Exploring the Iceberg: Caring for the Child with Herpes Simplex Encephalitis

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Background

Inflammation of the brain, known as encephalitis, is a relatively rare condition with an overall incidence of 3-8 cases per 100,000 patients [1, 2]. Its highest rates, are amongst children where it is associated with significant morbidity and mortality [3]. The most common identifiable cause of encephalitis in both adults and children is due to infection with the human herpesvirus; herpes simplex [4]. Herpes simplex encephalitis (HSE), is associated with a serious acute infection followed by significant long term sequelae. In this essay I will attempt to outline some of the effects of HSE, referring to two paediatric cases with this condition and exploring the impact it has on the child and their family.

Exploring the Iceberg

The heterogeneity of herpes simplex infection, varying both in presentation and severity, means attempting to define a ‘classical’ presentation of HSE is perhaps clinically unhelpful. I was able to appreciate the spectrum of this condition when, granted the opportunity to follow the stories of two young sufferers of HSE, I was introduced to two young children with the same diagnosis but significantly different needs. This, however, was not immediately evident from the acute presentation.

The first case, a 3 year old girl, A.B., first developed signs of HSE at 3 weeks of age. There was no significant antenatal history and a healthy baby
was delivered and discharged home with no complications. It was only at the beginning of her third week of life that baby A.B. developed yellow/white spots of differing sizes on her chin, corner of her mouth and tongue. This was followed by a febrile illness accompanied by periods of lethargy and her skin developed a mottled appearance, prompting an admission to the accident and emergency department. The initial impression was that of bacterial meningitis and a full septic screen, antibiotic treatment and admission to a paediatric ward was arranged. Unfortunately, A.B. continued to deteriorate and developed focal and generalised seizures requiring intubation and admission to intensive care at a specialist centre where the diagnosis of HSE was made. Intravenous acyclovir and antiepileptic drugs were administered, the latter being continued in differing combinations to control her seizures over her prolonged hospital stay. A similar initial pattern of presentation occurred with our second case, a 3 year old boy, C.D. At two months of age, following an uncomplicated perinatal period he was admitted to hospital with a fever, feeding difficulties and irritability. Empirical treatment for infections followed with provision of antibiotics and antiviral treatment as described in A.B.’s case. Later identified disseminated herpes simplex infection was then treated with intravenous acyclovir in a paediatric intensive care setting.

This characteristic progression from an initial period of normal development and wellness to one acutely complicated by infection is a feature shared by both cases. Interestingly, epidemiological study of HSE infection has shown no unique characteristics of gender, race, season or geographic location [5]. Instead, evidence suggests that susceptibility to infection in this neonatal period, most often the consequence of first contact with the virus [6-8] may be the product of a complex, and as yet incompletely defined, genetic
predisposition. The previous history of C.D.’s mother goes some way in supporting this – as a child she was infected with primary varicella zoster virus (a member of the herpesvirus family) and subsequently suffered from 3 episodes of shingles (reactivation of this viral infection) in later life. Is it possible that this represents a transmissible susceptibility within the family? From the literature, mutation in UNC93B [9] and TLR3 [10] both involved in IFN-γ, -α and -β immune responses have been identified in some cohorts of HSE patients. For this reason, both our cases underwent extensive genetic screening with the aim of establishing whether a genetic risk combined with an immature immune system in the neonatal period may have accounted for their increased susceptibility to infection [11].

The mechanisms of progression and pathophysiology of HSE is a further area of uncertainty. The non-specific nature of early symptoms and signs in children often presenting as a meningeal syndrome, behavioural changes or lethargy [12-15], confers a diagnostic challenge for the paediatrician. Although investigative techniques, such as polymerase chain reaction (PCR), used to detect viral DNA in the cerebrospinal fluid (CSF) have been shown to be highly specific for HSE, their sensitivity are far from definitive [2]. Furthermore, it is common practice in a clinical setting to adopt a low threshold for empirical administration of antibiotics and acyclovir to the febrile child. This coupled to the delay associated with obtaining a lumbar puncture sample (the median time of delay after encephalitis is suspected being 24 hours [16]) means that a negative PCR result often confers limited diagnostic value. Even biopsy of brain tissue, held to confer the best predictive accuracy, is limited due to the amount and selective area of tissue that can be sampled as well as the surgical complications associated with the procedure.
 Considering this, careful attention to clinical signs and symptoms along with early treatment with intravenous acyclovir have been the mainstay of management of children with suspected HSE, as highlighted in our cases above.

