Clinical/Scientific Notes

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BIOPSY-PROVEN IMMUNE RECONSTITUTION SYNDROME IN A PATIENT WITH AIDS AND CEREBRAL TOXOPLASMOSIS

Cerebral toxoplasmosis (CNST) is the most common opportunistic infection producing mass lesions in the CNS and frequently develops in patients with a CD4 count less than 100.[1] Clinical presentation includes subacute onset headache, confusion, and focal neurologic symptoms. Diagnosis is made by the presence of antitoxoplasma immunoglobulin G (IgG) in serum or CSF, mass lesions on neuroimaging, and the context of a compromised immune system without prophylactic therapy. Pathologic examination provides definitive diagnosis. CNST responds to various antibiotic regimens and typically requires indefinite prophylaxis in individuals who will remain immunocompromised.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in association with highly active antiretroviral therapy (HAART) in patients with AIDS. Paradoxical deterioration occurs in response to disease previously unrecognized by the suppressed immune system.[2] The most common associations are with mycobacterial, chronic viral, and invasive fungal infections.[2] To date, only 4 prior reports exist of IRIS associated with CNST[3-5] and there has been doubt regarding the existence of CNST-associated IRIS as a true disease entity.

Case report. A 42-year-old man was HIV positive for 4 years, and not on treatment due to noncompliance. Two years prior to presentation, he arrived in the emergency department with seizures. CT scan and EEG were normal. He eventually returned for follow-up 3 months prior to presentation with a CD4 count of 130/mm^3 (9% absolute fraction) and viral load >100,000 copies/mL. Treatment with HAART was initiated.

Having been compliant with HAART for 3 months, the patient presented to hospital with focal-onset generalized seizures. Bloodwork revealed a CD4 count of 290/mm^3 (17% absolute fraction). CSF analysis demonstrated elevated protein of 650 mg/L, but normal cell counts and CSF pressure. Testing for toxoplasmosis IgG, Venereal Disease Research Laboratory, JC virus PCR, cryptococcal antigen, and PPD were negative.

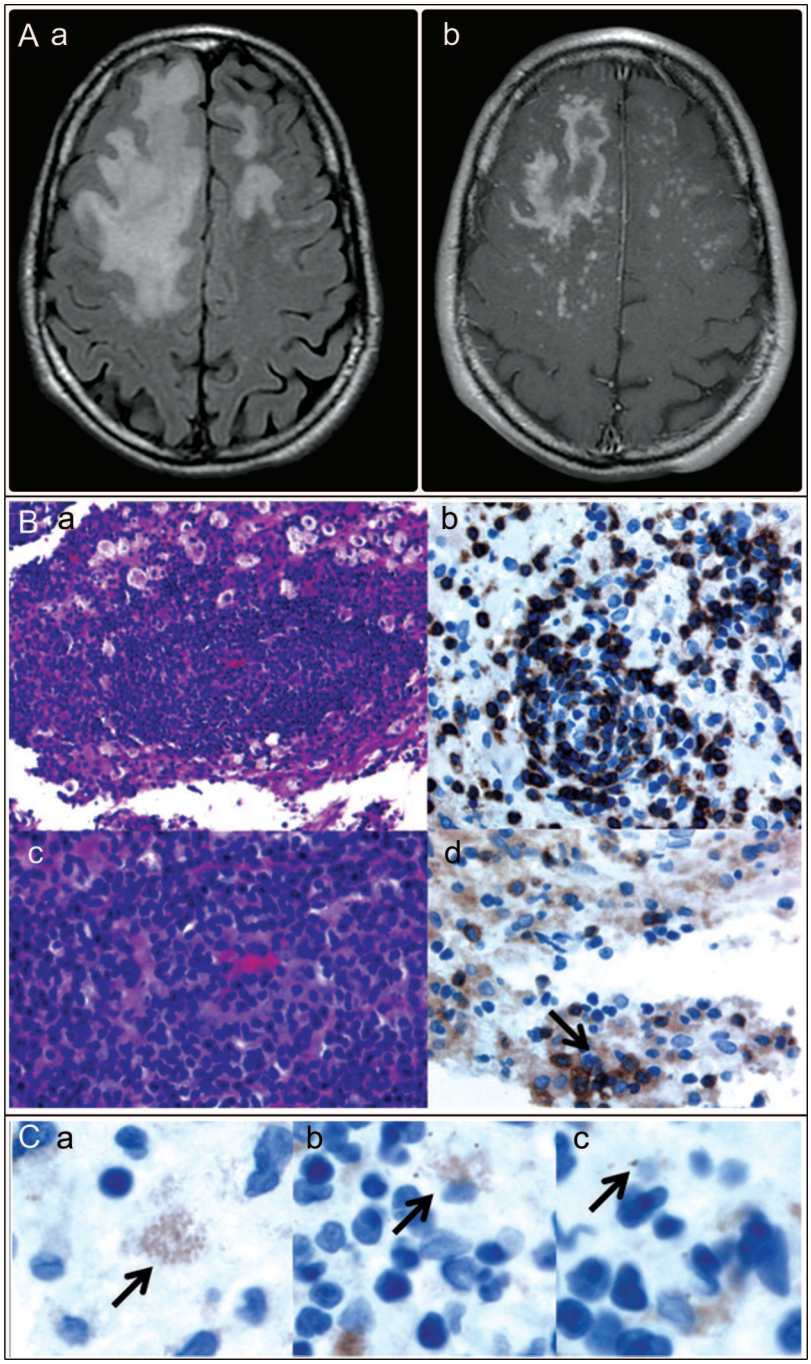
Neuroimaging with MRI showed T2 signal abnormality predominantly affecting the right frontal lobe more than the left, with an unusual speckled pattern of gadolinium enhancement (figure, A).

