1. Introduction

Encephalitis is an acute inflammation of the brain which can arise after infections such as septicemia or by primary extension of the inflammation in cases of cerebral abscess or meningitis. In a more restricted sense, it refers to a primary disease in which inflammation of the brain is caused by viral agents. Especially in children it may also arise via autoimmune or hypersensitivity reactions. Although, laboratory processes have sufficiently developed to isolate and demonstrate offending agents in most of the cases, a number of sporadic cases remain in which a viral etiology is suspected on account of general presentation. The symptoms of encephalitis include headache, fever, drowsiness tremors, vomiting and photophobia along with those arising from involvement of the central nervous system (Lishman, 2003; Maria & Bale JR, 2006).

The principal feature of cerebral involvement is disturbance of consciousness. Delirium may figure prominently in some varieties. Seizures are common especially in children and can be the presenting feature. Focal neurological signs depend on the site of inflammation and may vary. Changes in pupils and in deep tendon reflexes, ocular palsies, nystagmus, ataxia, pathological reflexes, and paresis of limbs are common. Dysphasia may denote involvement of the temporal lobe while urinary retention or paraparesis may reveal involvement of the spinal cord. Occasional cases may present with neuropsychiatric symptoms such as hallucinations, psychosis, changes in personality, dementia, delirium, delusions, affective changes, paraphilias, amnesia and parkinsonism. Those attracted attention in early epidemics of encephalitis lethargica and examples may still occur with other varieties (Lishman, 2003; Maria and Bale JR, 2006).

Although encephalitis may be an important cause of delirium and dementia as well as other psychopathology in childhood, those diagnoses present a diagnostic challenge to most child and adolescent psychiatrists leading to missed diagnoses (Cepeda, 2000; Jha, 2004; Nunn, Williams & Ouvrier, 2002, Schieveld et al., 2007). Also, encephalitis may be associated with significant childhood morbidity and mortality worldwide, however not much is known about the contemporary epidemiology and outcome (Galanakis et al., 2009).
The review and comparison of psychological consequences of various causes of childhood encephalitis may have the potential to elucidate the mechanisms of development of the human brain as well as improving our knowledge of child and adolescent neuropsychiatry. Up to now, publications tend to be isolated case histories or case series, from separate centers and this may preclude generalizations. The authors have also noted that, up to now no research group has attempted a collected presentation of cases published in Middle Eastern countries. Considering the potentially rewarding nature of this condition a critical review, especially using information from cases reported from the said countries, was deemed to benefit clinicians. In this review, first the classical accounts of neuropsychiatric consequences of encephalitis throughout the lifespan will be reviewed and augmented with the results of studies conducted to determine the neuropsychiatric consequences of childhood encephalitis, then a collected presentation of cases published in Middle Eastern countries will be attempted, lastly targets for future research and intervention will be delineated.

2. Methods

A literature search was conducted by using the PubMed search engine (http://www.ncbi.nlm.nih.gov/sites/entrez) and “childhood encephalitis” was entered as key-word. The data from the results of this search is combined with those from text-books to provide a “standard” description. Thereafter, the names of the countries in Middle-East were added to this key-word (i.e. “Turkey”, “Syria”, “Lebanon”, “Israel”, etc.) and separate searches were conducted. Data for cases were extracted. A search of the database yielded that 309 publications from Turkey and 409 from Israel were conducted on Encephalitis. Iran (n=37) and Lebanon (n=30) followed those countries. Lastly, targets for future research and intervention will be delineated.

3. Types of encephalitis and their consequences throughout the life span

3.1 Arthropod borne encephalitis

This group of illnesses, including Eastern Equine, Western Equine and St. Louis encephalitis as well as Japanese B encephalitis causes seasonal, recurrent epidemics in various parts of the world. Transmission is by insect bites which may include mosquitoes, ticks and mites. The illnesses especially affect the very young and the elderly. The onset is with fever, headache and gastrointestinal disturbances. Signs of meningeal irritation often accompany these with seizures and reduced consciousness. Delirium may be rarer in those cases. Focal motor signs may include cranial nerve palsies (especially the occulomotor nerve) and upper motor neuron pareses in limbs. Approximately 70% of cases may result in severe neurological damage or death (Lishman, 2003; Stone and Hawkins, 2007).

