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## Highlights

# Protecting the blossoming brain – Neurocritical care in children

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### ABSTRACT

This special issue of the *Biomedical Journal* is entirely dedicated to the latest updates regarding the medical efforts to preserve the fragile young brain after injury. Thereby, we learn about symptoms and diseases such as different forms of epilepsy, acute encephalopathy, increased intracranial pressure, and posthaemorrhagic hydrocephalus, as well as about their origins, such as infection, autoimmune diseases, preterm birth, or abusive head trauma. Moreover, diagnosis and surveillance techniques are discussed, including ultrasound of the optic nerve sheath diameter and multimodal monitoring. Finally, we discover various established and emerging therapeutic approaches, comprising target temperature management, ketogenic diet, and immunomodulation.

## Spotlight on reviews

### *Protecting the blossoming brain – neurocritical care in children*

This special issue appears in the honor of Taiwan having joined the Congress of Paediatric Care Consortium, as Huei-Shyong Wang reminds us in his editorial [1]. Looking back on decades of practical experience with the treatment of neurocritically ill children at the Chang Gung Children's hospital in Taiwan, he provides the reader with a concise overview of the issue's three main sections, comprising the latest treatments, monitoring methods, as well as known and new challenging conditions one encounters in the paediatric

intensive care unit [Fig. 1]. For the same reason, we will exceptionally highlight one review for every part.

#### *“Alimentary, my Dear Watson” - part I, update on neurocritical treatments in children*

Paleo, Keto, Atkins, Whole 30, Mediterranean, Dukan, South Beach – these are just a few examples of the stupendous and confusing amount of diets one stumbles across in a few clicks when asking the internet for alimentary advice, or even without asking, actually [2]. Although the concept just turned 100 years old, the ketogenic diet in particular has gained countless followers over the recent years on the ideological battleground that food has become [3].

During periods of low glucose availability, resulting from fasting or low-carbohydrate diets, the liver produces ketone

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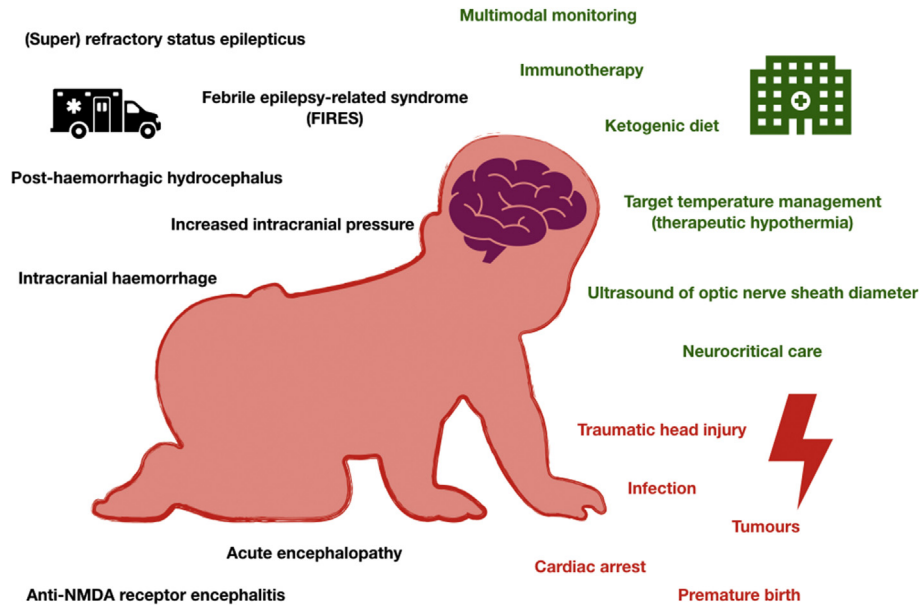


Fig. 1 Update in paediatric neurocritical care. Schematic summary of topics addressed in this issue. In black: symptoms and diseases affecting the brain. In red: possible underlying causes and origins. In green: state of the art diagnoses, monitoring techniques, and therapies.

bodies from fatty acids. These are subsequently converted into acetyl-CoA and enter the conventional citric acid cycle. To date, the consensus definition of a ketogenic diet is a high-fat, low-carbohydrate, adequate-protein diet [4].

