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Inflammation in epileptic encephalopathies

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Abstract

West syndrome (WS) is an infantile epileptic encephalopathy (EE) that manifests with infantile spasms, hypsarrhythmia (in ~60% of infants) and poor neurodevelopmental outcomes. The etiologies of WS can be structural-metabolic pathologies (~60%), genetic (12–15%) or of unknown origin. The current treatment options include hormonal treatment [adrenocorticotropic hormone (ACTH) and high dose steroids], the GABA aminotransferase inhibitor vigabatrin, while ketogenic diet can be given as add-on treatment in refractory IS. There is a need to identify new therapeutic targets and more effective treatments for WS.

Theories about the role of inflammatory pathways in the pathogenesis and treatment of WS have emerged, being supported by both clinical and preclinical data from animal models of WS. Ongoing advances in genetics have revealed numerous genes involved in the pathogenesis of WS, including genes directly or indirectly involved in inflammation. Inflammatory pathways also interact with other signaling pathways implicated in WS, such as the neuroendocrine pathway. Furthermore, seizures may also activate pro-inflammatory pathways raising the possibility that inflammation can be a consequence of seizures and epileptogenic processes. With this targeted review we plan to discuss the evidence pro and against the following key questions. Does activation of inflammatory pathways in the brain cause epilepsy in WS and does it contribute to the associated comorbidities and progression? Can activation of certain inflammatory pathways be a compensatory or protective event? Are there interactions between inflammation and the neuroendocrine system that contribute to the pathogenesis of West syndrome? Does activation of brain inflammatory signaling pathways contribute to the transition of WS to Lennox-Gastaut syndrome? Are there any lead candidates or unexplored targets for future therapy development for WS targeting inflammation?

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1. Introduction

West syndrome (WS) is an age-specific epileptic encephalopathy (EE), which typically occurs in infants and has poor epilepsy, neurodevelopmental prognosis and high risk of early mortality (Dulac 2001, Fukuyama 2001, Galanopoulou 2013, Galanopoulou & Moshe 2015). WS manifests with at least two of the following features: (a) ictal events of flexion or extension spasms, called infantile spasms (IS) that usually appear in clusters, (b) interictal chaotic high amplitude and multifocal epileptic interictal background (hypsarrhythmia), and (c) intellectual or neurodevelopmental disabilities (Galanopoulou & Moshe 2015).

A wide range of possible etiologies for WS have been described, ranging from structural or metabolic (including malformations, vascular, inflammatory or immune, hypoxia, etc.) to genetic, albeit in many infants the causes are yet unknown (Frost & Hrachovy 2005, Berg, Berkovic, Brodie, Buchhalter, Cross, van Emde Boas et al. 2010, Osborne, Lux, Edwards, Hancock, Johnson, Kennedy et al. 2010, Pellock, Hrachovy, Shinnar, Baram, Bettis, Dlugos et al. 2010, Paciorkowski, Thio, Rosenfeld, Gajecka, Gurnett, Kulkarni et al. 2011, Epi4K. Consortium, Epilepsy Phenome/Genome Project, Allen, Berkovic, Cossette, Delanty et al. 2013). Mortality can be significant ranging between 9–35% (Trevathan, Murphy & Yeargin-Allsopp 1999, Riikonen 2001, Autry, Trevathan, Van Naarden Braun & Yeargin-Allsopp 2010, Pellock, Hrachovy, Shinnar, Baram, Bettis, Dlugos et al. 2010), although higher rates have been reported with long-term follow up (Silanpaa, Riikonen, Saarinen & Schmidt 2016).IS can progress into other types of seizures and epilepsies, which might have poor response to treatment. Epilepsy develops in 50–70% of surviving children (Koo, Hwang & Logan 1993, Riikonen 2001) and evolution to Lennox–Gastaut syndrome has been reported in 15–25% of these patients, although reports of up to 54% have been published) (Lombroso 1983, Rantala & Putkonen 1999, Rantala & Putkonen 1999, Trevathan, Murphy & Yeargin-Allsopp 1999, Hrachovy & Frost 2003, Galanopoulou 2013). Cognitive and neurodevelopmental impairments may be significant and often leading to mental retardation (70–90%) (Koo, Hwang & Logan 1993, Sidenvall & Eeg-Olofsson 1995, Trevathan, Murphy & Yeargin-Allsopp 1999, Riikonen 2001, Galanopoulou & Moshe 2015). Further evolution to autism is seen in 15% although infants with IS due to underlying structural or metabolic pathologies are at higher risk (Riikonen & Amnell 1981, Saemundsen, Ludvigsson & Rafnsson 2008, Galanopoulou 2013). For example, in 57% of infants with IS due to tuberous sclerosis complex (TSC) had ASD (Hunt & Dennis 1987).