The sequels are directly related to the length of coma in the acute stage and inversely related to the age at infection. Residual deficits are reported in approximately 50% of infants less than one year of age while the rate is 20% for adults. Sequels in infants may include mental retardation, spastic paralysis, motor abnormalities and seizures. In adults, the sequels may include depressed mood and lethargy during recovery, occasional changes in personality and intelligence, and, rarely; ataxia, dysarthria and hemiparesis. Post-encephalitic parkinsonism is thought to be rare. Adult patients frequently report multiple, vague, somatic complaints. Depression, irritability, insomnia, forgetfulness, reduced concentration, and tremors may also be reported (Lishman, 2003; Stone and Hawkins, 2007). Recent studies conducted in Turkey and Middle-Eastern countries revealed that, Tick-borne and other arthropod related encephalitis may be commoner than thought before (Ergunay et al., 2007).
3.2 Enterovirus encephalitis
This group of viruses mostly produces aseptic meningitis rather than encephalitis. For poliomyelitis, spinal cord is the main target with usually slight encephalitis while coxackie and ECHO viruses can occasionally produce encephalitis. Outbreaks are commonest in summer and autumn. Children affected while they were less than one year old may occasionally be left with neurological impairment and seizures. Other serious sequels are reported to be rare. Muscle weakness may be marked however, true paralysis is rare. Very rarely, a mild post-encephalitic parkinsonism may be seen after those infections (Lishman, 2003; Stone and Hawkins, 2007).

3.3 Encephalitis lethargica
This atypical form of encephalitis, which was first reported by Von Economo in 1917, caused epidemics with chronic and severe sequels throughout 1918-1920 (Lishman, 2003). Although the epidemic has not recurred since then, isolated cases continue to be reported (Reid et al., 2001). The symptoms arise after a flu-like prodrome and include, fever, sore throat, headache, diplopia, alterations in consciousness, sleep inversion, catatonia and lethargy (Dale et al., 2004; Lishman, 2003). Akinetic mutism, oculogyric crises, parkinsonism, paresis, muscle pains, tremors, nuchal rigidity, and behavioral changes including psychosis are also reported (Vilenksy et al., 2006). Sequels include tics, psychosis, personality changes and post-encephalitic parkinsonism, the latter even arising years after the initial infection. The disease is polymorphic, although each epidemic was reported to share some features within itself. Reportedly, most epidemics had a seasonal pattern with peaks in winter (Lishman, 2003). The cause is still not known for certain, although recent research suggests an autoimmune reaction (Dale et al., 2004; McCall et al., 2008). Alternatively, some authors posit that the offending agent might be a variant of influenza (Vilenksy et al., 2007). A recent study revealed that influenza infection in mice may trigger an autoimmune response which destroys dopaminergic neurons, thereby bridging these two views (Jang et al., 2009). Regardless of cause, the disease was reported to have distinct forms; including a somnolent-ophtalmoplegic variety along with hyperkinetic, parkinsonian and psychotic forms. The somnolent-ophtalmoplegic variety or the basic form was reported mainly in sporadic cases and demonstrated somnolence after a prodrome of mild meningeal irritation, movement and ocular abnormalities and cranial nerve palsies. Initial presentation was with drowsiness, sometimes with mild delirium. This stage may be followed by recovery or a long term sleep which may even last for months. The sleep problems persisted even after recovery. Seizures, aphasias which may be temporary and cerebellar signs were also reported in those patients (Lishman, 2003).
In contrast, the hyperkinetic form was characterized by motor restlessness after the prodrome. Myoclonic twitches, chorea, anxiety were reported along with compulsive, tic-like movements, torticollis, torsion spasms, oculomotor symptoms and seizures. Delirium could be marked. This acute phase lasted for a few days, and followed by sleep abnormalities after recovery. Some patients may develop into somnolent-ophtalmoplegic or parkinsonian types after the acute stage, illustrating the polymorphic character of the disease (Lishman, 2003).
In the parkinsonian form; rigidity and akinesis are seen from the outset. The patient displays psychomotor retardation, hypophonia and increased latency of speech. While he/she was reported to be mentally intact, the muscle tone was increased and there were coarse tremors in their hands. Also, festinating gait, hypersalivation, catatonia, somnolence, sleep inversion
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and ocular motor symptoms can be seen. Many of those patients were reported to progress into chronic parkinsonian forms (Lishman, 2003).

Psychotic forms, which initially present with isolated psychopathology are rare and the presentation is with an acute organic reaction with stupor, depression, hypomania and catatonia. Impulsive and bizarre behavior with bewildered/fearful affect may be the only finding for several days. Controversially, it was posited that some cases might have occurred as isolated psychoses without somatic symptoms and they were called as “cerebral forms” (Lishman, 2003). There may also be other forms with bulbar palsies or involving isolated cases of chorea, neuritis and hiccoughs (Lishman, 2003).

