



Visual Impairment/Intracranial Pressure  
Research Clinical Advisory Panel  
Meeting

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Summary Report

June 27, 2012

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## **I. INTRODUCTION**

As part of the ongoing effort to understand and mitigate spaceflight related changes in visual acuity accompanied by anatomic ocular changes and increased postflight intracranial pressures (ICP), the Visual Impairment/Intracranial Pressure (VIIP) Research and Clinical Advisory Panel (RCAP) convened for its semi-annual meeting. The RCAP's charge includes review of direction, status, and progress of research and clinical activities of the VIIP project. The purpose of the meeting was to update the Panel members on the current clinical and research findings and to obtain feedback on clinical and research products and forward plans.

The meeting was held on June 27, 2012 at the NASA Johnson Space Center, with the RCAP members attending via teleconference and WebEx. Presentations were made by VIIP team members and a discussion was held to clarify further recommendations. The following is a summary of this meeting.

## **II. ATTENDEES**

### **RCAP Members (via teleconference)**

1. **David Baskin, M.D.** - Methodist Hospital; Houston, TX
2. **Michael Delp, Ph.D.** - University of Florida; Gainesville, Florida
3. **Conrad Johanson, Ph.D.** - Brown Medical School; Providence, Rhode Island
4. **Byron Lam, M.D.** – Baskin Palmer Eye Institute, Miami
5. **Andrew Lee, M.D.** - Methodist Hospital Research Institute; Houston, TX
6. **J.D. Polk, D.O., M.S., M.B.A.** – Department of Homeland Security, Washington DC
7. **Harold Rekate, M.D.** - North Shore Long Island Jewish Health System; Great Neck, NY

### **NASA Participants**

- |  |                                      |
|--|--------------------------------------|
| 1. <b>Barr Yael, M.D., M.P.H.</b>        | 11. <b>Oubre Cherie, Ph.D.</b>       |
| 2. <b>Fogarty Jennifer, Ph.D.</b>        | 12. <b>Sargsyan Ashot, M.D.</b>      |
| 3. <b>Francisco David</b>                | 13. <b>Schneider Victor, M.D.</b>    |
| 4. <b>Kundrot Craig, Ph.D.</b>           | 14. <b>Shepanek Marc, Ph.D.</b>      |
| 5. <b>Liskowski David – Ph.D.</b>        | 15. <b>Tarver William, M.D.</b>      |
| 6. <b>Maher Jacilyn</b>                  | 16. <b>Van Baalen Mary, Ph.D.</b>    |
| 7. <b>Moynihan Shannan, M.D., M.P.H.</b> | 17. <b>Villarreal Jennifer, M.S.</b> |
| 8. <b>Mullenax Carol, Ph.D.</b>          | 18. <b>Wear Mary, Ph.D.</b>          |
| 9. <b>Norsk Peter, M.D., Ph.D.</b>       | 19. <b>Wu Jimmy</b>                  |
| 10. <b>Otto Christian, M.D.</b>          | 20. <b>Zanello Susana, Ph.D.</b>     |

### III. MEETING AGENDA

<b>Time</b>	<b>Topic</b>	<b>Presenter(s)</b>
1:30	<b>Introductions/Agenda</b>	<b>Jennifer Villarreal</b>
1:40	<b>Clinical Status</b> <ul style="list-style-type: none"> <li>• VIIP Cases</li> <li>• Clinical Practice Guidelines (CPGs)</li> <li>• MRI Analysis</li> </ul>	<b>Bill Tarver</b>
2:15	<b>Hardware Development Status</b>	<b>Jimmy Wu</b>
2:25	<b>Choosing a Non-Invasive ICP for Flight</b>	<b>Jennifer Villarreal</b>
2:30	<b>Occupational Surveillance Data</b>	<b>Christian Otto</b>
3:40	<b>Review of Research Plan Tasks</b> <ul style="list-style-type: none"> <li>• New NRA Studies</li> <li>• Long term plans</li> </ul>	<b>Christian Otto</b>
4:00	<b>Discussion</b>	<b>Panel</b>
4:50	<b>What's Next?</b> <ul style="list-style-type: none"> <li>• Evidence Report</li> <li>• Research Plan</li> <li>• Standing Review Panel FYI</li> </ul>	<b>Jennifer Villarreal</b>
5:00	<b>Actions/Adjourn</b>	<b>Jennifer Villarreal</b>

## IV. SUMMARY OF DISCUSSIONS

### Introductions/Agenda

Jennifer Villarreal introduced the RCAP members and reviewed the agenda.