The first line treatment options for IS are hormonal therapies [adrenocorticotropic hormone (ACTH), glucocorticoid steroids] or the GABA aminotransferase inhibitor vigabatrin (Mackay, Weiss, Adams-Webber, Ashwal, Stephens, Ballaban-Gill et al. 2004, Pellock, Hrachovy, Shinnar, Baram, Bettis, Dlugos et al. 2010, Go, Mackay, Weiss, Stephens, Adams-Webber, Ashwal et al. 2012, Riikonen 2014, Galanopoulou & Moshe 2015).

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Ketogenic diet has been proposed as an alternative adjunctive therapy for IS to be considered after failure of corticosteroids and/or vigabatrin and has shown some efficacy in refractory IS (Hong, Turner, Hamdy & Kossoff 2010, Pires, Ilea, Bourel, Bellavoine, Merdariu, Berquin et al. 2013). A smaller percentage of patients with IS may respond to other antiseizure drugs (valproate, topiramate, zonisamide) or vitamin B6 (Pellock, Hrachovy, Shinnar, Baram, Bettis, Dlugos et al. 2010, Riikonen 2014). Considering the devastating prognosis of patients with WS, the identification of better therapies for WS has been the focus of both clinical and preclinical studies using the animal models. Inflammation has attracted interest as a potential target for new therapy development for WS due to the availability of clinically available drugs targeting the inflammatory signaling pathways and the emerging evidence for a potential role in the pathogenesis of WS.

In this review, we will focus on selected inflammatory pathways and molecular targets investigated in infants and animal models of WS; discuss the evidence that inflammation could be a cause of WS, its associated comorbidities, progression and/or evolution of West syndrome into Lennox-Gastaut syndrome or simply a consequence. Finally, we will present an update on the progress in new inflammation-targeting therapies based on recent clinical and experimental evidence from animal models (multiple hit rat model of IS).

2. Inflammation and neuroinflammation: definitions, targets and role in epilepsy and seizures

Inflammation can be defined as the body's immune system response to various stimuli, involving the cascade of reactions and signals which lead to activation of innate immune cells (in particular neutrophils and macrophages) and adaptive immune response (in particular lymphocytes, which further remove the targeted pathogens). The innate immunity is a nonspecific defense mechanisms activated either immediately or within hours after antigen invasion. The adaptive or acquired immunity is a specialized process involving antigen presentation that aims to eliminate or prevent pathogen growth. Inflammation can be nonsterile or sterile, depending upon whether the trigger is a microorganism or a non-infectious pathogen/antigen. Both types of inflammation manifest with recruitment of neutrophils, macrophages and production of pro-inflammatory cytokines and chemokines (e.g., tumor necrosis factor alpha [TNF-α] and interleukins [IL])(Chen & Nuñez 2010).

Neuroinflammation is the innate immunological response within the nervous system, involving microglia and astrocytes (Graeber, Li & Rodriguez 2011). Today, brain inflammation or neuroinflammation have been associated with many central nervous system (CNS) pathologies (Dey, Kang, Qiu, Du & Jiang 2016). Such processes may have beneficial effects, protecting against exogenous insults or promoting healing, but under certain situations they can be pathogenic. Prior studies associated elevated levels of pro-inflammatory cytokines with seizures, the pathogenesis of epilepsy, and pathologies manifesting epilepsy (Table 1) (Vitaliti, Pavone, Mahmood, Nunnari & Falsaperla 2014). Recent studies have introduced the neurological sequelae, in which pro-inflammatory cytokines with proictogenic properties (such as IL-1β, high-mobility group box 1 [HMGB1], cyclooxygenase-2 [COX-2], prostaglandin E2 [PGE2], IL-6, TNF-α and nicotinamide

