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Hyperpyrexia in life-threatening central nervous system infection – It is the timepoint of fever which matters: A plea to select the best timing and optimal methods of temperature management

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Since Hippocrates' times, it has been known that fever and even more, hyperpyrexia in a potentially fatally ill neurocritical care patients, in particular in severe central nervous system (CNS) infections is detrimental, heralding poor prognosis, and adding to morbidity and mortality.^[1] Aggressive management of body temperature is commonly agreed to be essential and is suggested to improve outcome in patients with intracranial pathologies.^[2] Both acute bacterial meningitis (ABM) and viral encephalitis may – rather early in their course – lead to diffuse brain edema,^[3-5] thereby increasing the intracranial pressure (ICP) and reducing the cerebral perfusion pressure, both through increased ICP and decreased mean arterial pressure, the latter frequently being part of an accompanying sepsis syndrome or, even worse, septic shock syndrome.^[6] Brain tissue hypermetabolism may be part of early hyperpyrexia whereas subsequent hypometabolism may indicate that tissue/cells already have suffered from substantial damage. Both fludeoxyglucose positron emission tomography (PET) and cerebral microdialysis have yielded results in favor of exactly this course of metabolism, i.e., an early hypermetabolic state being followed by a late hypometabolic state within the encephalitic brain.^[7,8]

In patients suffering from impaired consciousness due to ABM, up to two-thirds show increased ICP when measured early.^[4] Aggressive reduction of this increased ICP has been shown to reduce mortality from 30% to 10%;^[4] in bacterial meningitis, beside diffuse brain edema, hyperemia of brain areas and secondary disturbance of microcirculation within the affected intracranial structures leading to, highly impaired arterial/arteriolar microcirculation, as well as partially occluded/thrombosed venules/venous vasculature add to increased ICP with the potential of severe secondary damage of brain tissue.^[3]

Whereas in the early phase of acute infectious disease of the meninges and the brain tissue, the pathogen plays the key role in maintaining and aggravating infection and inflammation as evidenced by PET- and microdialysis studies in viral and bacterial infections of the brain,^[7,8] it will be the secondary damages throughout the course of the infectious CNS disease which add substantially to morbidity and mortality.

Antimicrobial chemotherapy is given with the aim to kill the causative pathogens as quickly and as early as possible. It is exactly

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during the early phase of the disease when the brain reacts toward the rapidly multiplying pathogens with what recently has been called “Pathogen Associated Molecular Pattern” (PAMP).^[9] It seems logical and essential that the rapidly multiplying pathogens provoke a wide range of immunological host reactions, fever being only the visible tip of the “iceberg” of them. Therefore, the foremost aim at this, early, stage of disease must be to constrain the causative pathogens (e.g., *Streptococcus pneumoniae* – pneumococci) and to reduce the overwhelming immune reaction, as it is done in case of ABM.^[5,10,11] In a patient suffering from pneumococcal ABM, the early combination of bactericidal or-lytic antibiotics (e.g., third-generation cephalosporin) with a 4-day- course of dexamethasone improves outcome.^[5,10,11] If, however, steroids are given to a comatose pneumococcal ABM patient too late, or in a prolonged way, the positive effects might be even reversed.^[10,11] Liston and Masters have clearly shown that during the later course of life-threatening ABM it is the then Damage Associated Molecular Pattern (mechanisms) (DAMP) which plays the pivotal, more crucial, more important role.^[9] This DAMP, i.e., largely damaged neuronal cells, provoke a different upregulation of immune responses, with fever or even hyperpyrexia.^[12,13] The secondary damages of ABM are aggravated by this hyperpyrexia^[3,11,12] and by secondary oxygen and nutrition deprivation of already partially damaged neuronal cells.^[12-14]

Taking these two completely different types of fever into account, it seems all too logical that in the early phase of ABM moderate therapeutic hypothermia (TH) by physical means might be detrimental, this fact has been shown recently to hold true in practice in the French ABM-hypothermia study.^[15] The results of this prospective randomized controlled French ABM-hypothermia study suggest a detrimental effect of moderate hypothermia when given during the first 24 h of ABM. In these French patients, dexamethasone was administered rather late (up to 5 h after the first dose of antibiotic), and even more importantly, the moderate TH (33°C–34°C) (applied for the first 24 h) patients were withheld antipyretic pharmacotherapy, which – in contrast – was given liberally and as deemed necessary by the treating intensivist, to the “normothermic” patients’ group.^[15] It clearly might be reasoned that during the acute ABM phase, i.e., when PAMP most matter, antipyretics might even increase the beneficial effect of steroids as long as their potential negative side effects are monitored for and appropriately taken care for. However, it seems equally logical that during the later phase of the ABM, when the DAMP eventually prevails and leads to a tilt of the delicate immunological homeostasis. This so-called Homeostasis Associated Molecular Pattern (HAMP),

adding to secondary brain/neuronal cell damage, might even more benefit from TH or, at least, targeted temperature management (TTM). Not controlling the body temperature after TH might have contributed to secondary brain/neuronal cell damage.^[1,2] Therefore, it is safe to assume that continuing TTM could save such partially damaged and functionally impaired neuronal cells over the critical period of ABM, i.e., far beyond the first 24 h. This potential to improve the devastating outcome was clearly missed in this patients’ group.

In view of this recently proposed concept of PAMP – DAMP – HAMP,^[9] we suggest to test, both in animal and in comatose patients with severe acute bacterial (preferably pneumococcal) meningitis and viral encephalitis the concept of differentiated temperature management throughout the course of disease. In the early phase, i.e., within 24–72 h, “aggressive” administration of antipyretics should supplement the steroid and antibiotic therapies. In the later course (beyond day 4) in every patient, still suffering from increased ICP, brain edema, arterial, or venous complications normothermia should be aimed at and meticulously maintained – by all means – until the clinical, monitoring, and neuroimaging evolution suggests that DAMP and HAMP have been overcome.

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