While the general public associates the ketogenic diet primarily with promoting fat-burning and weight loss, scientific studies on the subject have also exponentially increased over the two last decades, however with a different emphasis. Notably, its implication in the treatment of epileptic seizures has received much attention [5].

Here, Lin et al. review the state of the art regarding the application of ketogenic diets for paediatric neurocritical care, and argue that its use has great potential to be extended for a broader spectrum of cases [6].

The authors first provide the reader with a precise definition and the different subtypes of ketogenic diet, as well as with its main use for chronic intractable epilepsy. With both a reminder of the high mortality rates from super-refractory status epilepticus and successful case reports at hand, they then argue that a ketogenic diet has also a high potential as an adjuvant therapy for alleviating the latter or febrile infection-related epilepsy syndrome in an emergency setting.

With regard to the fact that these patients are often impaired for normal feeding, further studies evaluating the feasibility of intravenous administration of a ketogenic diet are mentioned, with the overall conclusion that it has proven both practicable and beneficial, as long as it is paralleled by the close surveillance of serum pancreatic enzymes and lipid profiles.

Subsequently, Lin and colleagues stress that besides the treatment of acute and chronic status epilepticus, the ketogenic diet might be of high value for patients suffering from

traumatic brain injury. Indeed, the standard glucose metabolism has been shown to turn against the brain after injury by promoting oxidative stress, cell death, and inflammation. Switching the brain metabolism to ketones not only avoids the latter, but is also more energy efficient and improves cerebral blood flow.

Finally, the authors address the question if the ketogenic diet could be suitable for very young patients. Only a few studies for infants under 2 years or 3 months and the chronic stage of status epilepticus are available, but they seem to indicate that the therapy is well tolerated under close surveillance. The reason for the constant monitoring is that pushing the organism towards production and use of ketone bodies is not without dangers. Excessive ketosis, as seen in type 1 diabetes patients, lowers the pH of blood and urine, and can lead to osmotic diuresis and dehydration [7].

Altogether, the evidence compiled in this review undeniably promotes an expansion of the treatment spectrum by ketogenic diet.

#### *The eyes are the window to the brain – part II, the recent advance in paediatric neurocritical monitoring*

Neurosurgery is without doubt one of the most complicated medical interventions to date, and yet it is possibly also the oldest type of surgery that we have archaeological evidence of. A burial site from France dated back to 6500 BC holds proof of “trepanning”, a procedure consisting in drilling or scraping a hole into the human skull in order to expose the *dura mater*, and similar cases have been discovered from Neolithic times on all over Europe, as well as in the Americas and China. Bone re-growth is proof that many patients survived the procedure [8]. Trepanning is assumed to have served at least two purposes: the release of either evil spirits or pressure on the brain

after head wounds, and the latter is still the last resort measure now termed craniectomy - to get excessively increased intracranial pressure (ICP) back under control [9].

As a matter of fact, downstream effects on the cerebral tissue by - brain trauma or unrelated pathologies can sometimes cause greater damage than the initial injury. One frequent mechanism is the raise in pressure of the cerebrospinal fluid (CSF) inside the skull, caused by intracranial haemorrhages, oedema, tumours, or acute liver failure, to give a few examples. The ensuing compression of delicate neural tissues can lead to ischaemia, necrosis, and subsequently to neurological damage ranging from vision impairment to death [10]. Countermeasures stretch from the administration of antihypertensive agents to decompressive craniectomy, but whatever the chosen treatment, early detection is key [11,12].

However, the current standard ICP measurement methods are invasive, as they necessitate the insertion of a sensor into the brain ventricle or the parenchymal tissue, thus requiring highly specialised equipment and entailing additional risk factors, such as bleeding and infection. Several non-invasive alternatives are available, but they are either costly, time-consuming, only available in specific infrastructures, such as computed tomography and MRI, or of limited reliability, like tympanic membrane displacement. Nonetheless, evaluable data has begun to accumulate for the use of non-invasive methods in adult subjects, but little is known regarding their relevance in neurocritically ill children.

