The Visual Impairment Intracranial Pressure Summit Report

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Executive Summary Visual Impairment Intracranial Pressure Summit

Space Life Sciences at Johnson Space Center held a Visual Impairment Intracranial Pressure (VIIP) Summit on Feb 8 – 10, 2011. The purpose of the meeting was to solicit input and recommendations from a diverse group of experts from the fields of medicine and research and to function as the forum in which the scope of the problem is defined. The group of experts that comprised the VIIP Summit panel were also asked if they would be interested in serving on a standing review panel (SRP) which would provide guidance for the future research project.

The three day agenda allowed for introductions of the clinical topic, and current spaceflight operations and environmental conditions by NASA personnel on the first day. The remainder of the summit was devoted to discussion topics led by summit participants and a final review of the discussions and documentation of recommendations. Feedback from the participants was that the summit format was very successful.

The VIIP panel stated that the vision, physiological, and anatomical changes observed in long duration astronauts as documented in the seven cases presented are unlike any clinical entity they have seen as a collective. These changes, including elevated intracranial pressure, optic nerve sheath distention, globe flattening, and choroidal folds, do not appear to be severe enough to cause blindness near term but it is unknown if there could be long term sequelae. The VIIP panel noted that NASA is doing an adequate job of monitoring and documenting changes in vision and the anatomy of the eye such as papilledema, choroidal folds, enlarged optic nerve sheath diameter optic nerve sheath diameter (ONSD), and axial length of the globe, etc. However, a higher resolution inflight retinal imaging system that would allow early diagnosis of choroidal folds as well as mild retinal and optic nerve pathology is needed. Given the potentially nature of these changes, a method of early diagnosis could prove extremely valuable.

The panel placed an emphasis on correlating Magnetic Resonance Imaging (MRI) with ultrasound, primary in-flight imaging modality, so that in-flight images can be interpreted with respect to the preflight baseline (MRI being the terrestrial gold standard). The panel also emphasized the need to establish the role of intracranial pressure (ICP) in the in-flight and post-flight changes in vision and eye anatomy. To do this, NASA needs to directly measure ICP before and after flight in all long duration astronauts. This would determine if exposure to microgravity is causing increased ICP. It was recommended by the panel that NASA should establish an in-flight capability to monitor ICP. The panel recognized that in-flight lumbar puncture for the direct measure of ICP (the current gold standard) does carry additional risk and encouraged the development and/or validation of a non-invasive method for spaceflight.

The VIIP panel also recognized the role of other physiological alterations; since we have measured elevations in ICP following space missions it is tempting to assume that ICP changes are solely responsible for the optic nerve sheath, choroidal folds, axial length, and visual changes observed. However, as discussed at the summit, several factors indicate that a rise in ICP is not the sole cause of such findings. First, none of the astronauts with disc edema, globe flattening, choroidal

folds, or hyperopic shifts presented with headaches, visual obscurations, diplopia, or other clinical symptoms suggestive of increased ICP. In a terrestrial setting, headache is experienced by more than 90% of patients with elevated ICP and 75% experience visual obscurations. Additionally, the prominent degree of globe flattening, disc edema, widened optic nerve sheaths, and choroidal folds documented in the seven long durartion astronaut cases seem out of proportion to ICP measurements observed post-flight. Thus, the panel recommended that NASA should consider the possibility that microgravity fluid shifts may cause optic nerve and ocular changes even in the absence of a greatly elevated ICP. While it is extremely important to document changes in ICP and optic nerve sheath diameter as noted above, it is important to keep in mind that the organ most affected by any such changes is the eye itself.

To date NASA has measured intraocular pressure, visual acuity, cycloplegic refraction, Optical Coherence Tomography (OCT) and A-scan axial length changes in the eye largely before and after spaceflight. It would be beneficial for NASA to seek technology that would allow for precise in-flight objective measurement of these parameters. The technology that offers the most potential is OCT. This is a new, non-invasive technology that uses light to accurately depict the internal structures of the eye and also captures the anterior portion of the optic nerve and layers of the retina. It is accurate to 5 microns and is far more precise than Magnetic Resonance Imaging (MRI), Computerized Axial Tomography (CAT), or ultrasound. NASA's pre and post-flight OCT studies have proven that it can detect minute nerve fiber layer edema thickening not observable by any other means. This thickening may represent the first quantitatively observable pathologic change during spaceflight and its measurement could be instrumental in the early recognition of microgravity-induced eye and optic nerve changes: OCT could be an on board "early warning system". Finally, it is important to rule out the possibility that ocular hypotony could be responsible for the disc edema, globe flattening and other changes observed. This can only be done by measuring Intraocular Pressure (IOP) during spaceflight. It is recommended that NASA determine how to best obtain these measurements.

The Panel considers the changes in eye and increased intracranial pressure a syndrome because it is a constellation of diverse symptoms ranging in severity and duration. The VIIP panel emphasized the need for case definition based on what has been observed and documented thus far in order to identify and characterize past (to the degree possible with retrospective analysis) and future cases.

The VIIP panel also recommended research to establish risk stratification and underlying mechanisms based on anatomy (ex. crowded optic disc, angle of the optic disc and optic nerve interface, tortuousity of optic nerves, contribution of jugular and parajugular vessels for cerebrovascular outflow, incompetent jugular valves, etc.), physiology (ex. low cranial and vascular compliance, poor cerebral vascular auto regulation, magnitude of in-flight venous congestion, degree of catabolism (i.e. bone and muscle loses)), genetics (blinded screening to detect the presence or absence of a gene in the populations described in the case classifications above), and epigenetics (blinded screening to detect genes that are impacted (i.e. directionally modulated - increased or decreased expression)) by the spaceflight environment which includes microgravity, chronic CO2 exposure, limited diet, stress, etc.). The detailed report contains the specific Panel recommendations.