### Clinical Status

Bill Tarver presented an overview of the VIIP cases, noting that the latest case was the first to undergo the full range of recommended evaluations from preflight to postflight, including a postflight lumbar puncture (LP) at R+12 days (which documented a CSF opening pressure of 28.5 cm H<sub>2</sub>O) followed by acetazolamide treatment. A second LP at R+6 weeks showed that the CSF opening pressure had dropped to 19 cm H<sub>2</sub>O at which time acetazolamide treatment was discontinued. A follow up LP has not yet been obtained to verify continued resolution of ICP, but he has shown clinical improvement in visual acuity, and his optic-disc edema, which was still present at R+6 weeks, has now completely resolved.

Data collection in all crewmembers was noted to be more robust at this time, occurring in a more organized fashion.

The recommendations of the RCAP from the December meeting were reviewed:

- The CPG is being amended as recommended
- Work is underway to institute MR venography
- Work is underway to fly an Optical Coherence Tomography (OCT) device on ISS
- Work is underway to select a non-invasive ICP measurement device

The pre- and postflight tests have not changed since the December RCAP meeting and currently include 2D ultrasound, 3T MRI, and vision exams. Out of 36 ISS crewmembers, 5 have been confirmed as non-cases (<0.50 diopter cycloplegic refractive change), 16 are currently unclassified (due to insufficient evidence, some having flown in the early days of ISS when little or no testing was done), and 20 have been classified as CPG class 1 through 4 as follows:

- CPG class 1 n=2
- CPG class 2 n=8
- CPG class 3 n=1
- CPG class 4 n=4 (all had LPs)

IP crewmembers are not currently included in these counts.

Points of discussion during this part of the meeting included the following:

- The threshold of CSF opening pressures above which NASA considers the ICP to be high is 25 cm H<sub>2</sub>O and above. Treatment of crewmembers with high ICP will continue until the opening pressure is below 22 cm H<sub>2</sub>O.

- In the four crewmembers that underwent postflight LPs, the LPs were conducted at different time points: the 1<sup>st</sup> case underwent LP two years postflight, while the last case had an LP at R+12 days. RCAP members recommended that the timing for LP data collection be more standardized in the future.
- The three untreated Class 4 crewmembers did not have a follow-up LP after their initial LPs.
- From terrestrial experience, the lowest ICP that can cause papilledema is usually 25 cm H<sub>2</sub>O. However, patients may have ICP in the 30s without papilledema, while some patients (for example with head trauma) can deteriorate clinically with an ICP of 19. Venous compliance plays a role, as can be seen in patients whose ICP changes up or down with head movement to one side or the other, secondary to changes in venous compliance brought about by venous compression affecting venous drainage from the brain.
- Optic disc changes seen in crewmembers could be unrelated to increased ICP and therefore should not be referred to as papilledema.
- Crewmembers have not been treated with acetazolamide on orbit.
- Work is underway to decrease sodium content of ISS foods.
- Work is underway to lower CO<sub>2</sub> levels on ISS. Levels are significantly lower now, but not “Earth normal”. Current operating levels onboard the ISS are still 10 times higher than ambient terrestrial levels.
- Submariners have been reported to complain of elevated CO<sub>2</sub> symptoms (such as headaches), but it is unclear at this time whether this population has ever been evaluated for presence or absence of the findings seen with the VIIP syndrome.
- NASA has recently learned that a manuscript published by the Russian behavioral health team in the late 1990s reported that 50% of Mir cosmonauts were found to have optic-disc edema postflight. Russian space life scientists report that they are not aware of VIIP findings among their ISS crewmembers, and have hypothesized that the Advanced Resistive Exercise Device (ARED) onboard the ISS, which is used by U.S. but not by Russian crewmembers, may be a contributing cause. The Russians are willing to start visual testing on their crewmembers.
- The question of whether the crewmembers may have high ICP prior to flight, perhaps secondary to a pre-existing condition or use of performance enhancing drugs, was discussed. It was emphasized that NASA needs to monitor ICP both pre- and postflight, perhaps by using non-invasive ICP with MRI, using protocols akin those developed by Noam Alperin.
- No changes in cognition have been measured in crewmembers. Cognitive deficits have been associated with long standing increased ICP terrestrially.