With the aim of attracting attention to the urgent need for trustworthy, straightforward non-invasive ICP monitoring techniques, which allow additionally for real-time follow-up, Lin et al. have compiled the available relevant literature for adult patients, and some preliminary conclusions relating to their use in children [13]. The review focuses on the potential of point-of-care ultrasounds (POCUS) of the optic nerve sheath diameter (ONSD), as this strategy combines good results in adults, feasibility, and the possibility for continuous monitoring [14].

The optic nerve can be considered a direct prolongation of the brain; thus, the optic nerve sheath surrounds technically an extension of the intracranial subarachnoid space. As a consequence, an increase of pressure inside the latter leads to the distension of the optic nerve sheath. One major advantage of ONSD measurement by POCUS is the simplicity of data acquisition and the possibility to average several measurements from different angles. Lin et al. describe the ideal technical setup, but also warn from a series of possible pitfalls that can arise either from technical sources, such as probe size and resolution, anatomical particularities, such as the fact that the optic nerve is not always straight in children, or errors in the deciphering of structures. Furthermore, the authors demonstrate that the real challenge lies in the interpretation of the measurements. Especially in children, both the ONSD and the ICP can vary according to multiple factors, starting with age, and so does the limit value from which on the ICP is considered abnormal, given that fluctuations are more common in younger individuals. Nonetheless, for all subjects over 1 year of age, the correlation between ONSD and ICP is certainly quite individual-specific, yet good. Hence, the real strength of the method lies in its ability to reflect changes of the ICP in real time.

The authors come to the conclusion that, despite the fact that POCUS of ONSD does not provide the accuracy of an invasive measurement technique and thus can't replace it yet, the method can be readily applied at little cost and minimal risk. On condition that equipment, image quality, and readout become standardised, they recommend strongly for its implementation as a continuous monitoring tool in complement with other diagnostic tools.

#### *Brain on Fire – part III, specific challenging neurocritical diseases in children*

The 2016 biographical drama film “Brain on Fire: My Month of Madness” from 2016 depicts the descent into hell of Susannah Calahan, a young journalist who suddenly starts to suffer from unexplained psychotic attacks and seizures.<sup>1</sup> When she is within a hair's breadth to be sent off into the psychiatric ward, a neurologist recognises *in extremis* that she suffers actually from an auto-immune disease – anti-NMDA receptor encephalitis – ultimately leading to her cure.

The N-methyl-D-aspartate receptor (NMDA receptor) is one of the three classes of ionotropic glutamate receptors found in neurons. Activation through glutamate or glycine binding triggers the influx of positively charged ions, and has been found to play a significant role in synaptic plasticity [15]. Excessive  $Ca^{2+}$  influx via overactive NMDA receptors causes excitotoxicity and has been related to several neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease, thus the use of uncompetitive agonists has been suggested for treatment, while preserving the physiologically crucial function of the receptor [16]. The latter is compromised by anti-NMDA receptor encephalitis, mediated by antibodies targeting the receptor, leading to fever, delusions, hallucinations, seizures, and ultimately disturbance of breathing and heart rate [17]. 80% of the cases are female and younger than 45, mainly because half of them originate from ovarian teratomas. Other causes can be viral infections, but much uncharted territory remains to be explored in the case of this disease, which was discovered only recently: the first report stems from Dalmau et al. in 2007 and represent possibly the first concrete proof that autoimmunity can affect behaviour and cognition [18].

Bearing in mind that anti-NMDA receptor encephalitis is frequent in young adults and children, and misdiagnosis still frequent, Kuang-Lin Lin and Jann-Jim Lin provide in their present review a detailed description of the disease's clinical presentations at the acute stage [19]. They recapitulate the five typical phases of the disease, which seemingly jump from pillar to post - starting with infection-like symptoms that turn into psychiatric troubles and culminate in autonomic instability – and strongly recommend that patients should be treated by a multidisciplinary team, given the diversity of symptoms to cover. Moreover, as rapid treatment is key for complete recovery, the authors advise stage-based care even before confirmatory testing for autoantibodies. Once treatment is on track, the initial source of the disease needs to be identified, especially as the source is most of the time a tumour requiring removal, and otherwise often a treatable viral infection [20].

