

## Editorial

### Heat-related deaths are largely due to brain damage

With increase in global warming, the problems of hyperthermia have recently attracted worldwide medical attention. Deaths due to heat-related illnesses in large number of human population in recent years are now recognised as a great social and medical problem. Interestingly, details of mechanisms involved and probable therapeutic measures have still not been worked out and thus require further investigation using latest available technology.

Though heat-related illnesses are known since Biblical times<sup>1</sup>, they are seldom addressed as a medical or health catastrophe in our society. The intensity of heat stroke induced deaths are increasing with global warming and with worldwide increase in the frequency and intensity of heat waves<sup>2,3</sup>. In terms of clinical burden on the society and number of deaths occurring due to heat illness, hyperthermic brain injury is the third largest killer in the World after the cardiovascular and traumatic insults to the central nervous system (CNS)<sup>2</sup>. In spite of the seriousness of this problem, studies regarding effects of heat on the CNS are largely ignored<sup>3</sup>.

Heat stress and associated heat stroke are life-threatening illnesses in which body temperature rises above 40°C causing severe CNS dysfunction, *e.g.*, delirium, convulsion and coma. More than 50 per cent of heat stroke victims die within short period despite lowering of the body temperature and therapeutic intervention. Those who survive heat stroke often show permanent neurological deficit suggesting that heat as physiological or pathological stressor considerably influences the structure and function of the nervous system<sup>2</sup>.

Heat stress can be characterized as a disorder of thermal information processing system of the CNS. Excessive heat load will breakdown this system of

the CNS resulting in hyperthermia. Depending on the magnitude, severity and duration of hyperthermia, abnormal brain function will result probably due to release of several neurochemicals, and alterations in the cell signalling pathways. Most of the neurochemicals released in hyperthermia are known mediators of the blood-brain barrier (BBB) function and brain oedema formation<sup>4</sup>.

During summer season, heat waves are responsible for a large number of deaths in various parts of the globe including Europe, the United States of America and Canada. About 8,000 to 10,000 deaths have been recorded in southern Ontario during heat wave when the air temperatures range between 32-34°C<sup>5</sup>. The death rates due to heat-related illnesses are very high compared to mortality caused by other major natural disasters. Interestingly, high rate of heat-related mortality occurs in cities with relatively high levels of urbanization and high costs of living<sup>5</sup>.

The scientific reports on this subject date back to 1743 when 11,000 persons died in China during one hot weather condition in the month of July. Another incidence of heat death is recorded in 1841 in Liverpool, when 33 British soldiers died in a day due to hot weather in a ship coming from Muscat to Bushier. Similarly, during 1873 in the "Black Hole of Calcutta", 123 out of 186 prisoners under the British Raj died in one night<sup>2</sup>. This heat induced death is still noticed prominently in many parts of the world. Thus, in the Netherlands, about 1000 deaths due to hot weather in 1996 occurred in nursing homes of Rotterdam<sup>6</sup>. About 700 persons died in 1995 due to hot weather conditions in Chicago during summer months<sup>7</sup>. However, it is still unclear whether age, sex, drug abuse, alcoholism or individuals afflicted with acute and chronic diseases, such as diabetes, cardiovascular, endocrine or metabolic ailments,

depression, dementia will further influence the vulnerability of human populations to heat-related deaths.

Few sporadic reports describe post-mortem changes in human brain of heat stress victims<sup>8</sup>. However, in these investigations important components of the brain such as, hippocampus, spinal cord and vascular endothelium were not examined. The ultrastructural changes in the CNS were not recorded. Even after 59 yr of this report, new studies on human brain damage in heat stress are still not available. Thus, using modern technology and latest neuropathological techniques new studies on heat induced brain damage are urgently needed.

Another way to expand our knowledge on heat-related illnesses is to develop a suitable animal model of heat stress simulating clinical conditions. We developed a new mode of heat stress to induce clinical situation in rats that simulates clinical symptoms of alteration in behavioural and cognitive functions and is associated with profound brain dysfunction<sup>9,10</sup>. Using this model, our laboratory was the first to show that experimental or environmental heat stress without heat stroke is able to cause BBB disruption to protein tracers, viz., Evans blue and radioactive iodine<sup>11</sup>. Obviously, breakdown of the BBB results in extravasation of serum proteins and other unwanted substances in to the brain extracellular fluid compartment causing vasogenic oedema and cell injury<sup>12</sup>.

Our observations of BBB disruption in heat stress were further confirmed in an anaesthetised mouse model of hyperthermia using another protein tracer, horseradish peroxidase (HRP)<sup>13</sup>. In this experiment, HRP was visualised as an electron-dense product across the microvascular endothelium in several oedematous brain regions at the ultrastructural level<sup>13</sup>. There are evidences indicating that the peripheral nervous system (PNS) is also vulnerable to hyperthermia<sup>2</sup>. This suggests that individuals with peripheral nerve diseases such as diabetic neuropathy may be more susceptible to heat-related illnesses. The PNS is equipped with the blood-nerve barrier (BNB) very similar to the BBB and is mediated by identical neurochemical mediators<sup>14</sup>. It remains to be seen

whether the BNB is also altered following heat exposure or heat-related illnesses.

Thus, to explore suitable therapeutic strategy in heat-related illnesses, use of new technology and specific molecular markers to study neuronal, glial and myelin pathology by light and electron microscopy are needed in both experimental and clinical situations. A detailed knowledge of molecular mechanisms of heat induced CNS/PNS injury will provide new insight to develop potential therapeutic measures to minimise nervous system damage in the victims of heat stress and to alleviate their sufferings.

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