### **Hardware Development Status**

Jimmy Wu gave an overview of the following:

- Clinical vision-testing requirements and the two software packages that were selected to support these requirements (the Acuity Pro for contrast sensitivity testing with anticipated on

orbit delivery date of January 2013, and the Moorefield Motion Displacement Test for visual field thresholds, delivery date TBD).

- Fundoscopy requirements for improved resolution of current on-board capability. The Merge EyeScan video-fundoscope is anticipated on orbit by December 2012, but the earliest trained crew may not be on orbit until April 2013. The plan is for the current crew to continue with the current fundoscopy hardware which they were trained on.
- OCT requirements – The Heidelberg Spectralis met both research and clinical requirements, and is expected on orbit by early 2014. The device requires moderate engineering modifications to become space-flight worthy.

Costs for the above hardware and software are being split between NASA's Human Research Program (HRP) and NASA's medical operational (Med Ops) community.

### **Choosing a Non-Invasive ICP for Flight**

Jennifer Villarreal reviewed several devices under evaluation, and the human studies that are underway to evaluate them. After ground comparisons are completed, one device will be chosen for in-flight ICP measurements. Devices include the Vittamed and the Cerebral Cochlear Fluid Pressure (CCFP) analyzer which is integrated with the Distortion Product Otoacoustic Emissions (DPOAE) device. The VIIP team is working with CPHS and the FDA on an exemption, since the devices are not yet FDA approved.

#### **Points of discussion during this part of the meeting included the following:**

- It might be faster to test these devices on primates rather than on humans. All the devices could be tested simultaneously, and ICP could be raised or lowered under lab conditions. Only 3-4 primate subjects would be needed. The primate would be the best animal model because of their large size compared with other animal models. An alternative would be to use a porcine model. Pigs have large heads, large brains, and the ventricles can be easily tapped. It would take 6 months to set up such an experiment, the experimental conditions would be more controlled, and results would be quicker to obtain. Anesthesia of the animals would not interfere with the ICP measurements since ICP can be artificially modulated during the study.
- Several steps are required to answer the question of whether or not ICP is elevated in-flight. Given that the risk of invasive measurement in-flight is deemed too high, a non-invasive means is required. Currently, there is no accurate method of obtaining ICP non-invasively. Therefore, a device must be selected from among the current models in development following testing for accuracy of measurement. The unit must be deployed to the ISS, and then a sufficient amount of data must be collected throughout the mission on multiple crewmembers. The timeframe for collection once a unit is on ISS is likely two years at a minimum.

## **Occupational Surveillance Data and Review of Research Plan Tasks**

Christian Otto gave an overview of the current evidence obtained from the occupational surveillance, including the following:

- The Russians have reported “improved vision on orbit” suggesting hyperopic shifts
- ICPs in crewmembers (when measured postflight upon return to 1G thus following removal of the dependant variable of cephalad fluid shift) ranged from 21-29 H<sub>2</sub>O (normal 9.5-20 cm H<sub>2</sub>O)
- Potential long-term changes: Decreased near visual acuity, peripheral vision loss, neurocognitive changes
- Risk for change from baseline will likely be higher on longer exploration missions (dose-response)
- Crew reported changes in cognitive function on orbit and short-term memory problems post-flight. This kind of data doesn’t get communicated to Med Ops due to crewmember reluctance to share.
- Terrestrially there is a correlation of white-matter disease and normal pressure hydrocephalus (NPH)
- The crewmembers most severely affected have lower intraocular pressures (IOPs) pre- and postflight.
- There is likely interaction between the central nervous system (CNS), cardiovascular system (CVS), and the eye.
- Correlation has been found between VIIP signs and symptoms and: LDL, HgA1C, fasting serum glucose, homocysteine, BMI, % body fat, resting blood pressure, pulse pressure, decreased VO<sub>2</sub> max. All of these correlate with vascular compliance.
- Cases started with larger optic nerve sheath diameter (ONSD) preflight, but most of the cases had previous exposure to spaceflight (median of 15 days of flight) whereas most of the non-cases did not have prior flight time.