<sup>1</sup> [https://en.wikipedia.org/wiki/Brain\\_on\\_Fire\\_\(film\)](https://en.wikipedia.org/wiki/Brain_on_Fire_(film)).

Subsequently, Lin et al. elaborate on the usefulness of different monitoring techniques. Data interpretation is complicated by the fact that no clinical presentation is specific or present in all cases. For example, magnetic resonance imaging (MRI) and positron emission tomography PET-scan do sometimes, but not necessarily, detect anomalies, while electroencephalogram patterns are suggestive, but better be surveyed at high frequency. Importantly, the authors direct attention to the lower frequency of seizures in children compared to adults suffering from anti-NMDA receptor encephalitis.

Hereupon we transition to the description of therapeutic strategies, starting with those meant to mitigate acute symptoms, such as antiepileptic drugs, and life-threatening conditions, like autonomic dysfunction and hypoventilation. The latter are challenging because of the diversity in manifestation and severity, plus the obvious lack of cooperativity by delirious patients. Definitive cure can be achieved by eventual tumour resection and of course immunotherapy, notably when the re-emergence of novel autoreactive B cells is prevented.

Lin et al. conclude their review with a section on possible prediction criteria and biomarkers. Time of treatment onset aside, both rely without surprise mainly on the level of inflammation markers.

In summary, the review reflects very well the different facets of a recently recognised autoimmune disease, whose main challenge resides in the disjointed diversity of symptoms, leading to frequent misdiagnosis.

Of note, only one non-human occurrence of anti-NMDA receptor encephalitis is known: in 2011, the mass media phenomenon of the Berlin zoo in Germany – a polar bear cub named “Knut” – drowned after collapsing because of the disease.<sup>2</sup>

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## Spotlight on original articles

### *Receptors caught off-guard*

Toll-like receptors (TLRs) are a key component of the innate immune system. Together with C-type lectin receptors (CLRs), NOD-like receptors, and RIG-I-like receptors, they form the family of pattern recognition receptors (PRRs) in charge of detecting a large amount of pathogen-associated molecular patterns (PAMPs), such as for example bacterial lipopolysaccharides (LPS) or nucleic acids. Located either on the plasma membrane or in endosomal compartments, they trigger upon activation the production of pro-inflammatory cytokines, chemokines, and co-stimulatory molecules [21]. Moreover, they play multiple roles bridging the innate and adaptive immune system, notably by shaping B-cell differentiation and activation [22]. Unsurprisingly, an imbalance of TLR function entails drastic consequences, in form of either excessive inflammation or immune depression, and an abundance of studies furthermore suggests the implication of virtually all TLR members in autoimmune diseases.

Increased TLR7 and TLR9 signalling for instance stimulates abnormal B cell activation and survival, including of autoreactive B cells [22], which in turn leads to the persistence and reactivation of Epstein–Barr virus in myasthenia gravis patients [23]. Systemic Lupus Erythematosus (SLE), one of the most prevalent systemic autoimmune diseases, has been correlated with significantly higher expression levels of TLR7 and TLR8 [21].

As for autoimmune diseases targeting the nervous system, this issue contains a compelling review about encephalitis caused by auto-antibodies directed against the NMDA glutamate receptor [19], an only recently identified disease. A defective TLR3 pathway could possibly connect an increased susceptibility to the Herpes simplex virus (HSV) and ensuing anti-NMDA receptor encephalitis caused by the viral infection [24]. Multiple sclerosis (MS) is a tragic classic of autoimmune neurodegenerative diseases, characterised by demyelinating lesions in the brain and spinal cord. Less functional B regulatory ( $B_{reg}$ ) cells and TLR-triggered NF- $\kappa$ B signalling count among its origins [21,25]. Even mental disorders, such as schizophrenia, have been linked to unusual patterns of natural antibody production [25]. Additionally, TLR2/4 signalling is involved in neurogenesis [21], and schizophrenia might trace back to defects during early brain development [25].

In many cases, the abovementioned TLR dysfunction has been linked to mutations or single nucleotide polymorphisms (SNPs) in certain populations [21].

So far, the connection between TLRs and autoimmune diseases has been explained mainly by the overexpression or excessive activation of certain TLR members [21,23].