Post-summit activities will include the formal announcement of SRP members, documentation of the research scope, and development of the collaborative research team. Operational activities will continue as planned and documented and will be complemented by activities such as data-mining, case definition, and development of clinical practice guidelines for the treatment of spaceflight-induced visual impairment/increased intracranial pressure.

The Visual Impairment Intracranial Pressure Summit Report

INTRODUCTION

The Visual Impairment Intracranial Pressure (VIIP) Summit was hosted by the NASA Johnson Space Center Space Life Sciences Directorate on February 8-10, 2011 in Houston Texas. (Summit Agenda Appendix 1) There were approximately 75 attendees representing expertise in multiple disciplines including anesthesia, cardiology, engineering, epidemiology, medical physics, neurology, ophthalmology, neuro- ophthalmology, optometry, radiology, space physiology, space medicine, ultrasonography, and vascular physiology. The attendees included NASA civil servants, NASA contractors, non-NASA clinicians, and professors from various academic institutions (see Appendix 2). The attendees were further divided into co-chairs, panelists and non-panelists to identify the co-chairs and panelists as the group responsible for forming recommendations and producing this report.

This summit brought these experts together to discuss the documented cases of visual impairment (VI) and increased ICP in astronauts during and after long duration spaceflight on the International Space Station (ISS). The discussion entailed the immediate clinical diagnosis and treatment options, clinical tools that required additional research and development, possible underlying spaceflight physiology effects requiring investigation, and potential anatomical or genetic characteristics which may confer susceptibility or risk for developing the visual impairment and/or increased intracranial pressure after exposure to microgravity. The discussion and summit focused on seven documented cases which are summarized in the background summary (see Appendix 3) but did consider the possibility that all long duration astronauts experience the underlying physiological effect with only a subset manifesting symptoms and degraded function (i.e. visual impairment).

OVER VIEW OF VIIP SUMMIT

The VIIP panel stated that the vision, physiological, and anatomical changes observed in long duration astronauts as documented in the seven cases presented are unlike any clinical entity they have seen as a collective; the clinical signs and symptoms do not appear to be severe enough to cause blindness near term but it is unknown if there could be long term sequelae as a result of chronically elevated intracranial pressure such as macular degeneration.

NASA is doing an adequate job of monitoring and documenting changes in vision and the anatomy of the eye such as papilledema, choroidal folds, enlarged ONSD, and axial length of the globe, etc. The panel placed an emphasis on correlating MRI with ultrasound so that when ultrasound is used in-flight the images can be interpreted with respect to the preflight baseline (this work is currently being pursued by Space Medicine)

In order to establish the role of ICP in the in-flight and post-flight changes in vision and eye anatomy, NASA needs to directly measure ICP before and after flight in all long duration astronauts. This would determine if exposure to microgravity is causing increased ICP. It was recommended by the panel that NASA should establish an in-flight capability to monitor ICP. The panel recognized that in-flight lumbar puncture for the direct measure of ICP does carry additional risk and encouraged the development and/or validation of a non-invasive method for spaceflight.

The Panel considers the changes in the eye and increased intracranial pressure a syndrome because it is a constellation of diverse symptoms ranging in severity and duration. The VIIP panel also emphasized the need for case definition; based on what has been observed and documented thus far there are four potential categories that could represent case classification:

1. Microgravity-associated intracranial hypertension with visual impairment and altered ophthalmic anatomy (papilledema, choroidal folds, etc.)

2. Microgravity-associated intracranial hypertension without visual impairment (It is unknown if this situation is occurring because NASA is currently using visual symptoms to drive further investigation and is not currently looking for other potential symptoms such as neuro-cognitive deficits which would require much more sensitive and time consuming tests than are currently performed. Neuro-cognitive testing was recommended by the panel to elucidate if this situation is occurring)

3. Microgravity-associated visual impairment without intracranial hypertension (this is currently possible because NASA has only documented increased ICP in 4 of the 7 cases and some of the panel stated that the eye appears to be affected by microgravity in such a way that visual impairment results without a change in ICP)

4. Null Case: long duration astronauts return to Earth with neither visual impairment nor increased intracranial pressure

Based on the current cohort being discussed, one would state that the null hypothesis is presumed false and clinical testing and evaluation needs to be performed such as the testing associated with the current MR (Med B 1.10; Appendix 4) addressing vision and eye anatomy with additional testing establishing the role of increased intracranial pressure

The VIIP panel also recommended research to establish risk stratification and underlying mechanisms based on anatomy (ex. crowded optic disc, angle of the optic disc and optic nerve interface, tortuousity of optic nerves, contribution of jugular and parajugular vessels for cerebrovascular outflow, incompetent jugular valves, etc.), physiology (ex. low cranial and vascular compliance, poor cerebral vascular auto regulation, magnitude of in-flight venous congestion, degree of catabolism (i.e. bone and muscle loses)), genetics (blinded screening to detect the presence or absence of a gene in the populations described in the case classifications above), and epigenetics (blinded screening to detect genes that are impacted (i.e. directionally modulated - increased or decreased expression) by the spaceflight environment which includes microgravity, chronic CO2 exposure, limited diet, stress, etc.)