During recovery, patients report fatigue, depression and sleep problems. Focal neurological problems may also persist after recovery. Motor abnormalities and seizures were also reported to persist, albeit rarely. Hypothalamic damage may lead to endocrine abnormalities. According to earliest resources, 40% of the cases were fatal while 20% demonstrated complete recovery. The remainder had residual deficits, of which the most important were parkinsonism and personality changes. Also, among the patients with residual problems, approximately one half were permanently disabled, mostly due to progressive parkinsonism. As a result, the most important chronic sequel reported were parkinsonism, personality changes and mental retardation. Severe psychopathologies were also seen in varying numbers. The sequelae mentioned depended on the age at infection with adults developing parkinsonism and subcortical dementia, children personality changes and infants mental retardation. They were not related with the severity of the initial infection (Bruneau, 2005; Lishman, 2003). Parkinsonism may develop gradually from the acute stage onwards or may arise after full recovery (Lishman, 2003).

Post-encephalitic parkinsonism after encephalitis lethargica was the most common sequel, which developed insidiously. Typical pill-rolling tremor in this type of parkinsonism was reported to be rarer, with occasional coarse tremors and athetosis. Apathy was more striking with rigidity developing later. Stereotypies were also distinctive, developing in advanced cases. Within this picture, compulsive elements were observed in speech, thought and motor behavior. In some cases, reportedly, compulsive thoughts and urges may arise independently of motor phenomena. Oculogyric crises were also seen along with changes in the function of the autonomic nervous system. As reported in classical resources, suggestibility played a role in this picture. Punding, that is compulsive/impulsive behavior and interests arising after infection may be seen and be related with oculogyric crises (Bruneau, 2005; Lishman 2003).

Post-encephalitic personality change was mostly observed in children and adolescents. It was frequently accompanied by parkinsonism, sleep changes, obesity and endocrine abnormalities. The personality changes included emotional lability, hyperactivity and impulsive behavior. Some of those patients improved with puberty while 50% developed parkinsonism in their later years (Lishman, 2003).

Post-encephalitic psychoses after encephalitis lethargica were usually affective in nature. Paranoid-hallucinatory states were reported in 15 to 30% of patients while 10% displayed schizophrenia like psychoses. Severe cases of hypochondriasys were also reported. (Lishman, 2003).

As for current cases, it can be said that the diagnosis is mainly clinical with a high index of suspicion for patients with parkinsonism and sleep changes developing after an encephalitis along with oculogyric crises, ocular/pupillary abnormalities, involuntary movements and psychopathology. Sporadic cases may be milder than those described in epidemics and psychiatric symptoms may be prominent in the clinical picture (Lishman, 2003). Lopez-
Alberola et al., 2009). Cases which arose after seasonal influenza infections as well as infections with Ebstein-Barr virus have also been reported, therefore supporting the position that encephalitis lethargica may be a heterogenous presentation of infections affecting the circuits between frontal lobes and basal ganglia (Alarcón et al., 2011; Toovey et al., 2011).

3.4 Encephalitis due to herpesviridiae
This group involves encephalitis due to Herpes simplex, Ebstein Barr and Varicella Zoster viruses.

3.4.1 Herpes Simplex Virus Encephalitis (HSVE)
HSV is the commonest single cause of severe sporadic encephalitis with a high mortality and marked psychopathology both in the acute presentation and as sequels. It affects especially medial temporal and orbital lobes and causes sporadic encephalitis without seasonal variation among all age groups. It may be primary or due to reactivation. There is typically a rapid onset with fever, seizures, meningeal irritation, drowsiness/confusion, and focal neurological signs. A study conducted at a pediatric tertiary treatment center in Turkey found that 40 % of the patients applying for treatment with status epilepticus had either meningitis or encephalitis, underlying the pre-eminence of seizures in HSVE (Saz et al., 2011). Sometimes, psychiatric symptoms may be prominent at the onset. Hallucinations as part of psychiatric symptoms or part of delirium are typically vivid and colorful with marked emotional reactions. Restlessness and hyperactivity may be seen after recovery. Additionally, anosmia, olfactory and gustatory hallucinations, amnesia, symptoms of elevated intracranial pressure could be seen. Rarely, benign aseptic meningitis or recurrent organic psychoses may be seen. The sequels involve mental retardation in children, dementia in adults, seizures, dysphasia, personality changes, severe amnestic states, and bizarre behavior resembling Kluver-Bucy Syndrome throughout the life span (Arciniegas and Anderson, 2004; Lishman, 2003; Stone and Hawkins, 2007).

