Brain Damage After Heat Stroke

Céline Bazille, MD, Bruno Megarbane, MD, Dan Bensimhon, MD, Anne Lavergne-Slove, MD, PhD, Anne Catherine Baglin, MD, Philippe Loirat, MD, PhD, France Woimant, MD, Jacqueline Mikol, MD, PhD, and Françoise Gray, MD, PhD

INTRODUCTION

Heat stroke is a thermal insult to the cerebral thermoregulatory system controlling heat production and heat dissipation. The thermal insult may be endogenous in “exertional heat stroke” in soldiers and joggers or environmental in “classic heat stroke” (1–3). The latter is relatively common during heat waves, as seen in the 1995 Chicago heat wave, one of the worst of the 20th century, which resulted in hundreds of deaths (4, 5). Its incidence has been estimated as 17.6 and 26.5 per 100,000 persons, respectively, in Kansas City and St. Louis during the July 1980 heat wave (6). In August 2003, France sustained an unprecedented heat wave resulting in 14,800 excess deaths (7, 8), most often but not invariably in elderly or debilitated people (9, 10). Clinically, heat stroke is defined as an elevated core body temperature over 40°C and neurologic dysfunction (11, 12). Extreme fatigue, reddened face, hot dry skin or heavy perspiration, nausea, vomiting, diarrhea, confusion, dizziness, and uncoordinated movements are frequently associated. Potential immediate complications of severe heat stroke include shock, acute renal failure, rhabdomyolysis, acute respiratory distress syndrome, disseminated intravascular coagulation, and acid-base or electrolyte disturbances (11). Long-term neurologic sequelae occur in approximately 20% of patients (12). The neurologic complications of heat stroke have been clinically and radiologically documented in a number of recent studies (3, 13–16), but neuropathologic studies are extremely rare and old (17, 18). We report the neuropathologic findings in 3 French patients who experienced environmental heat stroke, 2 of whom died during the August 2003 heat wave and one after a heat wave that occurred in Paris in August 1995.

MATERIALS AND METHODS

Patients

Case 1

During an August 1995 heat wave in Paris, this 74-year-old woman was admitted to the intensive care unit (ICU) for hyperthermia (42.9°C), coma, and hypotension. Her medical history included hypertension, chronic alcoholism, depression, and mild cognitive impairment and she had received clomipramine, nifedipine, fenofibrate, and quinidine phenyl barbiturate. She was immediately intubated. Laboratory tests showed lactic acidosis and acute renal failure. There was no focal infection. External cooling in an air-conditioned room...
was promptly started. She rapidly developed shock and coagulation disorder. Supportive care included sedation, major fluid replacement, and bicarbonate. On day 2, she improved and was weaned from mechanical ventilation. However, when sedation was stopped, she manifested an extrapyramidal syndrome, including rigidity, facial and lingual dyskinesia, and ocular myoclonic movements. The level of consciousness was normal and all abnormal movement diminished when sleeping. Symptoms were unresponsive to anticholinergic medications but were mildly reduced with clomipramine reintroduction. Cerebral magnetic resonance imaging (MRI) with gadolinium injection was normal, and there were no lesions in the periventricular areas or in the central gray nuclei. The patient was transferred to the neurology department, where she died 2 months later from hospital-acquired pneumonia.