In their preliminary study, Hsieh et al. however propose a very different scenario for the case of febrile infection-related epilepsy syndrome (FIRES) [24].

FIRES got an official definition only recently, in 2017 at the occasion of the first international new-onset refractory status epilepticus (NORSE) and FIRES symposium. It is noteworthy that NORSE is a clinical presentation - and not one specific disease - in a patient without a pre-existing neurological disorder, active epilepsy, or a concrete cause. FIRES represents a subcategory of NORSE, with the additional feature of a prior febrile infection with fever approximately 2 weeks–24 h before the onset of refractory status epilepticus [27]. As discussed earlier in the review by Sakuma et al., FIRES is a major clinical challenge precisely because of the unknown source for the status epilepticus, leaving the medical personnel usually no other choice than the prolonged administration of anti-convulsants in large doses. Emerging therapies comprise ketogenic diet, target temperature modulation, and importantly, immunomodulation [28].

Here, the authors rather hypothesise that an insufficient TLR response would lead to a poor clearance of pathogens and debris, whose prolonged lingering in the system and tendency to mimic neural antigens could ultimately give rise to auto-antibodies [26].

In order to test their conjecture, they examine the TLR levels and responses in five children suffering from FIRES, confirmed by imaging and electroencephalography. Viral or bacterial infection and lower  $T_{reg}$  levels were found in three and four patients respectively.

<sup>2</sup> [https://en.wikipedia.org/wiki/Knut\\_\(polar\\_bear\)](https://en.wikipedia.org/wiki/Knut_(polar_bear)).



Subsequently, TLR expression and activity is tested *in vitro* in peripheral blood mononuclear cells (PBMCs) and monocyte-derived dendritic cells (MDDCs) derived from the patients. Although the expression levels of TLR1-9 did not differ from controls, the downstream responses of TLR3/4/9 were significantly attenuated, as confirmed by lower levels of a considerable number of cytokines and interferons.

The fact that no changes in TLR expression and cytokine profiles are observed between the acute FIRES state and 12 months post-treatment strongly suggests that the defective TLR function is a permanent issue and not a transient consequence of the status epilepticus itself.

As mentioned previously, TLR signalling is required for the maturation and activation of other immune cells. Accordingly, Hsieh et al. point out that the lower production levels of IL-6 and IFN- $\gamma$  probably connotes insufficient MDDC development [22].

Moreover, the lower number of T<sub>reg</sub> cells observed in four out of five patients also fits the pictures. T<sub>reg</sub> cells are an indispensable subunit of the adaptive immune system in charge of keeping it in check by ensuring immunological unresponsiveness to self-antigens. Insufficient control by these cells is one of the main causes of autoimmune diseases and allergies, while excessive tolerance is frequently induced by tumour cells [27]. In the case of FIRES, the former scenario could apply in synergy with the deficient TLR responses: emerging autoantibodies directed against pathogenic debris and neural epitopes would get unnoticed and allowed to expand because of lacking T<sub>reg</sub> control.

Well aware of the small size of the study, the authors call for cautious interpretation and more thorough investigation, yet these preliminary results should be reason enough to push for a larger examination of TLR gene variants and activity in FIRES patients, as this would be a crucial asset for the appropriate use of immunomodulation, such as anti-cytokine therapy [28].

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## Also in this issue

### Reviews

#### *Putting out the FIRES*

Immunotherapy has been in the limelight of therapeutic hopes for a little while now, principally because of its promises in fighting tumours [29–31], to a degree that the two terms became nearly inseparable.

However, immunotherapy is a more general denomination for treating a disease *via* the activation or suppression of the patient's immune system, as Sakuma et al. remind us in their concise review dedicated to the febrile infection-related epilepsy syndrome (FIRES) [28].

This neurological disease refers to an unelucidated status epilepticus following febrile infection, which can last for a lifetime and lead to cognitive impairment [27].

Considering that the mere consensus on its definition is extremely recent, in addition to a still mysterious aetiology, it is little surprising that therapeutic measures are limited so far to the repression of seizures, requiring generally a long-lasting

administration of large doses of barbiturates – a not very subtle method entailing many complications [32].

On these grounds, the authors summarise the known clinical features of FIRES, and the standard care procedure based on electroencephalography and anticonvulsants, whose various drawbacks are outlined.