Points of discussion during this part of the meeting included the following:

- Data from mice flown on STS-135 showed that the cerebral arteries constricted less than in controls, and also became more distensible. Those vessels responded opposite to what is seen in tail suspended rats. It appears that vascular remodeling occurred during spaceflight, possibly secondary to an increase or decrease in flow or pressure, with a chronic state of vascular relaxation allowing a chronic increase in blood-flow. This is in contrast to in-flight rat experiments that found hypertrophy of cerebral vessels, and atrophy of lower limb arteries. Therefore, it is possible there is a difference between the two species of rodents. Experiments will be repeated next April, with mice flying on a Russian Bion for 30 days. Monitoring parameters will include heart rate and arterial pressure with invasive instrumentation. Invasive ICP monitors will not be flown due to the fact that animals

instrumented in this way have not fared well in previous in-flight studies. A study to compare tail-suspended mice and rats is also planned, in order to evaluate potential differences.

- The higher ONSD seen in the cases – how much of that is due to previous flight exposure? The statistical differences in ONSD between cases and non-cases, could they just be “noise” since they are different preflight? It is inferred that in individuals that have flown previously the optic nerve sheath (ONS) has stretched and has not returned to baseline. In some terrestrial idiopathic intracranial hypertension (IIH) patients the ONS may remain distended even after treatment. This appears to vary between individuals.
- An important hypothesis is the fact that with fluid shifting an elevated ICP may be reached where cerebral venous sinus stenosis may occur, thereby decreasing cerebral venous drainage, and increasing ICP, thereby establishing a positive feedback effect. If these constrictions persist postflight, they may contribute to the phenomenon of persistently elevated ICP postflight, in one case up to five years.
- Magnetic resonance venograms (MRVs) are being recommended for both pre- and postflight testing. The RCAP members noted that when performing MRVs on the crewmembers, the secondary veins need to be examined in addition to the larger (jugular) veins. In IIH patients the secondary veins were the ones distended. The primary risk with MRV is due to the intravenous gadolinium contrast, as there is a risk of developing nephrogenic systemic fibrosis. The risk is low, but is not zero. MRV images can be obtained without gadolinium contrast, however their sensitivity and specificity are significantly lower. It should be noted that MRV assessment is the clinical standard of care in the assessment of IIH patients.
- Lymphatic drainage is a potentially important variable. A significant portion of the CSF drains to the lymph and if that avenue is compromised that would add another variable. Miles Johnston from Toronto is recommended as a consultant since he is a lymphologist.
- Acetazolamide shuts down aquaporin 1 (AQP1), and perhaps that is why it was effective in reducing CSF pressure in the one crewmember that was treated.
- There are plans for assessing AQP1 regulation in animals in a recently awarded VIIP NRA. Dr. Charles Fuller will study rats in a prolonged hindlimb suspension model simulating to simulate cephalad fluid shift. It would be useful to determine if the AQP1 is upregulated transiently or if it creates a new set-point and remains elevated postflight.
- Since respiratory acidosis has little effect on CSF production, some of the RCAP members are not convinced that higher levels of CO<sub>2</sub> increase CSF production.
- Proton pump inhibitors (PPIs) have been shown to decrease CSF production in animals, and are used in veterinary care in the same dose as that used for reflux. PPIs have a safe use profile and may be worth evaluating for use in crewmembers for VIIP indications. As some crewmembers are already taking PPIs for reflux, LSAH will look into mining this data, and correlating PPI use with class of CPG.
- IOP and ICP seem to go hand and hand (but are reciprocal). It is possible that some individuals are prone to VIIP because of anatomical/functional differences, which cause them

to have lower IOP with higher ICP. Myopes do not seem more prone to VIIP, and a study looking at structural differences (such as optic canal size) is being planned.

- A discussion was held of the awarded NRAs and the ethics of flying cancer survivors on parabolic flights.