Case 2

During the August 2003 heat wave, this 80-year-old man was admitted to the ICU with coma, fever (42°C), and respiratory failure. He experienced hypertensive cardiomyopathy, atrial fibrillation, obesity, sleep apnea syndrome, and maturity-onset diabetes. His treatment included digoxin and fluididone. His mental status rapidly worsened and generalized myoclonus and shock were noted. He was promptly intubated. Laboratory tests showed severe lactic acidosis, acute renal failure, and disseminated intravascular coagulation. He was treated with external cooling, intravenous fluid, epinephrine, and continuous venovenous hemodiafiltration. Bacteriologic tests were negative. During the first week, he developed an ischemic colitis responsible for an *Enterobacter cloacae* bacteremia treated with adequate antibiotics. His general condition improved on day 15 and sedation was stopped. He was then able to understand simple commands, but an areflexic and hypotonic quadriplegia was diagnosed with spontaneous facial, buccal, and palatal myoclonus. Cerebral MRI did not show any abnormalities in the cortex, but there was mild cerebellar atrophy and increased signal in the central tegmentum of the midbrain at the anterior aspect of the periaqueductal gray matter (Fig. 1a). Neurophysiological tests showed severe axonal neuropathy of all 4 limbs. Paresis was attributed to heat stroke and ICU myopathy. Death occurred 1 month later as a result of hospital-acquired pneumonia.

Case 3

During the August 2003 heat wave, this 63-year-old man was admitted to the ICU for heat stroke. He had chronic alcoholism and schizophrenic psychosis treated with olanzapine. He was found outdoors unconscious with generalized seizures. His temperature was 43.2°C. On admission, he was unresponsive in hypotonic coma and was immediately intubated. Laboratory tests showed an elevated serum lactate, a mild elevation in plasma creatinine, and a decreased platelet count. Routine toxicologic screening was negative; there was no infection. Cerebral computed tomography scan did not show any cerebral hemorrhage or infarction, and electroencephalogram disclosed diffuse slow delta-wave activity with no reaction to stimuli. Rapidly he collapsed, became oliguric, and developed disseminated intravascular coagulation. Despite prompt external cooling and supportive care, he died from multiorgan failure 28 hours after admission.

**Methods**

Postmortem autopsy was performed within 24 hours after death in all 3 cases. In the first case, a complete postmortem examination was performed. Autopsy was limited to the brain, spinal cord, and samples of skeletal muscle in case 2 and to the brain in case 3. Gross examination of the brain was performed after 1 month 10% buffered formalin fixation on coronal sections of the cerebral hemispheres and sections of the cerebellum and brain stem perpendicular to its axis.

For light microscopy, large slices involving the cerebral hemispheres at 4 levels (frontal lobe and rostrum of corpus callosum, mammillary bodies, thalamus and lateral geniculate nucleus, and occipital horn of the lateral ventricle), and the brainstem/cerebellum at the level of the dentate nuclei, were embedded in paraffin. 15-μm-thick sections were stained by hematoxylin and eosin (H&E) and cresyl violet combined with Luxol fast blue (Klüver and Barrera stain). Smaller blocks were also taken from a number of regions of the central nervous system, including the cerebral cortex with underlying white matter, deep gray nuclei, hypothalamus, midbrain, cerebellum, brainstem and, in case 2, spinal cord, and embedded in paraffin. Five-μm-thick sections were stained with H&E, Masson’s trichrome, Bodian silver impregnation combined with Luxol fast blue and Woelcke stain for myelin.

On selected 5-μm-thick sections, immunohistochemistry was performed using an avidin–biotin complex, peroxidase-based method with the following commercial antibodies: a polyclonal antibody raised against the glial fibrillary acid protein (GFAP) (anti-GFAP; Dako, Glostrup, Denmark, 1/1000), a monoclonal antibody raised against the precursor of the protein beta amyloid (anti-Alzheimer precursor protein A4; Boehringer Mannheim, Philadelphia, PA, 1/200), and a monoclonal antibody raised against heat shock protein (HSP) 70 (NCL-HSP70; Novocasta, Newcastle upon Tyne, UK, 1/20). All sections were counterstained with hematoxylin. For all techniques, controls included the omission of the primary antibody and simultaneous staining of known positive or normal material.

Apoptotic cells were looked for using the in situ end labeling (ISEL) technique to identify internucleosomal DNA fragmentation. This was performed using the Apoptag kit (Oncor, Gaithersburg, MD) according to the manufacturer’s recommendations and modified using an alkaline phosphatase technique to avoid false positivity related to lipofuscin as previously described (19).