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adenine dinucleotide phosphate-oxidase [NOX2]) play an important role in seizure generation and exacerbation (Vezzani, Auvin, Ravizza & Aronica 2012, Wu & Huang 2015, Dey, Kang, Qiu, Du & Jiang 2016). IL-1β and HMGB1 induce the proinflammatory innate immunity IL-1 receptor type 1 (IL-1R1)/toll-like receptor 4 (TLR4) signaling (Ravizza, Kostoula & Vezzani 2013, Vezzani, Lang & Aronica 2016) leading to neuroinflammation, its perpetuation and thus modulating seizure susceptibility, lowering seizure threshold and epileptogenesis (Maroso, Balosso, Ravizza, Liu, Aronica, Iyer et al. 2010, Riazi, Galic & Pittman 2010, Vitaliti, Pavone, Mahmood, Nunnari & Falsaperla 2014, Vezzani, Lang & Aronica 2016).

Toll-like receptors (TLRs) are the key proteins in the mammalian innate immune response to both infectious and non-infectious CNS diseases, including epilepsy (Akira, Takeda & Kaisho 2001, Akira, Uematsu & Takeuchi 2006, Kawai & Akira 2010, Wang, Lin & Yang 2011, Pernhorst, Herms, Hoffmann, Cichon, Schulz, Sander et al. 2013). Each TLR family member, with the exception of TLR3, signals through the MyD88-dependent pathway, initiated by the MyD88 adaptor protein, resulting in the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (a mediator of acute inflammation (Lawrence 2009)), mammalian target of rapamycin (mTOR) (central pathway, involved in regulation of multiple processes including inflammation (Galanopoulou 2013)) and generation of the pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor alpha (TNF-α) (Takeda & Akira 2004, Wang, Lin & Yang 2011, Ravizza, Kostoula & Vezzani 2013). This evidence arose from surgically resected epileptic tissues of adult and pediatric patients with epilepsy showing the presence of inflammatory molecules in activated glial cells, neurons and endothelial cells of the blood-brain barrier (BBB) and indicating the strong link between inflammation and seizures (Crespel, Coubes, Rousset, Brana, Rougier, Rondouin et al. 2002, Ravizza, Boer, Redeker, Spliet, van Rijen, Troost et al. 2006, Aronica, Boer, van Vliet, Redeker, Baayen, Spliet et al. 2007, Ravizza, Gagliardi, Noe, Boer, Aronica & Vezzani 2008, Maroso, Balosso, Ravizza, Liu, Aronica, Iyer et al. 2010, Vezzani, French, Bartfai & Baram 2011, Zurolo, Iyer, Maroso, Carbonell, Anink, Ravizza et al. 2011, Balosso, Ravizza, Aronica & Vezzani 2013, Iori, Maroso, Rizzi, Iyer, Vertemara, Carli et al. 2013, Pernhorst, Herms, Hoffmann, Cichon, Schulz, Sander et al. 2013).

Additional studies have also shown that loss of blood brain barrier (BBB) integrity may be an important link between neuroinflammation and epileptogenesis (Fabene, Navarro Mora, Martinello, Rossi, Merigo, Ottoboni et al. 2008, Kim, Kang, Dustin & McGavern 2009, Ransohoff 2009, Bar-Klein, Cacheaux, Kamintsky, Prager, Weissberg, Schoknecht et al. 2014, Friedman, Bar-Klein, Serlin, Parmet, Heinemann & Kaufer 2014, Vitaliti, Pavone, Mahmood, Nunnari & Falsaperla 2014, Salar, Lapilover, Muller, Hollnagel, Lippmann, Friedman et al. 2016). Overactivated mast cells, which can be potentially activated by stress hormones, such as corticotropin-releasing hormone (CRH), lead to BBB disruption (Theoharides 1990, Esposito, Chandler, Kandere, Basu, Jacobson, Connolly et al. 2002, Theoharides & Konstantinidou 2007, Vitaliti, Pavone, Mahmood, Nunnari & Falsaperla 2014). In addition, extravasation of albumin during vascular injury activates the transforming growth factor beta (TGF-β) receptor I signaling pathway and contributes to epileptogenesis (Bar-Klein, Cacheaux, Kamintsky, Prager, Weissberg, Schoknecht et al. 2014). Losartan, an inhibitor of the angiotensin II type 1 receptor and blocker of TGF-β

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signaling prevented epileptogenesis in a model of BBB disruption induced by deoxycholate (Bar-Klein, Cacheaux, Kamintsky, Prager, Weissberg, Schoknecht et al. 2014).

