Malignant Brain Stem Hyperthermia Caused by Brain Stem Hemorrhage

Chifumi Kitanaka, MD; Yasushi Inoh, MD; Tomikatsu Toyoda, MD;
Tomio Sasaki, MD; Tsuneyoshi Eguchi, MD

Background We report two cases of brain stem hemorrhage characterized by severe hyperthermia, rhabdomyolysis, acute renal failure, and a rapidly fatal course.

Methods A 55-year-old man and a 65-year-old man were admitted with coma-producing brain stem hemorrhage accompanied by hyperthermia. Both underwent ventricular drainage.

Results Within 1 day of onset, both patients developed hyperthermia of over 41°C, increased serum creatine phosphokinase (CPK) level indicating rhabdomyolysis, and acute renal failure. One patient died on the second day and the other on the third day after onset despite supportive treatment.

Conclusions These cases of brain stem hemorrhage with fulminant hyperthermia should be distinguished from those with simple hyperthermia. They may represent a kind of malignant hyperthermia, in which case dantrolene sodium might be beneficial. Monitoring serum CPK levels would be of help in making the diagnosis early in the course. (*Stroke.* 1994;25:518-520.)

Key Words • brain stem • hemorrhage • hyperthermia

Brain stem hemorrhage is occasionally accompanied by hyperthermia. Although hyperthermia is regarded as an ominous prognostic sign,[1] death usually occurs as a result of severe brain stem destruction, not hyperthermia. We report two cases of brain stem hemorrhage accompanied by severe hyperthermia closely related to the unexpectedly rapid and fatal clinical course. To our knowledge, no such cases have ever been reported.

Case Reports

Case 1

A 55-year-old hypertensive man became comatose shortly after taking a bath (day 0). He had no significant past or family history suggesting malignant hyperthermia (MH). On admission, he was semicomatose. The Glasgow Coma Score was E1V1M3. Both pupils were miotic but reacted to light. Tetraparesis and decorticate posture on noxious stimulation were observed. The deep tendon reflexes were exaggerated. The patient's body temperature was 40.2°C. His blood pressure, 246/140 mm Hg, was controlled with nitroglycerine. Diazepam, diphenylhydantoin, and pancuronium bromide were administered to control generalized shivering, and endotracheal intubation was performed. The admission serum creatine phosphokinase (CPK) level was 233 IU/L. A computed tomographic (CT) scan revealed a hematoma extending from the pontine tegmentum to the midbrain, accompanied by hydrocephalus (Fig 1). Right ventricular drainage was performed under local anesthesia, but the patient's condition remained unchanged. Shivering of the lower half of his body lasted until the morning of the next day (day 1), when the CPK level was 2663 IU/L. The patient's body temperature was decreased once to 36.4°C by alcohol cooling and indomethacin administration, but at around 9 AM on day 1 it rose rapidly, reaching 41°C within 1 hour. This hyperthermia was refractory to any treatment, and the patient's body temperature remained above 39°C thereafter. At 8 PM on day 1, gastrointestinal bleeding and epistaxis occurred. His skin became cyanotic and cool. The platelet count was 15 000/mm³, and fibrinogen degradation product level was 40 μg/mL, suggesting disseminated intravascular coagulation syndrome. Antithrombin III was administered, but decline of urine (dark brown in color) output ensued, and the patient became totally anuric. Blood pressure began to fall on the morning of day 2, and the CPK level increased to 205 400 IU/L by evening. Despite aggressive supportive treatment, the patient died on the morning of day 3. Autopsy permission was refused.