**RESULTS**

Complete postmortem examination in the first case only revealed bronchopneumonia. Comparable neuropathologic changes were found in the 3 cases. The main lesion was severe diffuse loss of Purkinje cells equally involving the vermis and cerebellar hemispheres, which was associated with proliferation of Bergmann glia (Fig. 1b). The rare remaining
Purkinje cells showed pyknotic nuclei and shrunken eosinophilic homogenized cytoplasm; they were not stained by ISEL, whereas some endothelial cells that served as internal controls were stained (Fig. 1c). Granular neurons were relatively spared and silver impregnation showed preservation of basket fibers. Degeneration of the axons of Purkinje cells resulted in myelin pallor of the white matter of the folia and of the fleece of the dentate nuclei. The damaged axons were identified using β-amyloid precursor protein immunostaining (20) and were numerous around the dentate nucleus, where the processes of Purkinje cells converge. There was bilateral symmetric neuronal loss in the dentate nuclei, in which most remaining cells were positive by ISEL, and degeneration of the cerebellar efferent pathways. The superior cerebellar peduncles, decussation of the superior cerebellar peduncles (Wernkeinck commissure), and dentatothalamic tract (thalamic fasciculus) showed myelin pallor, and nerve cell degeneration was found in the centromedian nucleus (CMN) of the thalamus extending to the ventrolateral nucleus.

There were some differences between the cases. In cases 1 and 2, the lesions of the cerebellum and cerebellar efferent pathways were more chronic. There was intense proliferation of Bergmann glia, and changes in the cerebellar efferent pathways included myelin loss with infiltration by lipid-laden macrophages and reactive astrocytes. In contrast, in case 3, proliferation of Bergmann glia was less conspicuous and lesions in the cerebellar efferent pathways were acute with vacuolation of the myelin sheath, which was particularly striking around the dentate nuclei. Similarly, in the CMN of the thalamus, and to a lesser extent in the ventrolateral nucleus, the changes were chronologically different. In case 1, neuronal loss was associated with reactive astrocytosis; in case 2, most nerve cells had disappeared, leaving empty vacuoles, but cellular remnants could be seen within some vacuoles and were usually stained by ISEL. Astrocytosis was discrete and only identified by GFAP immunostaining. In case 3, there were a number of vacuoles containing “ghost” nerve cells, astrocytosis was inconspicuous, and ISEL stained a number of neuronal nuclei.
immunoreactivity was found within rare senile plaques. In case 1, perineuronal cells were stained. In case 2, there were almost no Purkinje cells left and mild HSP 70 expression was found within Bergmann glia; in the hippocampus, only slight positivity was found within rare senile plaques. In case 1, expression of HSP 70 was not seen in the cerebellum or the hippocampus.

In addition, case 1 had marked involvement of the substantia nigra, including neuronal loss with extracellular pigment and gliosis and, in case 2, skeletal muscles showed severe denervation associated with fiber atrophy, myosinolysis, and muscle fiber necrosis, characteristic of critical illness neuromyopathy (21).

All 3 cases showed diffuse astrocytosis of the deep gray matter mostly in the basal ganglia and to a lesser extent in the cerebral cortex. There were no other significant changes. In particular, Ammon’s horn and other areas susceptible to hypoxia were spared; there were no focal ischemic, hemorrhagic, or infectious lesions; medullary olives were unremarkable. In case 2, spinal cord examination was available and did not show any significant changes, in particular neuronal loss was not seen in the anterior and lateral horns.