There is a two way interaction between inflammation and seizures. Inflammation can decrease the seizure threshold and cause more severe seizures and comorbidities (Mazarati, Maroso, Iori, Vezzani & Carli 2011, Vezzani, French, Bartfai & Baram 2011, Vezzani, Aronica, Mazarati & Pittman 2013). On the other hand, seizures, independently of their trigger, might cause neuroinflammation in structures involved in the onset, control, and generalization of epileptic activity, and may worsen outcomes (Rizzi, Perego, Aliprandi, Richichi, Ravizza, Colella et al. 2003, Dube, Vezzani, Behrens, Bartfai & Baram 2005, Marcon, Gagliardi, Balosso, Maroso, Noe, Morin et al. 2009, Dube, Ravizza, Hamamura, Zha, Keebaugh, Fok et al. 2010, Auvin, Cilio & Vezzani 2016).

In epilepsy, several pathogenic mechanisms leading to epileptogenesis and its progression or contributing to pharmacoresistance have been associated with pro-inflammatory cytokines as predisposing factors (Vitaliti, Pavone, Mahmood, Nunnari & Falsaperla 2014). For example, cytokines may reduce astrocytic glutamate reuptake and increase the extracellular glutamate concentration leading to neuronal excitation (Ye & Sontheimer 1996, Takaki, Fujimori, Miura, Suzuki, Sekino & Sato 2012), leading to neuronal excitation. Increase in the expression of astrocytic glutamate transporters through treatment with ceftriaxone has been shown to reduce seizures in a mouse model of tuberous sclerosis (Zeng, Bero, Zhang, Holtzman & Wong 2010). Inflammation or its downstream signaling mediators may alter the neurotransmitter receptor composition or expression or function aggravating seizures, their comorbidities or their pathological sequelae, including cell death, neurogenesis, angiogenesis, synaptic re-organization, and BBB disruption (Lubin, Ren, Xu & Anderson 2007, Rigau, Morin, Rousset, de Bock, Lebrun, Coubes et al. 2007, Sankar, Auvin, Mazarati & Shin 2007, Yang, Liu, Chen, Zhang, Quan, Huang et al. 2010, Mazarati, Maroso, Iori, Vezzani & Carli 2011, Vezzani, French, Bartfai & Baram 2011, Vezzani, Aronica, Mazarati & Pittman 2013).

3. Does activation of the inflammatory pathways in the brain cause epilepsy in WS?

Clinical evidence

In WS, there are numerous etiologies recorded, including at least 60 known genes affected, numerous chromosomal abnormalities or other structural and metabolic etiologies (Galanopoulou & Moshe 2015). Few of the genes linked with WS are components of neuroinflammatory pathways, including complement regulatory factors (CD46), glucocorticoid signaling, (glucocorticoid modulatory element binding protein 2 GMEB2, glucocorticoid receptor NR3C1), mTOR pathway [Tuberous sclerosis complex 1 and 2 (TSC1 and TSC2), STE20-related kinase adaptor alpha (STRADα), Phosphatase and Tensin Homolog Tumor suppressor (PTEN), Phosphoinositide 3-kinase adapter protein (PIK3AP1)], TNFα induced protein 6 (TNFAIP6)] [see Supplemental Table 1 in (Galanopoulou & Moshe 2015)]. Malformations of brain development and focal cortical dysplasias are also common pathologies in infants with WS, which have been linked with