HAART was continued, empiric pyrimethamine and clindamycin were initiated for suspected toxoplasmosis, and phenytoin was initiated for seizure prophylaxis. After a negative toxoplasmosis IgG, antibiotic therapy was discontinued. One week later, the patient deteriorated clinically, with unchanged neuroimaging. Toxoplasmosis therapy was restarted and stereotactic brain biopsy of the left frontal lobe lesion was obtained. Over the following 2 months, the patient gradually improved, with negligible residual deficits.

Neuropathologic examination including immunohistochemistry revealed an intense reactive immunologic response, characterized by a predominance of CD8 lymphocytes, bradyzoites, and tachyzoites (figure, B and C). Clonality studies including flow cytometry ruled out primary CNS lymphoma as an etiology.

Discussion. A neurologic syndrome developed in the context of a rapidly reconstituting immune system on HAART. This case meets proposed diagnostic criteria for IRIS,[2] given the rapidly increasing CD4 count, the neuropathologically confirmed inflammatory process, and clinical, neuroimaging, and neuropathologic features that are not typical for CNST alone. The development of CNST with a CD4 count of 290/mm^3 is unlikely. The neuroimaging is not typical for CNST, given the diffuse speckled gadolinium enhancement seen in both cerebral hemispheres, although it bears some resemblance to CNST in the immunocompetent.[6] To our knowledge, this imaging appearance has not been reported with CNST, and we suggest these changes are consequences of a competent inflammatory response. Neuropathologic examination revealed active toxoplasmosis infection, as demonstrated in the antitoxoplasma immunoperoxidase study. The organisms identified included scattered individual small round to oval tachyzoites distributed throughout the tissues, within macrophages, and within small cystic structures (bradyzoites). Although the infection was not extensive, and the intensity of the immunoperoxidase reaction appeared somewhat attenuated, this was attributed to the sequelae of effective antitoxoplasmosis antibiotic ther-

Figure MRI and neuropathology



(A) Transverse axial T2 fluid-attenuated inversion recovery image (a) demonstrates signal abnormality in the white matter of both frontal lobes, predominant on the right. T1 postgadolinium image (b) at the same level reveals a speckled gadolinium enhancement pattern and a possible ring-enhancing lesion in the right frontal lobe. (B) Intense angiocentric inflammatory infiltrates (hematoxylin-eosin 10× [a] and 100× [c]). CD8 immunoperoxidase study (b) demonstrates predominance of T8 lymphocytes. CD4 immunoperoxidase study (d, indicated by arrow) revealed occasional $CD4^+$ T-cell infiltrates. (C) Antitoxoplasmosis immunoperoxidase study demonstrates active toxoplasmosis infection with a cyst containing bradyzoites (a), a macrophage with immunoreactive material surrounded by 3 discrete tachyzoites (b), and another example of a discrete extracellular organism at (c) (indicated by arrows).

apy preceding the biopsy, in association with a competent inflammatory response. An intense inflammatory response with a predominance of CD8 lymphocytes was also demonstrated, which is typically observed in IRIS but not previously reported in CNST alone. Neuropathology of CNST typically reveals encysted bradyzoites and clusters of tachyzoites with variable inflammatory response corresponding to the competency of the patient's immune system.[7]

Consideration should be given to the fact that this patient experienced clinical improvement while on empiric therapy for toxoplasmosis, and clinical deterioration coincided with interruption of therapy. Anti-toxoplasma IgG was negative, which occasionally occurs, even in pathologically confirmed CNST.[1]

Of the 4 previously reported cases of CNST-associated IRIS, 2 cases included neuroimaging (CT scans) and a complete case description appeared in 1 case.[3-5] CNST should be considered as an uncommon association with IRIS and our case provides the first neuroimaging and neuropathologic evidence to this effect.