SPECIFIC RECOMMENDATIONS

In order to interpret and implement the specific recommendations of the VIIP panel we have broken down the material into primarily two categories: clinical management and fundamental research areas. The material in each of those categories will undergo further discrimination by the VIIP project team with guidance from the SRP in order to determine 1) what can be immediately implemented or requires additional research and development for clinical management and 2) prioritization of objectives captured in the fundamental research areas.

A. Clinical Management		
Immediate Operational Implementation	**Research and Development Required**	**Epidemiology**
1. Pre-flight and post-flight lumbar puncture of all long duration astronauts to determine intracranial pressure (timeframe: L - 6 months and R + 4-5 days and R + 2 months; must be coordinated with MRI and ultrasound) (Action required for medical requirement (MR) development.) 2. Coordination of MRI and ultrasound images to enhance ability to interpret inflight ultrasound images (Action required for MR change.) 3. Enhanced analysis of current pre- and post-flight OCT findings such as RPE angle 4. Improved in-flight fundoscopic imaging capability (optimization of current in-flight hardware underway) 5. Blinded readings of previous and future diagnostic imaging to minimize potential bias 6. Consider the possibility of obtaining more than one pre-flight measurement of ICP(lumbar puncture) due to normal variability of this measurement	1.Assessment of Compliance: Vascular compliance; MRI assessment of cranial and spinal compliance Decreased compliance results in greater transmission of hydrodynamic forces causing increased deficits 2.Assessment of role of jugular and parajugular vessels in cranial outflow Is venous outflow compromised leading to venous congestion and increased ICP? 3.In-flight optical coherence tomography (OCT) capability (under assessment by Space Medicine hardware team) Improved assessment & monitoring of ocular changes resulting in visual acuity change. 4.In-flight non-invasive intracranial pressure monitoring device (validation of commercial hardware has been initiated) Noninvasively monitor ICP in-flight 5. Assessment of cephalad fluid shift and transmission of hydrodynamic forces on ocular anatomy and function to understand the cause(s) of altered visual acuity a. Does IOP change in-flight? b. What is the relationship between ICP, ONSD, choroidal engorgement and IOP? c. What is the relationship between papillary protrusion secondary to ICP and the degree of papilledema d. Is episcleral pressure increased causing decreased aqueous humor outflow? e. What is the relationship between age and ocular changes in-light? f. Does age and the structure of the lamina cribosa impact the degree of visual acuity change? 6. In-flight venous congestion via ultrasound to determine whether jugular venous pressure increases in ug a. What is jugular venous pressure in-flight? 7. Determine the etiology of post-flight cotton wool spots (Is it Ischemia-secondary to axoplasmic stasis?) 8. Options for non-pharmaceutical means to reduce cephalad blood volume included lower body negative pressure (LBNP) and thigh cuffs (brazlet). Both will have to be evaluated for operational feasibility and potential for extended use or development of a prescription for optimal use (ex. mins or hrs of exposure per day, days per week, etc.) Ground and Inflight assessment of Braslet and LBNP on ICP, venous pressure, and ocular anatomy 9. Options for pharmaceutical intervention will require ground testing and intense monitoring if used pre and post-flight. The following drugs have been proposed and require further investigation into dose, duration, and possible multi-drug approaches: a. Acetozolamide, b. Topiramate, c..Inodmethicin, d..Furosamide, e. Bumetanide, g. Neptazane, h. Angiotensin Converting Enzyme inhibitors	Case definition for data mining purposes – all long duration astronauts who have demonstrated post-flight refractive changes should be considered a suspected case; cases could be further differentiated to specify those with definitive imaging studies establishing the post-flight presence of papilledema, increased optic nerve sheath diameter, and altered OCT findings The intent is to define the susceptibility factors, improved case definition, better understand whether phenomena is all-or- nothing versus a physiological continuum. Examples of suspected aggregating variables for known cases include: increased blood pressure, serum lipids, serum homocysteine, and lowered maximal oxygen uptake.

B. Fundamental Research Areas					
Physiology and Anatomy (human and animal models)	**Role of animal models (hind limb unloaded (HU) rat; other animal models?)**	**Hardware**	**Genetics**	**Biomarker**	**Other Imaging Methodologies**
1. Characterization of human spaceflight physiology a. Plasma volume b. Cephalad fluid shift c. Central venous pressure d. Venous congestion e. CSF Absorption – inflammatory cytokines, signaling molecules (see subarachnoid hemorrhage like condition - scarring), arachnoid villi; venous lymphatics – elongation stretching neural and vascular structures (How does spinal elongation associated with spaceflight affect this?) 2. Role of In-Flight Environmental Factors (requires ground research before proceeding to flight studies) a. CO2 (collaboration with Navy) b. High salt diet c. Resistive exercise	1.Vascular remodeling; differential functional outcomes (increased or decreased contractility) 2.Can intervention (like ANP) reverse choroid plexus damage 3.Time course study - Assessment of recovery 4.Potential chronic instrumentation 5.Time course and dose response to CO2 assess CSF production, absorption 6.Assess alterations in integrity of BBB – changes in tight junctions, etc 7.Assess blood retinal barrier – endothelial cell tight junctions 8.Assess effectiveness of intranasal administration of diamox, octreotide	1. Ultrasound: new hardware in certification process; goal is launch to STS-135 launch date TBD 2. OCT: may be implementable as a small project; more investigation is necessary to ensure requirements are defined and met. 3. Laptop based vision test: current programs need to be evaluated by subject matter experts; definitely implementable quickly 4. Panoptic: in discussions with subject matter experts on image quality issues 5. Tonometry: working on the final analysis of ground data and a plan to analyze activation and check out data; assessing acceptance criteria	Advanced Biomarker studies: 1. gene expression - done w/o mapping to individual to avoid DNA fingerprinting, all can be measured from peripheral blood samples, case control design is statistically powerful (small sample size can detect change (n<10)); Unsupervised classification at False Discovery Rate 0.0001 2. epigenetic modifications of gene expression 3 .proteomics 4 .metabonomics 5. CO2 retaining variants – need to establish functional effect 6.Aquaporin 1 7. SNPs (which genes to target?) 8. Copy number variants	Blood (serum): 1)S-100, albumin 2)platelet count 3)CRP,other inflammation markers 4)IGF 5)Somatostatin 6)TTA CSF: 1)Myelin basic protein 2/IGG index 3)oligo-clonal bands 4)ANP or BNP 5)Vasopressin 6)Q albumin 7)Aquaporin (to determine if choroidal cell damage has occurred?) 8)Cytokines, inflammation markers 9)IGF 10)Somatostatin 11)TTA Assess amount of CSF fluid is needed and what risk it poses for LP side effects such as headache	1.Transcranial Doppler 2.Near infrared spectroscopy 3.Ophthalmodynanometry-Central retinal venous pressure may correlate well with ICP but concerned about lookin at the end affected organ 4.Venous Doppler ultrasound a. Assess anatomy and venous drainage patterns with different postures including upright, HDT head turning