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abnormal expression of components of the mTOR signaling: TSC1 or TSC2 in Tuberous sclerosis complex (TSC), PTEN in hemimegalencephaly, STRADα in polyhydramnios, megalencephaly and symptomatic epilepsy syndrome (PMSE), and overexpression of phosphorylated S6 ribosomal protein (pS6) in focal cortical dysplasias type IIB (Baybis, Yu, Lee, Golden, Weiner, McKhann et al. 2004, Chu-Shore, Major, Camposano, Muzykewicz & Thiele 2010, Orlova, Parker, Heuer, Tsai, Yoon, Baybis et al. 2010, Galanopoulou, Gorter & Cepeda 2012, Epi4K. Consortium, Epilepsy Phenome/Genome Project, Allen, Berkovic, Cossette, Delanty et al. 2013, Lim & Crino 2013, Pardo, Nabbout & Galanopoulou 2014). Among the acquired pathologies leading to IS, hypoxic–ischemic injury, CNS infections, perinatal strokes, metabolic disorders, or autoimmune conditions may also manifest inflammatory changes [(Mota, Rezkallah-Iwasso, Peracoli & Montelli 1984, Steele, Cheah, Veerapandiyan, Gallentine, Smith & Mikati 2012) and reviewed in (Pardo, Nabbout & Galanopoulou 2014)].

Clinical observations show the involvement of immune and inflammatory processes in WS as manifested by altered blood or CSF levels of various cytokines prior to treatment although differences across studies are noted (see Table 2 for summary of published data). Among the studies that correlated the treatment response to the inflammatory indices before and after treatment, there is evidence that some of these changes are linked to treatment response (e.g., IL-1ra elevation or reduction of blood IL-1β or reduction in CD4+ or CD4+/CD8+ ratios (Ohya, Nagai, Araki, Yanagawa, Tanabe, Iyoda et al. 2009, Shiihara, Miyashita, Yoshizumi, Watanabe, Yamada & Kato 2010, Yamanaka, Kawashima, Oana, Ishida, Miyajima, Kashiwagi et al. 2010). However, conclusive studies are needed as well as confirmation by animal models.

An interesting link has been described in tuberous sclerosis (TSC), which is a genetic pathology which can manifest IS (Curatolo, Seri, Verdecchia & Bombardieri 2001, Chu-Shore, Major, Camposano, Muzykewicz & Thiele 2010, Chudomelova, Scantlebury, Raffo, Coppola, Betancourth & Galanopoulou 2010). The overactivated mammalian target of rapamycin (mTOR) complex 1 (mTORC1) in TSC is associated with loss of function mutation in TSC1 and TSC2 genes (Crino 2010, Raffo, Coppola, Ono, Briggs & Galanopoulou 2011). Inhibitors of mTOR pathway, such as rapamycin, may reverse some of the pathologic sequelae of the mTOR overactivation which lead to pathologies associated with epilepsies (e.g., dysplastic neurons, gliosis) and epilepsy development (Wang, Barbaro & Baraban 2006, Talos, Kwiatkowski, Cordero, Black & Jensen 2008, Li, Lee, Liu, Banasr, Dwyer, Iwata et al. 2010, Sharma, Hoeffer, Takayasu, Miyawaki, McBride, Klann et al. 2010, Raffo, Coppola, Ono, Briggs & Galanopoulou 2011, Parker, Orlova, Parker, Birnbaum, Krymskaya, Goncharov et al. 2013). Clinical studies specifically demonstrating the efficacy of mTOR inhibitors (e.g., everolimus, rapamycin) in WS patients with mTOR dysregulation are lacking, largely due to the difficulty in testing new therapies in very young patients, rendering the need for obtaining answers in animal models critical.

Interestingly, outcomes in WS patients were affected by the etiology, response to ACTH treatment, coexistence of other types of seizures, time lag in treatment initiation and response (primarily affecting the cognitive outcome) and persistent EEG abnormality (Koo, Hwang & Logan 1993, Pellock, Hrachovy, Shinnar, Baram, Bettis, Dlugos et al. 2010).

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Although the mechanism of action of ACTH may not be entirely anti-inflammatory, studies have shown evidence of reduction of some of the elevated pro-inflammatory cytokines in WS patients treated with ACTH (Table 2). Shiihara et al. (2010) have proposed that impaired immune system may be more a consequence of the WS rather than a cause, although there is no clinical definitive evidence yet for this hypothesis. More studies are necessary to prove this hypothesis, focusing on comparison of the immunologic parameters between patients with WS (before therapy) and controls, as well as WS groups before and after treatment (including follow-up periods). Additionally, some of the reported markers may have a dual action (either pro- or anti-inflammatory), such as TNF-α (Zakharova & Ziegler 2005). Difficulties related to number of patients with WS, different patient groups and controls (or absence of controls), as well as variations in principal parameters evaluated and source of specimen collection, complicate the analysis of the previous studies and thus a need in new clinical studies is critical for better understanding of the underlying mechanisms of inflammation and their role in contribution to epilepsy development in WS.