The challenges of this acute period can perhaps be likened to the tip of an iceberg. The initial acute presentation, remains a fraction of the overall burden of the condition, and often may not be representative of the magnitude and complexity of disease that lies beyond in the chronic period. Although the importance of prompt treatment with acyclovir cannot be overstated, these chronic sequelae of infection persist for much longer and can continue disguised during periods of apparent convalescence [18]. Just as icebergs can share similar tips while disguising vastly differing structures below the water, in the same way similar acute presentations can evolve into significantly different chronic disease phenotypes.

This divergent progression from the acute to the chronic stages of disease can be appreciated in our two cases. Baby A.B., following discharge home, continued to have refractory symptomatic epilepsy with later development of a non-epileptic movement disorder. Due to the complexity of this disorder, which exhibited a number of different seizure types that occurred in clusters, there was considerable difficulty in effective control using anti-epileptic drugs. Clinically defining which abnormal movements could be attributed to her epilepsy become extremely challenging without concomitant EEG monitoring, and A.B. mother’s judgement was often relied on to make this distinction. A number of combinations of anti-epileptic drugs were dispensed during A.B. regular outpatient clinic appointments with the view of controlling both seizure activity and irritability. This latter symptom impinged
heavily on her awareness and ability to interact and soon become the most challenging and distressing aspect of her management, for both her family and the professionals caring for her. Magnetic resonance imaging (MRI) scans taken of A.B. during this period, indicated extensive inflammation in the temporal and parietal lobes of both hemispheres. This considerable damage manifest in severe visually impairment as well as feeding and reflux problems necessitating the insertion of a percutaneous endoscopic gastrostomy (PEG-J) as a method of delivering nutrition.

Baby C.D., on the other hand, continued to have outbreaks of cutaneous herpes simplex, presenting with diffuse blistering lesions that required short courses of intravenous acyclovir treatment to be given in hospital. These attacks correlated well with the periods in which weaning from his prophylactic oral acyclovir regimen was attempted. These frequent reactivations did not include neurological symptoms, they provided a distinct example of the neurotropic nature of herpes simplex virus with characteristic establishment of latent infection [19]. In the subsequent months, a mild developmental abnormality was noted in the form of a hemiplegic cerebral palsy of the right side resulting in preferential use of the left arm and difficulty with transitional movements. This hemiparesis was remedied through support from a splint on the right leg and now only manifests as a limp when C.D. becomes tired. Other issues relating to gastric reflux are now controlled with appropriate medication.

Theses pronounced differences in disease severity may relate to a process of atrophy, degeneration and cyst formation in distinct anatomical structures within the brain [18]. The timing and intensity of this inflammatory insult seem to be crucial contributory factors and can be correlated with signs
and symptoms. An example being the high frequency of seizures in the acute period of HSE infection relating to the propensity of the virus to involve temporal lobe and hippocampal structures [20]. Likewise, the presence of post-encephalitic epilepsy, often relating to widespread lesions load within the brain, translates to a pattern of multifocal epilepsy seen later in the disease [20]. When relating inflammatory activity to clinical presentation it is important to remember that although HSE is often a monophasic disease, chronic persistent and relapsing forms have been documented in the literature [21-24]. The latter being exemplified in the reactivation of infection seen with W.B. following cessation of oral acyclovir prophylaxis. Identifying the underlying pathophysiology will aid in considering appropriate management for seizure control as well as limiting further damage via this dynamic process.

The progression of HSE with time uncovers further challenges, with often less apparent, but equally significant, difficulties relating to concentration, memory, behaviour and other executive skills. Adapting to these changes often involve patience on the part of the carer and implementation of a structured routine to avoid difficulties commonly encountered by the child in carrying out everyday activities. This approach, described as antecedent behaviour management (The Encephalitis Society Parents’ Handbook, [25]), provides a proactive goal-orientated approach to prevent inappropriate behaviour before it occurs due to limitations of analysis and self-awareness of poor behaviour in a number of children affected by encephalitis. Similar approaches regarding education and social development are also guided by the individual abilities of the child and strategies to adapt to novel environments. It is imperative to appreciate the importance of continuing this support into later teen years increasing learning difficulties
and isolation can be experienced within the more rigid secondary school system. Often due to the extended period of seemingly asymptomatic convalescence between the acute insult and ongoing difficulties, the two are often not paired together as related events [26]. Furthermore, insufficient neuropsychiatric testing at the time of initial HSE infection often results in an inadequate baseline from which to assess later measurements of [27].