C. Other Issues to Follow Up:

The following two areas discussed during the VIIP summit as having value to the development of a research plan and potential resource for investigators to pursue preliminary data given the resource constrained nature of flight samples

1. Animal tissue repository characterization – Life Science Data Archive (LSDA) for arachnoid granulation for morphological changes, CSF
2. Human tissue (National Disease Research Interchange - NDRI) – can request human tissue for experimentation

D. Summary of Recommended Prioritization for Specific Recommendations

Immediate:

1. Correlate pre-flight and post-flight MRIs with Ultrasound

2. Directly measure ICP (lumbar punctures) pre-flight and post-flight on all long duration astronauts (consider a way to include cosmonauts to increase our sample size)

3. Consider the possibility of obtaining more than one pre-flight measurement of ICP(lumbar puncture) due to normal variability of this measurement

4. Enhanced analysis of OCT findings such as RPE angle

5. Blinded readings of previous and future diagnostic imaging to minimize potential bias

6. Measurement of in-flight IOP on all astronauts

7. Improved in-flight fundoscopic imaging capability

8. Measurement of pre-flight and post-flight compliance (cranial, spinal, vascular)

Near-term:

1. Establish a case definition for this syndrome based on current Medical Requirements Integration Documents (MRIDs) and clinical findings

2. Develop a Clinical Practice Guideline for this syndrome based on current MRIDs, case definition, and clinical findings

3. Establish a reliable and accurate non-invasive in-flight capability to measure and monitor ICP, compliance and cerebral blood flow

4. Develop more sophisticated in-flight neurocognitive testing (this will require pre-flight baseline neurocognitive testing)

5. Establish risk stratification and underlying mechanisms for this syndrome based on anatomy and physiology

Long-term:

1. Characterization of Human Spaceflight Physiology and Anatomy (human and animal studies)

2. Develop and/or utilize advanced imaging modalities (Near Infrared Spectroscopy (NIRS), Transcranial Doppler (TCD), Ophthalmodynanometry, Venous Doppler Ultrasound)

3. Genetic testing

4. Use of biomarkers in blood and Cerebrospinal Fluid (CSF)

5. Animal tissue repository characterization

6. Human tissue (investigate utility of National Disease Research Interchange)

Appendix 1: **Visual Impairment Intracranial Pressure Summit Agenda**

AGENDA

VISUAL IMPAIRMENT – INTRACRANIAL PRESSURE SUMMIT

Universities Space Research Association

3600 Bay Area Blvd @ Middlebrook, Houston, TX 77058. Phone: 281-244-2000

February 8-10, 2011

Day 1 - February 8, 2011 [7:30 am – 4:35 pm]

7:30-8:00	**Sign In**	
8:00-8:05	**Welcome, Room Logistics, & Rules of the Meeting**	J Fogarty
8:05-8:15	**Meeting Agenda Review & Objective**	C Otto
8:15-8:30	**Introduction of Panel**	Panel Members
8:30-10:15	**Clinical Summary of Visual Impairment and Intracranial Pressure Problem**	JD Polk B Gibson and A Pass
10:15-10:30	BREAK	
10:30-11:15	**Space Physiology**	C Sams
11:15-12:00	**ISS Medical Operations Summary**	S Hart
12:00-1:00	LUNCH	
1:00-1:45	**ISS CO_2 Issue**	D Alexander
1:45-3:00	**Epidemiology Summary**	M Van Baalen
3:00-3:15	BREAK	
	Topic #1 – Operational Constraints of Detection, Therapeutics, and Monitoring*	
3:15-3:30	Introduction to Topic	D. Hamilton, S. Hart, J. Polk
3:30-4:15	Open Discussion	Lead by Co-Chairs
4:15-4:30	Summary of Possible Research Elements & Ops Suggestions	Lead by Co-Chairs
4:30-4:35	Discussion	