Inflammation in animal models of IS: the multiple-hit rat model of IS

Several animal models of IS or WS or epileptic spasms have been developed [reviewed in (Galanopoulou & Moshe 2015); also see (Dube, Molet, Singh-Taylor, Ivy, Maras & Baram 2015, Pirone, Alexander, Lau, Hampton, Zayachkivsky, Yee et al. 2016)]. The investigation of inflammatory pathways in IS has been done so far in the multiple-hit rat model, which will be described below.

In the multiple-hit rat model of WS, the intent was to generate a lesion that disrupts cortical-subcortical communication networks that were hypothesized to underlie the pathogenesis of IS (Lado & Moshe 2002). Spasms in this model are induced in male Sprague-Dawley rats by acute intracerebral infusion of the cytotoxic agent doxorubicin and TLR-4 agonist lipopolysaccharide (LPS) on postnatal day 3 (PN3) followed by a single intraperitoneal injection of brain serotonin synthesis blocker p-chlorophenylalanine (PCPA) on PN5 (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010). PCPA was added due to old reports on abnormal serotonin metabolism in patients with IS (Silverstein & Johnston 1984, Langlais, Wardlow & Yamamoto 1991, Yamamoto 1991, Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010). LPS is a prototypical inducer of inflammation in both periphery and in the brain, known to lower seizure threshold when added with proconvulsant compounds and worsen seizure sequelae (Sayyah, Javad-Pour & Ghazi-Khansari 2003, Sankar, Auvin, Mazarati & Shin 2007, Galic, Riazi, Heida, Mouihate, Fournier, Spencer et al. 2008). Spasms in this model appear at PN4 and continue until PN13 with epileptic patterns, including electrodecremental responses and fast oscillations with an epileptic interictal background (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010, Ono, Moshe & Galanopoulou 2011, Raffo, Coppola, Ono, Briggs & Galanopoulou 2011, Briggs, Mowrey, Hall & Galanopoulou 2014). The multiple-hit model manifest a structural lesion, mainly right hemispheric [described in (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010, Briggs, Mowrey, Hall & Galanopoulou 2014, Jequier Gygax, Klein, White, Kim & Galanopoulou 2014)] and is considered as model of the more severe type of WS due to structural lesion which is refractory to current treatments (ACTH-refractory, partially

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sensitive to vigabatrin) (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010). In addition to the epilepsy phenotype, the multiple-hit model also demonstrates transient impairment of neurodevelopmental milestones around the period of spasms, learning deficits (Barnes maze PN16-19), and impaired social interactions, consistent with the more severe prognosis of WS due to structural lesions. As expected, phenytoin has no effect on spasms in this model (Ono, Moshe & Galanopoulou 2011). This model has been extensively used for the screening of new potential therapies for IS, including a promising experimental drug CPP-115 (more potent vigabatrin analogue with lower risk for retinal toxicity) (Briggs, Mowrey, Hall & Galanopoulou 2014) which was recently clinically tested in a case report with very similar efficacy (Doumlele, Conway, Hedlund, Tolete & Devinsky 2016). In addition, other new drugs showing efficacy in this model include a drug with broad-spectrum anti-epileptic effect in experimental animal models of seizures (carisbamate) and an mTOR inhibitor rapamycin (Ono, Moshe & Galanopoulou 2011, Raffo, Coppola, Ono, Briggs & Galanopoulou 2011).

Among the three drugs tested in this model, we found that doxorubicin and/or LPS are sufficient to induce IS. Histopathologically, we found pronounced inflammation in the cortical region around the infusions, including astrocytosis [glial fibrillary astrocytic protein (GFAP) positive cells], microglia, and evidence of mTOR overactivation, as shown by increased pS6 immunoreactivity (Raffo, Coppola, Ono, Briggs & Galanopoulou 2011). There is also increased levels of cytokines (IL-1β, TNFα) or downstream targets (e.g., NF-kB) in the peri-infusional cortical region (unpublished observations, by A. Galanopoulou). Proof of concept that inflammation alone can induce spasms was provided by the right intracerebral LPS infusion, which can induce spasms with decremental responses in young rats (Ono, Briggs, Chudomelova, Raffo, Moshé & Galanopoulou 2011).