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MELATONIN DEFICIENCY AND DISRUPTED CIRCADIAN RHYTHMS IN PEDIATRIC SURVIVORS OF CRANIOPHARYNGIOMA

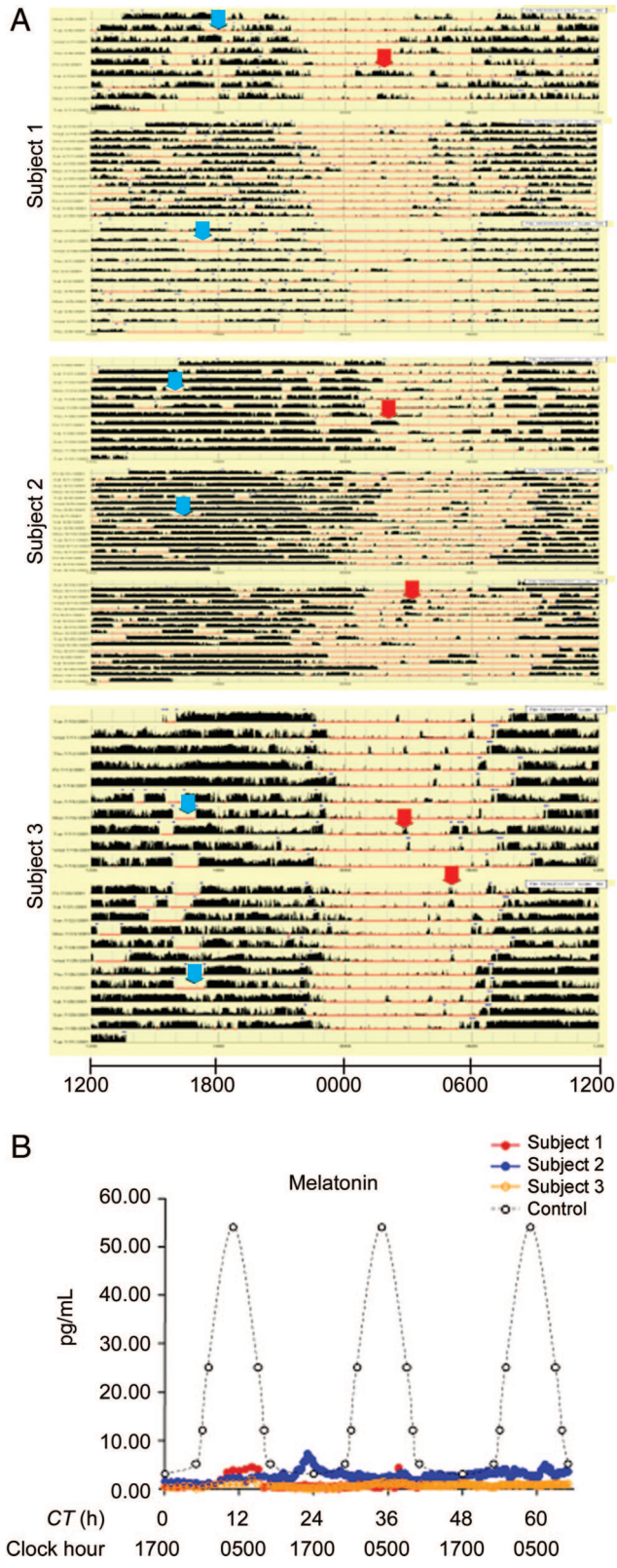
Craniopharyngiomas are the most common extraneural tumors of the CNS in children.[1] Because craniopharyngiomas usually grow along the anatomic midline, the tumors or their treatments (surgical excision and radiation) frequently lead to hypopituitarism, visual field defects, obesity, sleep abnormalities, and daytime hypersomnolence (DH).[2,3] DH persists despite hormone replacement or treatment of commonly associated obstructive sleep apnea (OSA). We hypothesized that disrupted sleep patterns in patients with craniopharyngioma result from dysfunction of the hypothalamic circadian pacemaker located in the suprachiasmatic nucleus, which controls the timing of the daily sleep propensity rhythm. Daily variations in levels of the pineal hormone melatonin serve as a marker of the function of this system. Low salivary melatonin has been documented in obese craniopharyngioma survivors and melatonin supplementation has proved beneficial in some cases; however, a detailed analysis of circadian rhythms in this patient population had not been performed.[4]