VISUAL IMPAIRMENT – INTRACRANIAL PRESSURE SUMMIT		
Day 2 - February 9, 2011 [7:30 am – 5:05 pm]		
8:00-8:05	**Welcome Back and Review of Agenda**	J Fogarty
	Topic #2 – Neuro-Ophthalmology*	
8:05-8:20	Introduction to Topic	S. Katz (J. Rizzo)
8:20-9:05	Open Discussion	Co-Chairs
9:05-9:20	Summary of Possible Research Elements & Ops Suggestions	Co-Chairs
	Topic #3 – Cerebrovascular/Fluid Shifts (*including cerebral edema)**	
9:35-9:50	Introduction to Topic	M. Bershad (D. Baskin)
9:50-10:35	Open Discussion	Co-Chairs
10:35-11:50	Summary of Indications of Possible Research Elements from this Topic	Co-Chairs
	Topic #4 – Analogs	
	Topic #4a – High Altitude*	
1:00-1:15	Introduction to Topic	R. Roach
1:15-2:00	Open Discussion	Co-Chairs
2:00-2:15	Summary	Co-Chairs
	Topic #4b – Bed Rest*	
2:15-2:30	Introduction to Topic	R. Cromwell
2:30-3:15	Open Discussion	Co-Chairs
3:15-3:30	Summary	Co-Chairs
	Topic #4c –Animal Models*	
3:45-4:00	Introduction to Topic	Motamedi/Delp
4:00-4:45	Open Discussion	Co-Chairs
4:45-5:00	Summary	Co-Chairs
5:00-5:05	**End of Day Summary and Reminders**	

AGENDA

VISUAL IMPAIRMENT – INTRACRANIAL PRESSURE SUMMIT

Day 3 – February 10, 2011 [7:30 am – 5:05 pm]

7:30-8:00	**Sign In**	
8:00-8:05	**Welcome Back and Review of Agenda**	**J Fogarty**
	Topic #5 – Assessment of Summit Recommended Countermeasures*	
8:05-8:20	Introduction to Topic	J. Fogarty
8:20-9:05	Open Discussion	Lead by Co-Chairs
9:05-9:25	Summary of Indications of Possible Research Elements from this Topic	Lead by Co-Chairs
9:25-9:45	BREAK	
9:45-11:45	**Review of Summit Discussion from Days 1,2, and 3**	**J Fogarty**
11:45-1:00	LUNCH	
1:00-5:00	**Panel Discussion (Panel Only) – Leads, J Fogarty and C Otto**	

1. Summary of Research Elements suggested during Topics 1-5
2. Discussion and Cleaning Up of Suggested Research Elements
3. Prioritization of Research Elements
4. Description of VIIP Project Plan – How it all flows together
5. Summary of Research Plan (including choice of Research or Science Advisory Panel)

5:00-5:05 **End of Summit Summary and Thank You**

Co-Chairs of the Visual Impairment – Intracranial Pressure Summit

Dr. Jennifer Fogarty, PhD
Visual Impairment – Intracranial Pressure Project Manager
NASA Johnson Space Center

Dr. Christian Otto, MD
Visual Impairment – Intracranial Pressure Research Project Scientist NASA
Johnson Space Center, Universities Space Research Associate (USRA)

Appendix 2: VIIP Summit Attendees

VIIP Summit Co-Chairs		
Jennifer Fogarty, PhD NASA Johnson Space Center - VIIP Project Manager	Christian Otto, MD NASA Johnson Space Center - VIIP Research Lead	
VIIP Summit Panelists		
Noam Alperin, PhD University of Miami	Steven E. Katz, MD Ohio State University	Joseph F. Rizzo, MD Massachusetts Eye & Ear Infrm Opthalmology
David S. Baskin, MD Methodist Hospital	William Andrew Kofke, MD, MBA, FCCM University of Pennsylvania	Robert Roach, PhD University of Colorado
Eric Michael Bershad, MD Baylor College of Medicine	Benjamin D. Levine, MD University of Texas, Southwestern Medical Center at Dallas	Val M Runge, MD University of Texas Medical Branch
John B. Charles, PhD NASA Johnson Space Center -HRP Chief Scientist	Thomas H. Mader, MD NASA Opthomology Consultant	Niels H. Secher, MD, DMSc University of Copenhagen
Jonathan B. Clark, MD National Space Biomedical Research Institute	Vince Michaud, MD NASA Headquarters	Jose I Suarez, MD Baylor College of Medicine
Mike D. Delp, PhD University of Florida	Massoud Motamedi, PhD University of Texas Medical Branch	Rosa A. Tang, MD, MPH, MBA University of Houston
Conrad E. Johanson, PhD Brown Medical School	Steven H. Platts, PhD NASA Johnson Space Center - Cardio Lab	Emanuel Tanne, MD The Intracranial Hypertension Research Foundation
VIIP Summit Attendees		
David J. Alexander, MD NASA Johnson Space Center - Flight Doc	Stephen F. Hart, MD NASA Johnson Space Center - Flight Doc	Anastas F. Pass, OD MS JD FAAO Uh/NASA Opthomology Consultant
Rafat Ansari, PhD NASA Glenn Research Center	Katherine Helmick MS, RN, CNRN, CRNP Department of Defense Traumatic Brain Injury Center of Excellence	Lori Ploutz-Snyder, PhD NASA Johnson Space Center - Exercise Countermeasures
Liz Bauer NASA Johnson Space Center - VIIP Research Deputy	Wayne G. Horn, MD CDR, MC, USNR (Ret) United States Navy	James D. Polk, MD NASA Johnson Space Center - Space Med Division Chief
Jacob Bloomberg, PhD NASA Johnson Space Center - Neuro Lab	John James, PhD NASA Johnson Space Center - JSC Chief Toxicologist	Brad Rhodes NASA Johnson Space Center - Space Med Deputy/Prog
Michael Chandler NASA Johnson Space Center - Med Ops Deputy	Smith Johnston, MD NASA Johnson Space Center - Flight Doc	Clarence C. Sams, PhD NASA Johnson Space Center - ISSMP Chief Scientist
Barbara Corbin NASA Johnson Space Center - HRP Deputy	Sean R. Keprta, MS CIH NASA Johnson Space Center - Clinic Services Branch Chief	Ashot Sargsyan, MD NASA Johnson Space Center - Advanced Projects
Ronita Cromwell, PhD NASA Johnson Space Center	Eric Kerstman, MD NASA Johnson Space Center - Advanced Projects	Gwyn Smith NASA Johnson Space Center - Health System Hardware
Dick Danielson, PhD NASA Johnson Space Center - Audiologist	Keith Killu, MD Henry Ford Hospital	Scott M. Smith, PhD NASA Johnson Space Center - Nutrition
Jeff Davis, MD NASA Johnson Space Center - Space Life Sciences Director	Larry Kramer, MD University of Texas Medical School of Houston	Victor Schneider, MD NASA Headquarters
Tamara Durham NASA Johnson Space Center - VIIP Project Deputy	Kjell Lindgren NASA Johnson Space Center - Crew Office	Jeffrey P. Sutton, MD, PhD National Space Biomedical Research Institute
Doug Ebert, PhD NASA Johnson Space Center - Advanced Projects	Robert J. Marchbanks, PhD Byrns Dell	Terrance Taddeo, MD NASA Johnson Space Center - Med Ops Chief