**DISCUSSION**

Although heat stroke is not rare (6), and the neurologic complications of hyperthermia are relatively well described both clinically (13) and radiologically (14–16, 22), there are few neuropathologic studies of patients who died from heat (18). This probably reflects the favorable outcome of the disorder (<10% mortality) with appropriate treatment (3) and the absence of autopsy in inadequately treated patients, of whom more than 50% may die. In our 3 cases, heat stroke had developed during summer heatwaves, facilitated by the patients’ anticholinergic medications (clomipramine in the first patient and olanzapine in the third one). The history of chronic alcoholism was probably a predisposing factor in the second patient. All 3 patients developed coma, coagulation disorders, shock, and acute renal failure. The third patient died from multiorgan failure, despite active external cooling and maximal supportive therapy. The first and second patients developed neurologic sequelae with severe extrapyramidal dyskinesia, myoclonus, and critical illness myopathy responsible for the unfavorable final outcome. The second patient also had cerebellar atrophy and hypersignal intensity in the central part of the central tegmentum of the midbrain at MRI.

There were no cerebral or systemic changes to indicate that the central nervous system changes in our 3 cases may have resulted, directly or indirectly, from a cause other than hyperthermia. The slight diffuse astrocytosis of the gray matter was likely the result of nonspecific terminal metabolic disturbances. In the 3 patients, the predominant neuropathologic change was severe, almost total, loss of Purkinje cells. The lesions were restricted to Purkinje cells and differed from the neuronal changes in anoxia/ischemia that affect the Purkinje cells but also involve the neocortex, Ammon’s horn, and basal ganglia (23), which were spared in our 3 cases. The lesions also differed from alcoholic cerebellar degeneration in that they were diffuse, involving similarly the cerebellar hemispheres and the vermis, and were not associated with involvement of the internal granular cells or with lesions of the inferior olives (23). Purkinje cell loss is consistent with clinical reports of delayed cerebellar syndrome with radiologic cerebellar atrophy (15, 16, 22, 24) in patients who sustained heat stroke.

Similar Purkinje cell loss has also been described after neuroleptic malignant syndrome (25–27). Lithium neurotoxicity was suspected as the cause of the neuropathologic changes in some studies (28, 29), but most authors now agree that hyperthermia, a consistent feature in all cases, was responsible for Purkinje cell damage (28, 30).

In case no. 1, there was also marked neuronal loss and extracellular pigment in the substantia nigra. These changes have not been previously described after heat stroke, but they may have contributed to the extrapyramidal syndrome seen in this patient. Postheat stroke parkinsonism associated with cerebellar dysfunction has already been reported clinically (13).

On the other hand, neuronal loss in the anterior and intermediolateral horns of the spinal cord have been observed in a patient who died 15 days after a classic heat stroke with flaccid quadriplegia (31). In patient 2, who had areflexic and hypotonic quadriplegia, the spinal cord did not show any involvement of the motor or autonomic neurons and the symptoms are more likely the result of involvement of peripheral nerve and skeletal muscles similar to those described in patients with intensive care neuromyopathy (21).

The selective vulnerability of Purkinje cells to heat stroke may explain the increased HSP 70 expression in the few remaining Purkinje cells and adjacent Bergmann glia in our cases 2 and 3, whereas expression in the hippocampus was minimal in case 3 and restricted to senile plaques in case 2. The latter finding supports a previous report of abnormal expression of antioxidant enzymes and HSPs topographically associated with senile plaques (32). Accumulation of HSP 70, a chaperone protein, was initially associated with thermotolerance, the ability to survive otherwise lethal heat stress, and tolerance to a variety of stresses (12). Heat shock response is regarded as a useful indicator of central nervous system cells undergoing stress (33). In keeping with our findings, experimental studies have shown that HSP 70 expression is markedly increased in the cerebellum, primarily in glia, in response to hyperthermia (34, 35), and not, or to a minor extent, in other central nervous system regions (36). Our observations are also consistent with previous studies showing that HSP 70 production after cerebral insult is maximal by 3 days and diminishes by 1 week (37). HSP expression was maximal in the cerebellum of case no. 3 who died 28 hours after admission (i.e., between 2 and 3 days after heat stroke). It was mild in case 2, who died 1 month after the heat stroke, and absent in case 1, who survived 2 months after the heat stroke. The mechanism of heat-induced neuronal damage in the cerebellum is not clear. In our cases, ISEL was not positive in Purkinje cells. Although ISEL positivity just marks DNA breakage and may occur in a variety of

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nonapoptotic conditions, its negativity supports the experimental evidence that hyperthermia triggers apoptosis in dividing cells but not in mature postmitotic cerebellar cells (38).