Exploration of the therapeutic potential of various anti-inflammatory drugs in the multiple-hit rat model, produced few notable results. Following a pulse, high dose rapamycin treatment started after spasms' onset between PN4-6, spasms stopped and pups showed a partial improvement of learning in the Barnes maze after spasms stopped (PN16-19), suggesting of partial disease modification (Raffo, Coppola, Ono, Briggs & Galanopoulou 2011). Administration of an anti-inflammatory, anti-oxidant drug that inhibits NF-kB and cytokine production as a single dose given after spasms manifested, celastrol, also acutely reduced behavioral and electroclinical spasms in this model (Shandra, Wang, Mowrey, Moshé & Galanopoulou 2015). Of interest, the NF-ƙB pathway can be inhibited by ACTH peptides and melanocortin receptors (MCRs, thought to be activated by ACTH) (Moustafa, Szabo, Ghanem, Morandini, Kemp, MacNeil et al. 2002, Catania 2007). On the other hand, the proconvulsant hormone CRH can inhibit NF-kB in human melanocytes (Zbytek, Pfeffer & Slominski 2006), emphasizing the need to test the effect of modulators of such signaling pathways in vivo, since the mechanisms of action may be complex. However, the interesting results of celastrol in an ACTH-refractory model of IS raise the possibility that targeting a downstream mediator of ACTH with possibly a more specific inhibitor might have better therapeutic effect.

Although the multiple-hit and related inflammation induced models of IS provide a good proof of concept evidence that inflammatory pathways may contribute or suffice to generate

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IS epileptogenesis, further across model validation may be useful to determine the exact role of inflammatory cascades in the phenotype and treatment of WS across etiologies and pathologies.

4. Does activation of the inflammatory pathways in the brain contribute to the associated comorbidities and progression?

Between 1960–1988, 29 (10% of all patients) infants with IS admitted to the Children's Hospital of University of Helsinki, have had infections as the primary etiologic factor, including cytomegalovirus (CMV), congenital rubella, herpes simplex, enterovirus, adenovirus, encephalitis, meningococcus, pneumococcus and pertussis (Riikonen 1993). The outcomes in patients with IS of infectious etiology appeared to be particularly poor compared with outcomes of the total number of patients evaluated in the study and included mental retardation (90%) and convulsions (62%) and abnormal EEG (generalized disturbance, diffuse polyspike and slow wave discharges and focal abnormality) (89%) (Riikonen 1993). Twenty six (90% of the total) IS patients with infectious etiology (except 2 with acquired CMV infection and one with encephalitis with unknown etiology) developed intellectual disabilities, and 20 (69%) had cerebral palsy (Riikonen 1993).

Emerging data from experimental settings report that exposure to inflammation during critical developmental period in rats, leads to long-lasting brain excitability increase, reducing significantly the seizure threshold (Riazi, Galic & Pittman 2010). Further pharmacological targeting of the IL-1 receptor and TLR4 signaling pathways in rodents demonstrated tight connection between pro-inflammatory cytokines and epileptogenesis (Maroso, Balosso, Ravizza, Iori, Wright, French et al. 2011, Maroso, Balosso, Ravizza, Liu, Bianchi & Vezzani 2011). Evidence from the multiple-hit model in rats indicates evolution of spasms into other types of seizures, together with learning and sociability deficits after PN9 and in the adulthood, emphasizing a possible important role of inflammation and focal lesion in the development of seizures and epilepsy in patients with WS (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010, Galanopoulou 2013, Galanopoulou & Moshe 2016). The observation that anti-inflammatory drugs, like rapamycin, may prevent some of the learning deficits in the multiple-hit model (Raffo, Coppola, Ono, Briggs & Galanopoulou 2011), may also suggest that these pathways may be important determinants of the cognitive and neurodevelopmental outcomes. Whether concomitant inflammation may contribute to the pharmacoresistance of this model is also worth investigating, particularly in view if the beneficial effects of anti-inflammatory treatments in this ACTH-refractory model of IS.