David Francisco **NASA Johnson Space Center - Human Adaptation and Countermeasures Chief**	**Kathleen McMonigal, MD** **NASA Johnson Space Center - Institutional Review Board Chair**	**Bill Tarver, MD** **NASA Johnson Space Center - JSC Clinic Chief**
C. Robert Gibson, OD **NASA Opthomology Consultant**	**Lauren Merkle, EdD** **NASA Johnson Space Center - Deputy Prog Element Scientist**	**Mary Van Baalen** **NASA Johnson Space Center - Lifetime Surveillance Astronaut Health**
Edward Good, MD **Bay Area Hypersciences**	**Shannan Moynihan, MD** **NASA Johnson Space Center - Flight Doc**	**Sharmi Watkins, MD** **NASA Johnson Space Center - ExMC Element Scientist**
Dennis Grounds **NASA Johnson Space Center - HRP Director**	**Jerry Myers, PhD** **NASA Glenn Research Center**	**Andrew Watson, PhD** **NASA Ames Research Center**
Douglas R. Hamilton, MD, PhD **NASA Johnson Space Center - Advanced Projects**	**Peter Norsk, MD** **NASA Johnson Space Center - Human Health and Countermeasures Element Scientist**	**Mary Wear** **NASA Johnson Space Center - Epidemiologist**
Chris Hansen **NASA Johnson Space Center - ISS Chief Engineer**	**Cherie Oubre, PhD** **NASA Johnson Space Center - NxPCM**	**Jimmy Wu** **NASA Johnson Space Center - Advanced Projects**

Appendix 3: **VIIP Background and Summary of Cases**

Visual Impairment/Increased Intracranial Pressure (VIIP):

To date seven long duration astronauts have experienced in-flight and post-flight visual and anatomical changes including optic disc edema, globe flattening, choroidal folds, and hyperopic shifts as well as documented increased ICP. In the post-flight time period some individuals have experienced transient changes while others have experienced changes that are persisting with varying degrees of severity. While the underlying etiology of these changes is unknown at this time, the spaceflight community at NASA suspects that the microgravity-induced cephalad fluid shift and commensurate changes in physiology play a significant role. Given that all astronauts exposed to microgravity experience a cephalad fluid shift, and that both symptomatic and asymptomatic (with respect to changes in visual acuity) crewmembers have exhibited optic nerve sheath edema on MRI, it is likely that all astronauts develop microgravity-induced intracranial hypertension to some degree. The Space Life Sciences Directorate (SLSD) has assembled a visual impairment/increased intracranial pressure (VIIP) project team to address this issue using a comprehensive project plan with regard to operations and research. The operations arm of the project is addressing implementation of medical requirements pre-flight and immediate clinical needs of the NASA flight surgeons, such as diagnosis and treatment modalities and criteria, and how to respond to in-flight and post-flight clinical needs. The research arm is developing a multidisciplinary, collaborative research approach, that will consist of a steering committee, a scientific advisory panel, and a research collaboration team composed of clinical, translational, and fundamental research experts. This integrated approach is designed to effectively and efficiently address immediate clinical and operations needs while developing a collaborative research model.

NASA has determined that the first case of increased intracranial pressure with visual changes occurred in an astronaut during a long duration ISS mission. An astronaut reported visual changes after 3 months of a 6 month mission on ISS, necessitating the use of reading glasses when gazing at the earth. This individual experienced hyperopia during the flight, and post-flight fundoscopic exam and flourescene angiography revealed posterior choroidal folds, optic disc swelling and edema in both eyes and cotton wool spots in the left eye. Further testing was pursued including MRI, OCT and lumbar puncture (direct measurement of cerebral spinal fluid pressure, i.e. intracranial pressure) to further characterize the pathology. Findings included an increased cerebral spinal fluid pressure at a level that suggests the mild intracranial hypertension. The etiology of this increased ICP is unknown. Additional cases of altered visual acuity have been reported since this seminal case and one case has included the report of a scotoma (visual field defect) which resulted in the astronaut having to have a head tilt of 15 degrees to view instruments and procedures. These visual symptoms persisted for over twelve months after flight. This type of functional deficit is not only of concern to the individual but is of concern to the mission and ISS program managers.