Subsequently, alternative treatments, which could complement and diminish the use of anticonvulsants are discussed, including target temperature management and ketogenic diet.

Finally, Sakuma et al. stress the recent success of immunomodulation, in particular of anti-cytokine therapeutic strategies, and call for further investigation of this treatment option.

#### *Keeping a cool head*

A large panel of injuries and diseases can cumulate in acute encephalopathy, a rather general term labelling a syndrome of overall brain malfunction. Causes comprise viral infections, trauma, cardiac arrest, and status epilepticus [33]. In infants and children, nearly one third of acute encephalopathies result in permanent neurological damages, which might be avoided or at least reduced by timely neuroprotective strategies [34].

Lin et al. describe one candidate therapy, termed target temperature management (TTM), which consists in subjecting the patient to a state of controlled hypothermia [35]. The rationale behind the strategy is similar to the expected benefits from cooling down any injured tissue: decreasing inflammation, metabolic rates, and oxidative stress.

So far, TTM is used on adult patients with certain subtypes of cardiac arrest and has improved survival rates, but not necessarily neurological outcomes [36], but could prove a valuable treatment in children and a broader range of acute encephalopathy.

Here, the authors carefully review successively the different scenarios that can lead to acute encephalopathy in young patients, in combination with the detailed clinical reports of TTM attempts for each case. The data points towards TTM as a beneficial tool to prevent fever and exacerbated neural damage during the acute stage of the disease, but equally draws attention to the need of larger, protocol-based clinical trials.

To note, this issue contains additionally two original articles by the author's department, reporting encouraging first results regarding the use of TTM for the treatment of paediatric refractory status epilepticus [37], as well as the predictive value of seizure patterns during rewarming after TTM in neonates with hypoxic-ischaemic encephalopathy [38].

#### *Prevention is better than cure*

The abovementioned saying hits the mark when it comes to the brain, especially the injured one. In order to avoid irreversible damage by further deterioration or downstream complications, round the clock surveillance for the slightest warning signal is of utmost importance.

Yet the latter can arise from multiple parameters – cerebral activity, oxygenation, intracranial pressure, or metabolism – impossible to monitor by one single technique.

As a consequence, the best solution consists in using several independent methods and to intersect the results, termed multimodal monitoring [39].

In their review, Yang et al. sum up all the components of multimodal neurocritical monitoring that are currently in use - from checklist-based global neurologic status assessment, via the specific measurements of blood flow and oxygenation, to the well-known electroencephalography and the intracranial pressure (ICP) monitoring, as discussed by Lin et al. in this issue [13].

The authors conclude that multimodal monitoring is the right approach to ensure the early recognition of complications and patient-specific treatment. They plead for the integration of further sources, such as imaging and laboratory analyses, and ultimately stress the importance of common standards for formatting and data interpretation [40].

#### *Betrayal of innocence*

Kun-Long Hung shoulders the sorrowful task to address the only fully preventable injury to the paediatric brain, which is abusive head trauma (AHT) [41]. Previously also known as the “shaken baby syndrome”, it designates voluntary damage caused to a child’s head through blunt trauma or shaking, usually due to the caregiver’s frustration over the infant’s behaviour [42].

Subdural haematoma and retinal haemorrhages are among the most severe consequences and can lead to lifelong handicap or death.

Most notably, the medical staff has to operate on two fronts, trying to manage potentially fatal brain damage and limit secondary injuries on the one hand, and having often to deal with uncooperative caregivers.

The author provides a detailed account of the pathophysiology and the different clinical features typical for AHT, as well as of the recommended elements for clinical evaluation and prognosis.

Given that the subject technically exceeds the medical realm, with legal, sociological, and psychological implications [43], the author also emphasises society’s duty to ensure prevention via education and assistance.

#### *Too early for brains*

Worldwide, the preterm birth rate is of 11.1%, meaning that 15 million babies are born before 37 weeks of gestation every year, the leading cause of mortality in children aged <5 years, and of severe, life-long neurological sequelae [44].

Unsurprisingly, the immature brain is the most vulnerable part of preterm infants.