Case 2

A 65-year-old male with no personal or family history of MH suddenly became comatose while attending a conference (day 0). He was intubated and given diazepam at a nearby clinic and was referred to our hospital. On admission, he was semicomatose, and only abnormal flexion of the lower extremities was observed on painful stimulation. The pupils were deformed due to previous surgery for cataracts and were nonreactive to light. Gasping respiration was present. The patient was ventilated with a respirator after diazepam and vecuronium administration. The patient's blood pressure, 280/180 mm Hg on admission, was controlled with calcium antagonists. Body temperature was 39.1°C. The serum CPK level was 132 IU/L. CT scan revealed a brain stem hematoma extending from the medulla oblongata to the midbrain, accompanied by acute hydrocephalus (Fig 2). The patient was immediately taken to the operating room, where he underwent ventricular drainage. Anesthetic agents used were nitrous oxide, isoflurane, vecuronium, diazepam, and buprenorphine hydrochloride. Postoperatively, there was no definite change in the patient's condition, including body temperature (38.4°C). The CPK level on the morning of the next day (day 1) was 2210 IU/L. On the evening of day 1, the patient's body temperature began to rise rapidly (41°C at 6 PM and 42.2°C at 7 PM). At the same time, his urine output rapidly decreased from normal to total anuria. The patient's skin showed a mottled appearance, and his extremities were somewhat rigid. The CPK level was 2098 IU/L. Hyperthermia and anuria persisted despite sup-
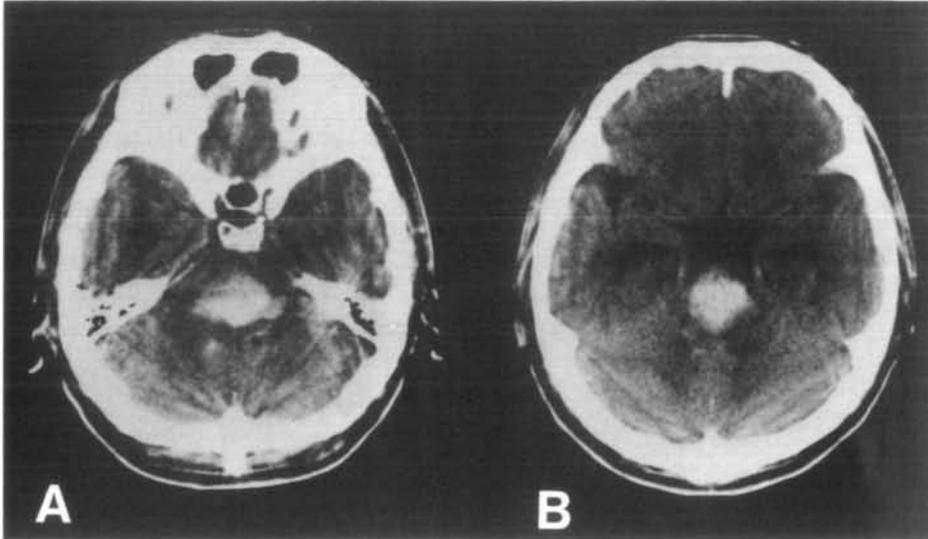
FIG 1. Computed tomographic scan of patient 1 on admission. The hematoma involves the dorsal pons (A) and extends up to the midbrain (B).

portive treatment, and the patient died around midnight, only 6 hours after the development of extreme hyperthermia.

Discussion

Fatal brain stem hemorrhage is often accompanied by hyperthermia as a result of the irritative disturbance of sympathetic pathways descending from the hypothalamus and other higher centers.[1] However, the clinical picture of the cases described above was completely different from that of severe brain stem hemorrhage simply accompanied by hyperthermia, including hyperthermia exceeding 41°C, elevated serum CPK level, acute renal failure, and a rapidly fatal clinical course. These clinical features remind us of MH and neuroleptic malignant syndrome (NMS).

MH refers to a clinical syndrome classically observed during general anesthesia, characterized by a rapid rise of body temperature and a high mortality rate. It is now recognized as a genetic disease of skeletal muscle. The triggering agents are usually volatile anesthetic agents and succinylcholine (SCh), which in patients genetically susceptible to MH cause hypermetabolism of skeletal muscle, hyperthermia, and rhabdomyolysis. Acute renal failure may develop as a result of myoglobinuria.[2]

NMS is a life-threatening complication of neuroleptic treatment characterized by fever (up to 42°C), rigidity, altered consciousness, and autonomic instability. Diminished dopamine neurotransmission caused by neuroleptic agents is considered to be of prime pathogenic significance. Hyperthermia may result from excessive heat production and inappropriate heat conservation due to hypothalamic malfunction. Patients with NMS may die from renal failure caused by rhabdomyolysis and myoglobinuria.[3]