Mild gliosis in the dentate nuclei has been seen in rare pathologic observations (29), but involvement of the entire cerebellar afferent pathways (superior cerebellar peduncles, Wernackk commissure, dentatothalamic tract, and CMN of the thalamus) in all our cases is a new finding. Neuronal lesions in the dentate nuclei and CMN clearly differed from those of Purkinje cells because they were not associated with HSP 70 expression and damaged neurons were strongly stained by ISEL. Demonstration of DNA breakage in the neurons of the dentate nuclei and CMN together with degenerative changes of the axons of Purkinje cells and neurons of the dentate nuclei and CMN, as stained by ISEL. Demonstration of DNA breakage in the lesions in the dentate nuclei and CMN clearly differed from the thalamus (40). Cerebellar afferents to the CMN suggested by Déjériné (41) have been demonstrated subsequently in cat (42), monkey (43), and humans (44). However, more recent studies supported the view that the cerebellar projections to the thalamus just coursed through the CMN and distributed to nuclei within the intralaminar nuclei or adjacent to them (mainly the ventrolateral nuclei) (45). Our findings tend to support the view of Déjériné and Déjériné (41) and subsequent anatomists (42–44) that at least some fibers arising from the cerebellum through the superior cerebellar peduncle terminate in the CMN.

The lesions of the dentate nucleus and its efferent fibers in the superior cerebellar peduncle may explain the occurrence of myoclonus after sedation of hyperpyrexia in cases 1 and 2 (ocular myoclonus movements in case 1 and facial, buccal, and palatal myoclonus in case 2). Palatal myoclonia extending to buccal, facial, ocular and, more seldom, skeletal muscles may result from lesions of the dentatothalamo pathway (46), which connects the dentate nucleus and the contralateral inferior olive after passing in the superior cerebellar peduncle, crossing the midline at its decussation, and passing by the internal and dorsal surface of the red nucleus before becoming part of the central tegmental tract (47). It is most often associated with a specific hypertrophic (presumably transsynaptic) degeneration of the inferior olive with characteristic fenestrated neurons (48). The absence of olivary hypertrophy in our cases, who survived only 1 month and 2 months after lesion of the dentate nucleus, tends to confirm the hypothesis already proposed by Guillain et al (49) that this lesion is not mandatory for myoclonus and only occurs in longlasting diseases (46).

ACKNOWLEDGMENTS

The authors thank Dr. Catherine Keohane for reviewing the English; and Marie-Annick Bretel, Patrice Castagnet, Katia Dossou, Isabelle Levesque, Claudine Poiron, and Carole Sanchez for technical preparation.

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In the 3 cases, neuronal loss and ISEL positivity in nerve cells in the thalamus predominated in the CMN; they were present to a much lesser extent in the ventrolateral and parafascicular nuclei. The ventrolateral nucleus is considered as the main thalamic projection of the efferent fibers originating from the dentate and fastigial cerebellar nuclei (40). The central lateral nucleus and the parafascicular nucleus, which belong to the same group of intralaminar thalamic nuclei, are also major connections of the deep cerebellar nuclei (40). Cerebellar afferents to the CMN suggested by Déjérine and Déjériné (41) have been demonstrated subsequently in cat (42), monkey (43), and humans (44). However, more recent studies supported the view that the cerebellar projections to the thalamus just coursed through the CMN and distributed to nuclei within the intralaminar nuclei or adjacent to them (mainly the ventrolateral nuclei) (45). Our findings tend to support the view of Déjérine and Déjériné (41) and subsequent anatomists (42–44) that at least some fibers arising from the cerebellum through the superior cerebellar peduncle terminate in the CMN.

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