An examination of medical data on the affected long duration ISS astronauts was performed to better characterize the constellation of symptoms and anatomical and physiological changes. Following exposure to spaceflight of five to six months duration, seven astronauts were discovered to have neuro-ophthalmic findings. These findings consist of disc edema in five astronauts, globe flattening in five astronauts, choroidal folds in four astronauts, cotton wool spots in three astronauts, nerve fiber layer (NFL) thickening by OCT in six astronauts, and complaints of a decrement in near vision in six astronauts. Five of the seven astronauts with complaints of altered near vision were documented to have a pre- to post-mission hyperopic shift of equal to or greater than + 0.50D spherical equivalent refraction in one or

both eyes (range +0.50D to +1.50D). These same five were noted to have globe flattening by MRI. Lumbar punctures performed in three astronauts with disc edema showed opening pressures of 22, 21 and 28 cm of water (H_2O) performed at 60, 19 and 57 days post mission, respectively. One astronaut has a sustained opening pressure of 22 cm H_2O 1700 days after flight. See Table 1 for summary.

An alteration in visual acuity associated with spaceflight is not a new finding, reports documented through medical testing, research, and anecdotal reports have circulated over the last 40 years. Recently, examination of data from approximately 300 post-flight questionnaires, documented that approximately 29% of short, and 60% of long duration mission astronauts, experienced a subjective degradation in visual acuity. It is important to recognize that visual symptoms reported by astronauts in the past were often minor, transient, not accompanied by other symptoms or significant clinical findings, and a common finding in the general population of 40-50 year old individuals. Increased ICP was not suspected and no testing was performed to evaluate changes. Due to more severe functional deficits in visual acuity, persistent symptoms, and the acquisition of detailed anatomical images suggesting architectural alterations, NASA is taking a much more aggressive approach to addressing this problem through the VIIP project.

The NASA Johnson Space Center, Space Medicine Division (SD), in collaboration with the SLSD VIIP project has implemented an expanded set of medically required pre-, in-, and post-flight testing (Appendix: MedB 1.10) to determine the existence and degree of the ophthalmic and intracranial pressure alterations. In order to facilitate the in-flight collection of data, SD and VIIP have increased the on-orbit imaging capability by recently flying a video fundoscope and state-of-the-art hand-held tonometer, and developing procedures for eye ultrasound to characterize globe flattening and increases in optic nerve sheath diameter. SD and VIIP are also developing a study to evaluate a non-invasive intracranial pressure monitoring device for the clinical evaluation of ICP pre-, in- and post-flight. This increased capability and expanded set of tests are used to inform the medical treatment of the individual astronauts as well as characterize the manifestation of the pathology in order to inform the astronaut corps and the spaceflight community in general. The results of these tests and images can function on an individual level to inform medical care and occupational health decisions, and on a population level, they can inform risk management decisions. Additionally, all of these data are used in conjunction with human research data acquired over the life of the space program, to determine the potential scope of the forward research plan.

The VIIP project is working in concert with the NASA Human Research Program (HRP) on the development of an integrated and collaborative research model. This model employs a SLSD/HRP steering committee, a scientific advisory panel (SAP) composed of internal and external experts, and a collaborative research team that integrates clinical, translational, and fundamental researchers. The SLSD/HRP steering committee provides the management oversight with respect to prioritization of resources. The SAP consists of internal and external experts from clinical, operational, and research backgrounds, who initially assist in the determination of the scope of the research project, and over the course of the project, acts as science advisors to facilitate effective and efficient communication of scientific findings as well as recommends a course of action when research decisions have to be made. The collaborative research team will be made up of investigators willing to work collaboratively, openly communicate their work, and be flexible with their research agenda as it will be frequently be informed by the decisions and priorities of the steering committee and the SAP.

Table 1: Summary of VIIP Cases:

Table 1 provides key points of clinical information for each crewmember obtained pre-flight, during the crew mission on the ISS and post-flight. Disc edema was graded with the modified Frisen scale. [OD=right, OS=left, OU=both eyes, sph=sphere, OCT=optical coherence tomography, MRI=magnetic resonance imaging, CSF=cerebral spinal fluid, NFL=retinal nerve fiber layer and R+=return to Earth; (presented by number of days (e.g., R+19 is 19 days after return to Earth)].