A simple change in perfusion, for instance, can be enough to trigger intraventricular bleeding from the extremely fragile vasculature of the immature germinal matrix, with severe consequences from death to hydrocephalus, as discussed thoroughly in the subsequent review [45].

Reyin Lien summarises here all the parameters that require constant monitoring in order to avoid injuries to the brain, or at least minimise their impact, as well as the available techniques and therapies to fulfil the task [46].

The author reminds the reader of the significant emotional and economic burden of long-term neurodevelopmental problems that stem from preterm birth, and emphasises that

in this case, the concept of neurocritical care has to be extended to take into account impacts on brain maturation.

After a summary of the most frequent brain lesions in premature infants, we learn about neuroprotective manoeuvres at the prenatal stage, at the moment of birth, and in the neonatal intensive care unit (NICU). Special attention is paid to the stabilisation of the cerebral blood flow and oxygen delivery, including monitoring techniques, guidelines, and results from clinical trials. In addition, Lien recommends CO<sub>2</sub> levels and brain activity surveillance, and emphasises the importance of complementary factors, such as nutrition, pain and infection control, and extensive physical care.

#### *Under pressure*

Following on from the previous review by Lien et al. on the general picture of neurocritical care required in premature infants [46], Meng-Fai Kuo focuses here on intraventricular haemorrhage (IVH) and post-haemorrhagic hydrocephalus (PHH) in these patients [45].

The high frequency of these complications 1–2 days after premature birth is due to the extremely fragile structure of the immature germinal matrix (GM), the highly vascularised region located between the lateral ventricles and the caudate nuclei, which plays a fundamental role during corticogenesis by generating the cells that migrate towards the cerebral cortex and differentiate into neurons and glia. A change in perfusion of the delicate tissue induces the breakdown of blood vessels, and the ensuing haemorrhage can enlarge the ventricles either through blood accumulation or the formation of blood clots blocking the flow of cerebrospinal fluid (CSF), further developing into ventriculomegaly or hydrocephalus [47].

So far, drainage of the cerebrospinal fluid and blood mix is about the only solution in these cases. However, achieving the latter without causing further harm in the form of infection or mechanical damage to the premature brain represents a major challenge. Moreover, installation of permanent devices is usually impossible in at this stage, thus requiring temporary solutions.

Mainly directed to fellow paediatric neurosurgeons, the review recapitulates the currently available surgical options for PHH management by temporising measures in premature infants. Based on the extensive practical experience of the author, it contains valuable detailed descriptions of the different surgical procedures, backed up by available data from the literature and clinical trials.

#### *Original articles*

##### *The benefits of being cold*

In this same issue of the *Biomedical Journal*, members of the Department of Pediatrics of the Kaohsiung Chang Gung Memorial Hospital in Taiwan advocate for a broader use of target temperature management as a neuroprotective treatment, notably in children [35].

Here, Hsu et al. from the above-mentioned department conducted a retrospective cohort study on paediatric patients with refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE) [48], who received either anticonvulsants alone, or in combination with therapeutic

hypothermia (TH) [37], for the purpose of comparing their clinical characteristics and outcomes.

Their study reveals that the group having received additional TH therapy experienced shorter seizure durations, recovered with less disabilities, and developed less frequently later chronic refractory epilepsy.

The authors conclude that TH seems to be a fairly safe method that helps to shorten seizure duration during the acute stages of RSE or SRSE, and improves long-term cognitive outcomes.

#### Thermodynamic predictions

To conclude the present triad on therapeutic hypothermia (TH), another subset of authors from the Chang Gung Hospital in Taiwan investigated this time if a correlation between seizure severity during TH treatment and clinical outcomes of neonates with hypoxic-ischemic encephalopathy could be observed.

Chen et al. carried out a retrospective cohort study using amplitude-integrated electroencephalography at the moment of TH administration, and comparing the patients for the presence of epilepsy 12 months later [38].

As anticipated, the new-born patients displayed a high incidence of seizures and post-neonatal epilepsy. Moreover, the authors observe that recurring seizures or status epilepticus during rewarming, but not during hypothermia, were associated with the presence of epilepsy after 12 months, thus adding a certain predictive power the target temperature management.

#### Conflicts of interest

The author declares no conflict of interests.

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