department of neurosurgery at the University of California, San Francisco, said at the annual meeting of the American Association for the Advancement of Science.

"The brain is not like the heart, where if you lose a certain percentage of your heart muscle then you'll have an unexpected reduction in cardiac function. The brain is a unique organ in that it's an organ of functional connectivity. You can have very small lesions in discrete pathways, which can have a phenomenal impact on outcome. Many of these lesions can only be seen with MRI, which is not routinely used for TBI."

He went on to note that the GCS was developed "before the advent of CT scans, so this is a very old system that we're using."

In 2007, Dr. Manley and a working group of TBI experts—including Prof. Sir Graham Teasdale, who developed the GCS—convened to explore the potential for improving TBI classification (J. Neurotrauma 2008; 25:719-38). It became clear to the group, Dr. Manley said, "that if we were going to try to change the field, we were going to have to start defining a common set of data elements and technical standards so that we could be able to collect the same information on patients from site to site and to make sure that assessment tools are applied in the same way."

Common data elements are needed in TBI research "because accurate collection of structured data is essential, especially if you want to do meta-analyses and if you want to share data," he added. "It reduces time, cost, and effort of initiating clinical trials and provides opportunities for lessons learned and best practices, even if a trial isn't considered successful."

The group's recommendations call for the following:

► **Broaden TBI trials.** They should include less severely injured patients.

► **Improve CT imaging classification.** "The systems that we use now are different from hospital to hospital and radiologist to radiologist," Dr. Manley said. "There is no standardization."

► **Increase use of early MRI.** "Many of us have seen a lot of value in using MRIs," he said. "We will get an MRI on a stroke patient in a moment, but we almost never get an MRI in a TBI patient. This is a cultural change that needs to happen in this field."

► **Examine phase II trials and surrogate end points more closely.** TBI patients "have such a long recovery: an injury, an acute hospitalization, rehabilitation, and then you look at an outcome at 6 months or a year," he said. "Lots of things happen during that time period."

► **Develop more complex statistical and bioinformatics tools.** TBI studies "aren't like cancer studies," he said. "You can't phenotype these patients as well as you can in studies of other diseases. We need some novel statistical methods to deal with the realities of studying these patients with life-threatening diseases."

In March 2009, Dr. Manley and about 160 other representatives from 49 agencies and institutes, including the Department of Defense, the Department of Education, and the National Institute of Neurological Disorders and Stroke convened in Washington to begin an unprecedented effort to develop standards for TBI data collection and to better define and classify TBI.

The experts were divided into numerous work groups charged with assembling white papers on specific areas of TBI research, including demographics and acute clinical assessment, biospecimens and biomarkers, neuroimaging, posttraumatic stress disorder, and outcome measures. White papers from the various work groups will be published later in 2010, and the TBI Common Data Elements will be available online at www.nindscommondataelements.org.

The next step in this multidisciplinary effort is to establish a prospective, multivariate TBI database to validate common data elements, including a contemporary snapshot of TBI and treatment and a cross-sectional overview of patients. "So rather than saying we're looking at patients with severe, moderate, or mild injury, we're going to be agnostic to [the label of] mild, moderate, and severe, and we'll look across the entire spectrum of injury," Dr. Manley explained.

The Glasgow Coma Scale was developed 'before the advent of CT scans, so this is a very old system that we're using.'

DR. MANLEY

The database "will also allow the researchers to validate prognostic models, establish process indicators, and develop improved TBI classification," he said.

Dr. Manley and his colleagues were recently awarded a National Institutes of Health Grand Opportunities Challenge Grant to pilot this effort. The global goal is to develop, test, and refine standards for data collection in TBI studies in a multicenter observational study of 1,000 patients at high-volume TBI centers, including UCSF; the University of Pittsburgh; Mount Sinai School of Medicine, New York; and Seton Hospital in Austin, Tex. Dr. Andrew Maas, of University Hospital Antwerp, Brussels, is leading a European group of TBI investigators that also will be contributing to this effort.