Even among recovered patients, subtle neuro-psychological deficits are observed, especially involving language and memory. Calculation, facial recognition and visuo-spatial abilities were also reported to be affected. (Ku et al. 1996; Ward et al. 2011).

3.4.2 Encephalitis due to EBV (Infectious Mononucleosis)
The most distinctive feature of this type of encephalitis is its picture of depression and fatigue in the recovery period. Reportedly, the two phenomena are not related (Lishman, 2003). However, in isolated cases more severe presentations and neuropsychological sequelae may occur (Dagdemir et al., 2008).

3.4.3 Varicella Zoster Virus (VZV)
Although the introduction of live attenuated VZV vaccine in 1995 helped to reduce the incidence and complications of varicella infections and sequels with this virus continue to be reported, mainly involving meningitis (Pahud et al. 2011). Although an eight year old male patient was reported to develop acute hemiplegia and obsessive-compulsive disorder secondary to a lesion of lentiform nuclei after a varicella infection and that he was reported to respond to sertraline treatment and to make a full-recovery, studies and/ or case series involving larger samples from both genders may be needed to elucidate the neuropsychological consequences of VZV infection (Yaramiş et al., 2009).
4. Other types of sporadic, viral encephalitis

This group includes mumps, adenoviruses, infectious hepatitis, rabies and influenza. Among those, mumps is the most important one, it may cause encephalitis even without overt disease. The virus can itself invade the central nervous system. It usually causes aseptic meningitis, with only occasional cases of encephalitis. Therefore, if encephalitis due to mumps is present then as a rule, co-morbid meningitis and sometimes myelitis is also present. The symptoms occur 2-10 days after parotitis or in some cases, may precede it (Lishman, 2003).

5. Long term consequences of childhood encephalitis

Studies conducted on the long term consequences of childhood encephalitis are scarce. However, it was reported that childhood encephalitis between 0-16 years at the time of infection caused mortality at a rate of 2.8 % while the rate increased to one third if the patients were less than three years of age (Lishman, 2003). The risk of mortality may be especially pronounced in patients less than one years old, those who are unconscious at the time of admission, within the first month and with infections by HSV (Lishman, 2003). After a follow-up of 10 years it was reported that 40 % of patients may have problems with motor functions/ academic achievement, 20 % may have epilepsy and a further 20 % displayed behavioral problems, mostly hyperactivity (Lishman, 2003).

5.1 Studies conducted on childhood encephalitis in Middle-Eastern countries

When the results of studies conducted on childhood encephalitis in Middle-Eastern countries were reviewed it was observed that they focused mostly on cases of HSVE, reflecting the international literature (Ibrahim et al., 2005; Yildirim 2008). Pediatric complications associated with Influenza and results of West Nile encephalitis were reported in studies conducted in Israel (Landau et al. 2011). Also, reflecting the 2009 pandemic of influenza, cases of meningitis and meningo-encephalitis in children were reported with influenza A (H1N1) infections from Turkey (Ozdemir et al., 2011, Yildizdas et al., 2011). However, neuropsychiatric and neurobehavioral consequences of childhood encephalitis were reported only in limited studies (Yildirim, 2008). According to those; pediatric HSVE caused deficits in IQ, short term memory and in language functions while deficits due to mumps meningoencephalitis were slight (Yildirim, 2008), though results of another study from Turkey may contradict the latter position (Aygın et al., 2001, Yildirim, 2008). Aygın and colleagues (2001), investigated the viral etiology of 36 children at a regional medical center in eastern Turkey in between 1995 and 1999 and reported that mumps was the most common pathogen in their sample (47.1 %) and that mental and/ or focal neurological deficits were observed in 52.9 % (Aygın et al. 2001). Isolated cases of neuropsychological consequences with VZV are also reported (Yaramış et al., 2009).

6. Conclusion

Although encephalitis may be associated with significant childhood morbidity and mortality worldwide, our knowledge about its contemporary epidemiology and outcome are limited, especially for the long term (Galanakis et al., 2009). Therefore, future multi-centre studies conducted on patients who recovered from childhood encephalitis may be necessary. Elucidation of neuropsychological deficits caused by varieties of childhood encephalitis may help us determine potential remedial methods for rehabilitation (Dewar and Gracey, 2007).
The Neuropsychiatric Consequences of Childhood Encephalitis: A Review of Cases from Middle-Eastern Countries

7. References


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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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