ISS Crew Member	*Mission Duration*	*Refractive Change*	*Intraocular Pressure (mmHg)*	*Fundoscopic Exam Postflight*	*Disc Edema (Frisén)*	*OCT Postflight*	*Eye MRI Postflight* / *Globe Flattening*	*CSF Pressure Postflight (cmH2O)*
CASE 1	6 months	Preflight: OD: -1.50 sph OS: -2.25-0.25x135 Postflight: OD: -1.25 -0.25x005 OS: -2.50-0.25x160	Preflight: 15 OU Postflight: 10 OU	• Choroidal folds OD • Cotton wool spot OD	Edema: No disc edema	• Choroidal folds still visible inferior to the OD disc (R+ >5yrs)	MRI not performed Globe Flattening: Not assessed	Not measured
CASE 2	6 months	Preflight: OD: +0.75 OS:+0.75-0.25x165 Postflight: OD: +2.00 sph OS: +2.00-0.50x140	Preflight: 14 OU Postflight: 14 OU	• Bilateral disc edema OD>OS • Choroidal folds OD > OS • Cotton wool spot OS	Edema: Grade 1 OD and OS	• NFL thickening c/w disc edema	Optic nerve sheath distension OD and OS Globe Flattening: OD and OS	Elevated • 22 at R+66 days; • 26 at R+17 months; • 22 at R+19 months) • 23 at R+>5yrs
CASE 3	6 months	Preflight: OD: -0.50 sph OS: -0.25 sph Postflight: Plano Plano	Preflight: 10 OU Postflight: 10 OU	• Bilateral disc edema OD>OS • Small hemorrhage OD	Edema: Grade 3 OD Grade 1 OS	• Severe NFL thickening OD>OS c/w Disc edema	Optic nerve sheath distention OD Globe Flattening: None observed	Elevated • 21 at R+19 days
CASE 4	6 months	Preflight: OD: -0.75-0.50x100 OS: plano-0.50x090 Postflight: OD: +0.75-0.50x105 OS: +0.75-0.75x090	Preflight: 15/13 Postflight: 11/10	• Disc edema OD • Choroidal folds OD	Edema: Grade 1 OD	• Mild NFL thickening OD>OS c/w disc edema • Choroidal folds OD	Optic nerve sheath distention and tortuous optic nerves OD>OS Globe Flattening: OD > OS	Elevated • 28.5 at R+57 days
CASE 5	6 months	Preflight: OD: -5.75-1.25x010 OS: -5.00-1.50x180 Postflight: OD: -5.00-1.50x015 OS: -4.75-1.75x170	Preflight: 14/12 Postflight: 14/12	• Normal	Edema: No disc edema	• Subclinical disc edema • Mild/moderate NFL thickening OD	Optic nerve sheath distention and tortuous optic nerves Globe Flattening: OD and OS	Not measured
CASE 6	6 months	Preflight: OD: +0.25 OS: +0.25-0.50x152 Postflight: OD: +2.00-0.50x028 OS: +1.00 sph	Preflight: 14 OU Postflight: 14 OU	• Disc edema OD • Cotton wool spot OS	Edema: Grade 1 OD	• Mild NFL thickening c/w disc edema • Choroidal folds OD	Optic nerve sheath distention OD>OS Globe Flattening: OD > OS	Not Measured
CASE 7	6 months	Preflight: OD: +1.25 sph OS: +1.25 sph Postflight: OD: +2.75 sph OS: +2.50 sph	Preflight: 16 OU Postflight: 12/14	• Disc edema OU • Choroidal folds OD>OS	Edema: Grade 1 OD and OS	• Moderate NFL thickening c/w disc edema OD and OS • Choroidal folds OD and OS	Optic nerve sheath distention OD and OS Globe flattening: OD and OS	Elevated • 28 at R+12 days (with +SVP) • 19 at R+ days

Appendix 4: Medical Requirement

MEDB 1.10 Eye Examinations

Pre-Flight MEDB (L-180 – L-30) All long duration crew members

Previous

- Refraction
- Near and far visual acuity
- Tonometry
- Automated visual fields
- Dilated fundoscopy
- Contact lens/spectacle storage plan
- Amsler grid
- Retinal photography
- Extraocular muscle examination
- Optical coherence tomography-spectral domain (OCT-SD)
- Pupil reflex
- Biomicroscopy
- A-Scan ultrasound

Red = performed per previous MRID
Blue = previously performed, but added to updated MRID

Additional

- PanOptic video fundoscopy baseline and training
- 3T orbital MRI with contrast
- 2-D imaging ultrasound baseline and training

In-Flight MEDB (L+30, R-30, L+100) All long duration crew members

Previous

- None required per MRID

Additional

- Near and far visual acuity
- Amsler grid
- Questionnaire
- Tonometry
- Dilated PanOptic video fundoscopy exam
- Remotely guided HRF eye ultrasound

Post-Flight MEDB (R+1 - R+3 or ASAP)
All long duration crew members

Previous

- Near and far visual acuity
- Tonometry
- Pupil reflex
- Extraocular muscle examination
- Biomicroscopy
- Questionnaire
- Amsler Grid
- Dilated fundoscopy
- Automated visual fields
- Refraction
- Retinal photography
- Optical coherence tomography-spectral domain (OCT-SD)
- A-Scan ultrasound

Red – performed per previous MRID
Blue = previously performed, but added to updated MRID

Additional

- 3T orbital MRI with contrast
- 2-D imaging ultrasound

Appendix 5: LIST OF ACRONYMS

ANP	Atrial Natriuretic Peptide
CAT	Computerized Axial Tomography
CSF	Cerebrospinal Fluid
H_2O	Water
HRP	Human Research Program
HU	Hind limb unloaded
ICP	Intracranial pressure
IOP	Intraocular Pressure
ISS	International Space Station
LSDA	Life Science Data Archive
MR	Medical Requirement
MRI	Magnetic Resonance Imaging
MRIDs	Medical Requirements Integration Documents
NDRI	National Disease Research Interchange
NFL	Nerve Fiber Layer
NIRS	Near Infrared Spectroscopy
OCT	Optical Coherence Tomography
ONSD	Optic nerve sheath diameter
SAP	Scientific Advisory Panel
SD	Space Medicine Division
SLSD	Space Life Sciences Directorate
SNPs	Single nucleotide polymorphisms
SRP	Standing Review Panel
TCD	Transcranial Doppler
VIIP	Visual Impairment Intracranial Pressure
VI	Visual Impairment