Committee on Clinical Investigations: Minutes of the November 13, 2002 Meeting

NEW PROTOCOLS, AMENDMENTS, GRANTS:

CCI#	Principal Investigator	Sponsor	Primary Reviewer	Secondary Reviewer
02-170	Gabriel G. Haddad, M.D.	NIH		

Title: SLEEP MECHANISMS IN CHILDREN: ROLE OF METABOLISM

FACILITIES: AECOM, MMC, GCRC, MRRC
ACTION: Approved, 14 in favor, 1 opposed, 1 abstention

Upon a motion duly made and seconded, the Committee voted to approve the study based on the risk/benefit ratio. The consent document requires revisions and is subject to approval by the Primary and Secondary reviewers or the committee chair, and approval by the Department of Health and Human Services Secretary. Re-review of the protocol is required in six months. A majority of the members, including the non-scientific member(s) were present during the discussion and vote. As standard operating procedure, the investigator and collaborators were not present during the Committee's private deliberation and vote.

Dr. Haddad is the newly appointed University Chair of the Department of Pediatrics, and a worldwide authority on sleep disorders in children and its effects on organ and tissue metabolism. Dr. Haddad has recently been informed that the NIH has encouraged the study of the physiological differences in brain metabolism during wakefulness and sleep in children. Of particular interest is the effect of sleep deprivation on brain metabolism during wakefulness and sleep in children. The NIH has indicated their willingness to support this protocol.

Sleep is a poorly understood physiological process that not only undergoes dramatic developmental changes from infancy through adulthood, but also is prone to sleep disturbances such as sleep deprivation. Sleep deprivation is very common, particularly in the adolescent years, and is associated with poor psychological health and adjustment, poor school performance and potentially greater risk due to accidental injury.

Specifically, investigators wish to understand underlying brain metabolism in adolescents from age 13-17. Subjects will be studied during wakefulness, and during sleep, either after a normal nights sleep or after a night of sleep deprivation. In collaboration with the new AECOM MRRC, the investigators will be monitoring brain glycogen content, glutamate turnover rate and glutamate-glutamine cycling. They hypothesize that sleep is characterized by lower metabolic brain activity as characterized by reduced glutamate turnover, and this reduction is prevented by sleep deprivation.

Additional hypotheses are that control mechanisms of glial cell glucose oxidation play an important role in glutamate/glutamine cycling, and represent an important pathway by which sleep deprivation results in increased brain activation during sleep. Lastly, they hypothesize that sleep deprivation results in reduced brain glycogen stores, which might be hypothesized to reduce attention/brain activity after sleep deprivation and particularly with skipping the morning meal. The application of MR spectroscopy to understand brain neurotransmitter and metabolic flux in sleep studies is a unique and novel aspect of this project that has never been performed before, and is possible in only a handful of centers around the world.

Subjects will be divided into four groups. The first two will receive in the 4Tesla human magnet a 90 minute infusion of non radioactive 13C acetate to raise acetate levels about 2 mm above basal. The second two will instead receive a 90-minute infusion of non-radioactive 13C glucose, enough to raise glucose levels to approximately 180 mg/dl. Each group will be further subdivided into those studied after normal nights sleep or after a night of sleep deprivation. The study is composed of 3 study visits.

The first outpatient visit is to assess for exclusions by history, physical and single blood sampling (15cc) to rule out diabetes, anemia, hepatic or renal disease. The second visit is over two days. The first is spent in the Children's Hospital research sleep laboratory, and EEG, EOG, EMG, E KG, respi-bands for chest and abdominal movements, pulse oxymetry, and audio and video recording monitor normal sleep intensively. On day two subjects are transported to the MRRC where they are studied in the magnet during wakefulness in conjunction with the control data.

The Committee discussed the payment schedule. Over all payment is $450 for the three visits, with a maximum of $100 to be given to the adolescents and $350 to the parents. It has been the Committee's practice not to pay minors in excess of $100 as this can be coercive. It is permissible to pay the parents for their time and inconvenience for accompanying the minor. The parents will have the discretion to determine how the money may be used. Recruitment for the study will be conducted through the local newspapers.

Committee Findings:

- The study is not approvable under 46.404 as it poses greater than minimal risk.
- The study is not approvable under 46.405, as it does not present the prospect of direct benefit to the individual subjects.
- The study is not approvable under 46.406, as the study procedures present a minor increase over minimal risk; the experiences to subjects are not reasonably commensurate with those inherent in their actual or expedited medical situations; and as healthy controls, the study will not yield generalizable knowledge about the condition.
- The study is approvable under 46.407 as the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and adequate provisions are made for soliciting the assent of children and permission of their parents or guardians, as set forth in 46.408, and
- The Secretary has determined either: that the research in fact satisfies the conditions of Sections 46.404, 405 or 406, or that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children; the research will be conducted in accordance with sound ethical principles; and adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 46.408. The CCI Chairman will write the Secretary seeking written approval of this study.
- The study poses more than minimal risk with no direct benefit to participants, and that the study presents a reasonable opportunity to further the understanding of prevention or alleviation of a serious problem affecting the health or welfare of children (1c).
- Re-review is required in 6 months.
- The protocol is methodology scientifically sound and adequately designed.
- The hypotheses, clinical objectives and planned analyses are clearly stated.
- The protocol includes how the data will be stored and the subject's confidentiality ensured.
- The inclusion/exclusion criteria are clearly stated. Pregnancy is an exclusion.

Informed Consent:

- There is a general lack of detail of the protocol including the exact procedures for monitoring sleep activities within the magnet environment and the time these will all take. This needs to be remedied. The description of the groups is also confusing and could benefit from a graphic diagram.
- Risks as enumerated are incomplete. They should include language that blood drawing includes a rare risk of bruising, bleeding and infection. Risks of sleep deprivation and the need not to engage in any risky activity such as using machinery or driving (for those with learner's permits). Also, this would not be a good idea the night before school. Additional discomforts that should be mentioned include sleeping with the head coil and on a hard bed frame within the magnet, and cold within the magnet bore. The fact that lidocaine containing numbing cream will be used should be in the consent. The protocol should be amended to exclude subjects with known lidocaine allergy.
- The payment schedule, as submitted is acceptable.
- A statement that unknown risks may occur needs to be added.
- The magnet is to be used under an IDE exemption, which the MRRC magnet has qualified for. The infusions are to be given under an IND waiver. The infusates are metabolites and qualify for IND waiver by the FDA. Investigators will however need to provide the CCI with the *QI* a data from the manufacturers or elsewhere-including evidence of pyrogen testing, and a statement that the infusates will be made up following GCP protocols.
- Consent must be obtained before the screening. A statement stating that this consent will be valid thru the duration of the study if the subject is enrolled in the study after completion of the screening.