"If we really want to transform TBI research, we're going to have to work in multidisciplinary teams," Dr. Manley concluded. "We need this infrastructure. We need the appropriate collaboration and tools."

Dr. Manley had no relevant financial conflicts of interest to disclose. ■

APOE e4 Status May Limit Long-Term Recovery From TBI

BY MICHELE G. SULLIVAN

WASHINGTON — Apolipoprotein E e4 genetic status appears to affect long-term recovery from traumatic brain injury significantly, particularly in those who carry two copies of the e4 allele.

At 2 years post injury, apolipoprotein E (APOE) e4 carriers were significantly more likely than noncarriers to have moderate or severe disabilities, and significantly less likely to have a good functional recovery, Jennie Ponsford, Ph.D., said at the World Congress on Brain Injury.

There appeared to be a dose-response effect, with homozygous e4 carriers having much worse outcomes.

DR. PONSFORD

"We know that the APOE e4 allele has an impact on a number of processes involved in recovery, including increased inflammation, diminished cholesterol synthesis, and reduced neurite outgrowth," she said in an interview. "These effects seem to go on for a long period of time, so it makes sense that their biggest impact would be seen when recovery is almost complete."

The observation of poorer recovery in e4 carriers suggests the possibility of targeted rehabilitation, suggested Dr. Ponsford, a neuropsychologist at Monash University, Melbourne, Australia. "If you know at the beginning of treatment, that this 25% of your population is going to have a poorer prognosis, you might be able to put more or a different kind of rehabilitation into effect early on."

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Major Finding: At 2 years after suffering a TBI, significantly more APOE e4 carriers had severe disability than did noncarriers (27% vs. 15%), and significantly fewer e4 carriers had good recovery (30% vs. 39%).

Data Source: A long-term follow-up study of 648 patients with traumatic brain injury.

Disclosures: Dr. Ponsford reported that she had no financial disclosures.

Dr. Ponsford presented a long-term follow-up study of 648 patients who were admitted to a regional rehabilitation center between 2000 and 2007. Most of the subjects were male (67%); their mean age was 35 years. The study examined the relationship between APOE e4 status and the initial Glasgow Coma Scale (GCS) score, days of posttraumatic amnesia (PTA), and the Glasgow Outcome Scale–Extended (GOS-E). The GOS-E rates long-term recovery on an 8-point scale, in which good recovery is a score of 7 or 8. All of the subjects gave a saliva sample for APOE genotyping.

Genotyping showed that 166 (26%) patients carried the e4 allele. Of these, 6 were homozygous (e4/ e4) and 160 were heterozygous (152 with e3/e4 and 8 with e2/e4). Of the remaining 482, 404 were e3/e3; 75 were e2/e3; and three were e2/e2.

Overall, the mean GCS score was 8, and did not vary significantly between the groups. APOE e4 had no significant effect on the mean length of PTA (31 days).

Recovery was assessed at 1, 2, and 3 or 5 years post injury; the mean time between injury and assessment was 1.9 years. After controlling for age and sex, Dr. Ponsford found that APOE e4 carriers had significantly poorer outcomes than noncarriers. Significantly more e4 carriers had severe disability than did noncarriers (27% vs. 15%), and significantly fewer e4 carriers had good recovery (30% vs. 39%).

"There also appeared to be somewhat of a dose-response effect, with homozygous e4 carriers having a tendency to have much worse outcomes," she said. The median GOS-E score for this group was 4.8, which was significantly lower than the median score of 6 in the e4 noncarriers and lower (but not significantly so) than those who were heterozygous for the allele.

However, she noted that the very low number of homozygous e4 patients made it impossible to draw any strong conclusions.

In addition to increasing inflammation and interfering with cell repair, the APOE e4 gene is involved in the binding and deposition of amyloid beta (Abeta), the protein thought to be involved in the development of Alzheimer's disease. Dr. Ponsford said there are no data to indicate that a traumatic brain injury predisposes a person to develop Alzheimer's. However, the gene's interaction with Abeta may impair recovery from a brain injury. ■