Methods. Subjects older than 8 years of age with self-reported DH requiring daytime stimulant medication were recruited from a pool of 42 craniopharyngioma survivors treated at the Children's Hospital Boston (CHB)/Dana-Farber Cancer Institute Brain Tumor Program between 1990 and 2002 by a single neurologist (S.L.P.). Four subjects were enrolled after informed consent was obtained in accordance with the Committee on Clinical Research. Three subjects (2 female, 1 male) ages 15, 15, and 22 completed the study. All had undergone both surgical extirpation and radiotherapy, were morbidly obese (BMI 41–54; normal 17–25), had panhypopituitarism requiring hormone supplementation, and had mild REM-related OSA, and 1 had a seizure disorder. Wrist actigraphy was obtained for 2 to 3 weeks prior to admission to the General Clinical Research Center sleep laboratory of CHB. During the ambulatory baseline weeks 1 and 2, subjects were not given any specific instructions regarding their sleep/wake schedules; during week 3, instructions to maintain strict and consistent sleep and waking times were given. Stimulant medications were discontinued in the third week but hormonal supplementation was continued throughout. Actigraphy data were analyzed to estimate sleep and wake periods in the 2 to 3 weeks before hospitalization (ACTION-W V2.0 and ACT-Millennium, Ambulatory Monitoring Inc., Ardsley, NJ). Subjects were then admitted to the hospital for 72 hours. Plasma melatonin was measured under dim light conditions (less than 10 lux) approximately every 20 minutes via indwelling IV catheter. IV access was lost in subject 1 following 40 hours of data collection. Two consecutive nights of 20-channel polysomnography (PSG) (Biologic Systems Corp., Mundelein, IL) were obtained. PSG records were scored according to standard scoring criteria.

Results. Actigraphy demonstrated rhythmic rest/activity patterns that were in general alignment with a 24-hour light-dark cycle; however, irregular bedtimes, frequent nighttime activity, and inappropriate daytime episodes of rest were observed despite a protocol of scheduled bedtimes and wake times (figure, A). In contrast, PSGs showed preservation of normal sleep architecture with confirmation of mild OSA in all subjects (data not shown). There were strikingly low mean 24-hour plasma melatonin levels in all subjects (2.7 ± 0.07, 0.82 ± 0.12, and 0.61 ± 0.02 pg/mL, respectively) compared to historical controls of 8 pg/mL (daytime hours) to 50 pg/mL (evening hours).[5] More importantly, average nocturnal melatonin levels (between 10 PM and 7 AM) were also markedly decreased (0.84 ± 0.82, 0.74 ± 0.29, 1.22 ± 1.27, respectively) as compared to historical controls (50–60 pg/mL; figure, B).[6]

Discussion. Sleep/wake cycles are hypothesized to result from a balance between both circadian and homeostatic influences. We have obtained evidence for both melatonin deficiency and irregular circadian function, as evidenced by substantial abnormalities in serially measured plasma melatonin levels in 3 survivors of craniopharyngioma. Our results are consistent with previous reports that have demonstrated normal PSGs in craniopharyngioma survivors.[3] Because melatonin rhythms serve as a marker for the functionality of the human circadian pacemaker, our data are suggestive of profound dysfunction in this system and consequent melatonin deficiency. We speculate that the complete loss of the circadian melatonin rhythm may reflect a disruption of daytime circadian arousal mechanisms, leaving homeostatic sleep drive unopposed and thus contributing to DH and sleep disruption in these patients. The observed absence of the nocturnal peak of melatonin suggests that symptoms in these patients may respond to exogenously administered melatonin during nighttime hours. Previous studies have demonstrated low sali-

Figure **Abnormal circadian behavior and melatonin levels in craniopharyngioma survivors**



(A) Ambulatory baseline recordings. Dark bars represent movement detected by wrist actigraphy; absence of dark bars indicates presumed sleeping bouts. Horizontal lines represent consecutive 24-hour periods. Clock hour is indicated on the x-axis. Arrows indicate examples of inappropriate presumed daytime sleep (red) or nocturnal arousal (blue). (B) Plasma melatonin profiles measured in craniopharyngioma subjects (colored circles) and controls (open circles). Clock hour is indicated on the x-axis. CT = circadian time in hours from onset of inpatient monitoring.

vary melatonin in obese craniopharyngioma patients with some improvement of self-reported DH with supplemental melatonin.[4,7] A multifocused approach to improve both DH and consolidation of sleep/wake rhythms could routinely include aggressive weight reduction, proper treatment of OSA, exposure to bright light upon awakening, and a 24-hour urinary measurement of the melatonin metabolite 6-hydroxymelatonin sulfate. Patients with melatonin deficiency may respond to exogenous melatonin supplementation.

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