Considering the complexity of needs relating to the underlying pathology and its clinical and social manifestations, it becomes evident that the care of a child with HSE is a multifaceted challenge involving a number of professionals and support groups. These sources of aid are not restricted to the medical aspects of disease (paediatricians, physiotherapists, occupation therapists, dieticians, GPs etc.) but also encompass community services relating to education, family issues, care provision and psychological support. As highlighted in our patient cases, the need and therefore use of these services may vary, their availability is vital to ensure that a holistic approach is taken to managing the disease, with the child’s wellbeing as a central focus. As increasing number of services are utilised in response to the child with multiple complex needs it become all the more important for each team to understand the goals of treatment and to work effectively within a multidisciplinary team (MDT) to ensure they are achieved. This combined MDT assessment approach was used successfully in the care of A.B., to address her complex needs. An agreed care plan was drawn up between the physiotherapists, occupational therapists, speech and language therapists, dieticians, paediatrician and specialist paediatric neurologist, with each member made aware of the challenges present and assigned a role in managing them.
Away from the medical environment the majority of care and adaptation is taken on by the families of children with HSE. Practical advice can be accessed via charitable societies, such as the Encephalitis society [25]. These provide information as well as a gateway for carers to make links with families in similar situations. Furthermore, they have a crucial role in ensuring that the services families are entitled to, as highlighted in National Framework Guidelines [28], are made available and easily accessible (correspondence with The Encephalitis Society).

All too often in our attempts to craft treatment regimens and coordinate hospital care for those with HSE, addressing the wellbeing of the full-time carers of these children becomes a forgotten priority. It is imperative to appreciate that unlike the role of the physician, focusing its attention and efforts for a fixed period of time with their patient, their commitment is relentless. This unmatched experience and in time veritable expertise relating to their child’s condition comes at a price involving struggling with symptoms, balancing family life and negotiating with social services and often culminates in frustration and profound exhaustion.

It is perhaps impossible for us to fully appreciate the magnitude of the responsibility carried by carers. Their efforts to secure the best treatment for their child, often leads to clashes with authorities and being labelled as a ‘difficult parent’. However, we can gain invaluable glimpses of insight by listening to the child’s story as told by their carer. I had the privilege of doing just this with the mother of A.B., who recounted her journey and through the description of her personal trials and tribulation she become a voice representing the shared concerns of all those that look after children with HSE. The initial acute presentation of A.B., as highlighted above, was given
new meaning as mother described having to record the numerous seizures experienced and fighting for her daughter to be given the attention of a specialist unit. She recalls the critical role of support from family and friends, whose travel and commitment caused them to share the exhaustion of the situation. The move from hospital to home was described as entering a new phase and though it was relief to return to family life it also signalled a new chapter of responsibility in caring for baby A.B. Since then a steady period of adaptation, perhaps out of necessity, has resulted in mother becoming an expert on her child’s condition, a wisdom that has aided the process of coming to terms with her daughter’s condition and strengthened the bond between them.

Much can be derived from these personal accounts as similar struggles are shared by other carers and thus become valuable indicator to where we should be directing our attention and providing our services. Often as doctors we maintain our focus on research into the medical aspects of disease, aiming to unpick the genetic links, understand the behaviour of pathogens and identifying appropriate treatments to tackle them. Though these are important questions to consider, taken in isolation we become like sailors falsely reassured that should we avoid the tips of the iceberg we will be able to navigate smoothly through uncertain waters. Far more practical considerations often have more tangible and profound effects and importantly appreciate the effect of the condition in everyday life. Calls from carers for greater co-ordination and communication between primary and secondary care resonate with sagacity and unsurprisingly have now been considered priorities in planned political reform [29]. An increase in the availability, funding and recognition of the work that support groups offer is required,
these are invaluable sources of friendship as well as information regarding medication, assessment and entitlement (see [25]). There is also a need to ensure equitable provision of Social Services that aim for consistency throughout the country with the welfare of each child, not simply of cost, as their primary concern. Similarly, equal opportunities and funding are required for education with appropriate special educational needs (SEN) support whether in mainstream schools or in specialist schools. Finally, and perhaps most crucially, a service providing high quality respite care is required for all families. This maintains the health and wellbeing of the carer but also of the rest of the family. As in the case of A.B., respite provides an opportunity to spend time with her other child, strengthen her relationship with her husband as well as to pursue an activity that provides a restorative break. The importance of allocating personal time in this way cannot be underestimated, especially when considering the psychological challenges associated with caring for a child with HSE. An appreciation of the efforts that carers place not just on an individual basis but to society as a whole, which would otherwise have to fund full-time nursing care to support children with severe HSE, is a necessary and ongoing priority.

It is imperative that our approach as physicians treating this condition is one of listening and appreciating the complexity of care required for these children. We all too often only see the tip of the iceberg, it is our duty as health care professionals to ensure we dive to deeper waters to appreciate the full extent of this condition, only then can we truly claim to be caring for the child with HSE.
N.B. The initials of the two cases discussed have been changed in the interest of confidentiality.

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References