## **Discussion**

Points of discussion during this part of the meeting included the following:

- RCAP members complemented the synthesis of all available information and agreed that the new set of studies is good. They stressed that at this point in time data is what is needed more than anything else. Numerous hypotheses have been proposed, and now data is needed. RCAP members are advocating that LPs be obtained in all crewmembers. NASA personnel reported that as far as obtaining LPs from crewmembers, no change has been implemented since December, but that HRP and Med Ops are advocating pre and postflight LPs. A preflight LP would be especially important as it would allow a comparison to postflight measures. The preflight LP would likely be collected one year prior to flight. While people may be apprehensive about invasive procedures, this data is needed.
- There is evidence from NPH of long-term effects that manifest after 10-15 years, including cognitive deficits. Therefore, there is a need for more sophisticated neurocognitive testing pre- and postflight. Currently only WinScat is performed on crewmembers. All the major medical centers have neuropsych specialists that may help, and protocols have been developed that can be applied. There is also a plan for data sharing with Dr. Seidler who is doing functional MRI imaging along with neurocognitive testing for the Behavioral Health Element.
- CSF pressure/volume dynamics should be examined along with venous pressure/volume in animals.
- It is time to start focusing on potential pharmacological agents to help decrease CSF formation and venous congestion.
- MRI flow studies should be considered. There are protocols used for NPH patients to determine whether a shunt would help them.
- Long-term effects need to be investigated, and it may be useful to do a prospective study on crewmembers that have flown over the past 20 years, including MRI imaging, ocular ultrasound, OCT and vision testing. Retired astronauts return to JSC for annual physicals which include visual exam, but MRI, OCT and ocular ultrasound has not been a part of these annual exams. The challenge of interpreting data from astronauts that have flown in earlier programs (Mir for example) and who are now in their 60s and 70s, is the degree of change that may have occurred due to aging. However, cohort comparison with an age matched group of non-astronauts may reveal differences that could be attributed to spaceflight. NASA is planning to compare data that is already available on long-duration ISS and short-duration shuttle crewmembers.
- So far the ocular findings discovered have mostly been structural, not functional.

- NASA members confirmed that they were satisfied with the response to the research announcement, there were many submissions and as many as possible were selected. Where possible, a biospecimen sharing program will be implemented.
- Fluid regulating peptides such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and arginine vasopressin (AVP) could be important. Because the CSF and plasma are separate compartments, levels in the blood may not correlate with levels in the brain. With brain edema from trauma there is a correlation between ICP and levels of these peptides, but it needs to be differentiated whether this is from increased ICP or from the increased brain edema. These peptides may alter the physiology differently in the blood-brain barrier, in the choroid plexus and in the vasculature. Elevated ICP may induce AVP as it is a protective brain peptide. However, increased AVP would also decrease osmolarity, increase free water, and increase edema. Perhaps blood samples for AVP could be a marker of ICP in-flight.
- All non-invasive tests on crewmembers should continue postflight for longer than 6 months.
- In IIH patients post treatment, following resolution of papilledema, clear evidence of peripheral visual loss has been documented. Unfortunately, peripheral vision loss of up to 50% goes unnoticed by those affected. However, it is not necessary to test peripheral visual fields in crewmembers, because once the optic-disc edema has resolved if OCT shows no loss in the retinal nerve fiber layer (RNFL), then visual fields should be stable. OCT findings would be sufficient for monitoring the health of the peripheral retina.
- The RCAP concurred with the studies currently in work, but stressed the need for non-invasive ICP hardware to go along with these studies. In addition, obtaining LPs in crewmembers is highly recommended. The severity of the VIIP risk was likened to repetitive sports injuries, and not knowing the actual ICP may have both legal and moral implications.

### **Actions/Adjourn**

Jennifer Villarreal summarized the forward work and requested that the RCAP review the evidence book and provide comments.

Actions were summarized as follows:

- The VIIP research team is to move forward with instituting a research protocol for LPs, since the clinical side is not ready yet to mandate LPs of all crewmembers.
- Bill Tarver will work on pursuing neuropsychological testing.
- David Baskin will provide neuropsych protocols used at Methodist and the MR flow protocol.
- Christian Otto will pursue collaboration with Dr. Seidler's (University of Michigan) study involving neurocognitive performance and functional MRI.
- Peter Norsk will pursue rat tissue sharing with Charles Fuller.

The meeting was then adjourned.