Our two patients had many of the features of these two malignant syndromes, but they differed in some important aspects. Neither had ever been administered neuroleptics, and neither had a family or personal history of MH (so-called "sporadic cases"[4]). Patient 1 received neither volatile anesthetic agent nor SCh, and patient 2 received only a small amount of isoflurane but no SCh. The rapid rise of body temperature was preceded by the increase of serum CPK and myoglobin in both cases.
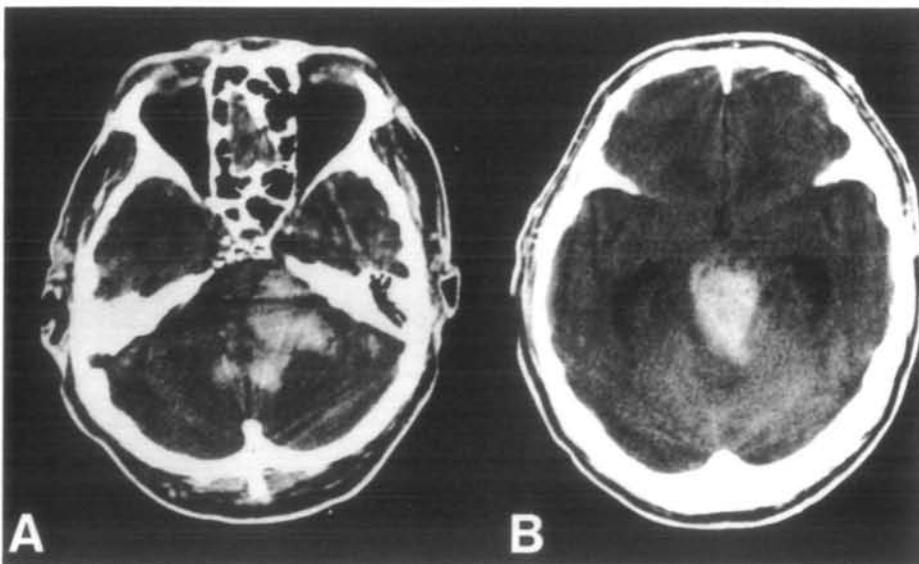

FIG 2. Computed tomographic scan of patient 2 on admission. The hematoma involves the left lateral pons (A) and extends up to the midbrain (B).

In reviewing the literature, we could find only one case of MH associated with intracranial hemorrhage.[5] The patient was a 65-year-old man who underwent surgery for anterior communicating aneurysm. In this case, severe hyperthermia developed during the operation, leading to death within 3 hours from the onset of hyperthermia. On postmortem examination, a hematoma was found in the anterior hypothalamus. He had no family history of MH. The authors concluded that anterior hypothalamic malfunction had played an important role in the development of MH. Although both halothane and SCh were used during the operation, the patient was rather old for MH and had undergone gastrectomy under general anesthesia uneventfully 20 years before. We also found a sporadic case of MH occurring in a boy with a nonhemorrhagic pontine tumor. Both halothane and SCh were used in this case. He survived MH, and his serum CPK level returned to normal.[6] The pontine tumor also was considered to have played a role in triggering MH.

From these observations, it is not difficult to hypothesize that injury to thermoregulatory centers or pathways by brain stem hemorrhage played a significant role in our cases also by one of two mechanisms: (1) increased sympathetic tone caused by brain stem hemorrhage may trigger MH in MH-susceptible patients and (2) disturbance of thermoregulatory centers or pathways alone may lead to unusual, unrestrained, shivering heat production or increase of peripheral vasomotor tone, resulting in rhabdomyolysis as well as extreme hyperthermia.

We consider that acute renal failure and disseminated intravascular coagulation syndrome occurring as a result of rhabdomyolysis were the major factors responsible for the rapidly fatal clinical course. As a natural conclusion, prevention of rhabdomyolysis is of primary importance. Unless MH is involved in the mechanism, nondepolarizing muscle relaxants may be of use in protecting the skeletal muscles from excessive shivering. Dantrolene sodium, the only known specific therapeutic drug for MH, is also effective for NMS and may be effective in the treatment of this condition. As this agent acts directly on the skeletal muscle cell and prevents its

hypermetabolism by inhibiting sarcoplasmic reticulum calcium release without affecting uptake,[2] it can be used whether MH is involved or not.

In retrospect, the delay in diagnosis was critical in both cases. If we had recognized the pathological condition and started treatment with dantrolene earlier, we may have altered the clinical course. As the malignant pathological processes seem to begin early, it is very important for physicians to check serum CPK levels when treating patients with brain stem hemorrhage accompanied by hyperthermia. We propose "malignant brain stem hyperthermia" as a practical term for this condition.

In summary, among cases of brain stem hemorrhage accompanied by hyperthermia, there exist some with a rapidly fatal course complicated by rhabdomyolysis and acute renal failure. This malignant condition may well be termed malignant brain stem hyperthermia. It remains unclear whether this is a type of MH or a condition mimicking MH that occurs in nonsusceptible patients. Although dantrolene sodium is expected to be beneficial in the treatment of this condition, avoiding delay in starting treatment is critical, thus necessitating early diagnosis. Because serum CPK levels increase early in the course, monitoring them will be of help in making the diagnosis.

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