5. Can activation of certain inflammatory pathways be a compensatory or protective event?

Paradoxical spontaneous remission of IS has been reported after viral infections (exanthema subitum, rotavirus gastroenteritis, measles, chickenpox) or acute febrile illness (Hattori 2001, Pintaudi, Eisermann, Ville, Plouin, Dulac & Kaminska 2007) suggesting that neuroinflammation may have complex effects on networks involved in IS. The exact

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mechanisms for these effects are unknown. The role of the cytokines in the processes linked with epileptogenesis can be complex, including a possible protective or compensatory role. Dual effects of neuroinflammatory pathways have been demonstrated with cyclooxygenase-2 (COX-2) inhibitors in post-status epilepticus injury, depending upon the context they are applied into (Jiang & Dingledine 2013). As an example, increased production of the pro-inflammatory cytokines can increase production of anti-inflammatory cytokines, such as IL-10. IL-10 expression also protects neurons and glial brain cells mainly by inhibiting pro-apoptotic cytokines and by stimulating protective signaling reactions (Qian, Block, Wei, Lin, Reece, Pang et al. 2006, Youn, Sung & Lee 2013). Alternatively, inflammation may affect neuroendocrine, stress related or other biological pathways which could alter the course of seizures. The full spectrum of inflammatory mediators in epileptic encephalopathies, like IS, needs to be more fully investigated.

6. Are there interactions between inflammation and the neuroendocrine system that contribute to the pathogenesis of West syndrome?

Based on the clinical evidence on the efficacy of therapy with ACTH and corticosteroids, a hypothesis has been proposed about a specific role of the immune and neuroendocrine systems in the pathophysiology of WS, although the precise mechanisms of action of immune suppressants in WS remain unclear (Wilson 1973, Rao & Willis 1987). The CSF levels of ACTH were found to be lower in patients with IS, lending a biological reason to justify the response of IS to ACTH (Baram, Mitchell, Snead, Horton & Saito 1992). In the same study, cortisol and CRH levels were not statistically different in WS patients than in controls. The emerging stress hypothesis of IS postulated that exaggerated response to otherwise anticipated stressors might be the pathogenic trigger in subjects predisposed to IS (Baram 1993). CRH was proposed to be the mediator of this stress-induced IS epileptogenesis and was indeed shown to have proconvulsant effects when injected intracerebrally (cerebral cortex or hippocampus) in PN5 and PN10 rats (Baram & Schultz 1991). However, the observed motor seizures responded to phenytoin but not ACTH and were thought to be limbic, rather than IS. Follow up studies by this group, utilizing a model of early chronic stress induced by “fragmented and unpredictable nurturing behavior” reported spasm-like events in 48% of rats originating from the amygdala or cortico-hippocampal regions (Dube, Molet, Singh-Taylor, Ivy, Maras & Baram 2015). Further characterization of this model is pending and the sensitivity of the spasms to drugs has not been tested yet.

Of interest, the influence of stress has been explored in the NMDA model of spasms (Mares & Velisek 1992) by exploring the impact of perinatal stress. Interestingly, prenatal stress (forced restrain) or prenatal betamethasone exposure or perinatal adrenalectomy accelerate the onset and/or increase the severity of spasms acutely induced by NMDA in rats (Velisek, Jehle, Asche & Veliskova 2007, Wang, Zhang, Liang, Yang & Zou 2012, Yum, Chachua, Veliskova & Velisek 2012). Interestingly however, prenatal betamethasone also increased the sensitivity of NMDA-induced spasms to ACTH, suggesting that ACTH may employ stress-related pathways in its effects on this model. The clinical and translational relevance of these observations need further investigation in order to clarify what constitutes a pathological

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exaggerated response to anticipated everyday common stressors, and what elements (genetic, biological, epigenetic) shift stress responses from being adaptive to being pathogenic.

7. Does activation of brain inflammatory signaling pathways contribute to the transition of WS to Lennox-Gastaut syndrome?

Lennox-Gastaut syndrome (LGS) is an EE, typically appearing between the second and sixth year of life and is characterized by an electroclinical triad of generalized slow spike wave (SSW) activity in the EEG, various epileptic seizures (particularly tonic [stiffening] and atonic [drop]), and intellectual disabilities (Beaumanoir 1982, Markand 2003). The severity of this syndrome in particular is that it is difficult to control seizures and there is a need in life-long treatment (Beaumanoir 1982, Donat & Wright 1991).

While there is a debate whether or not WS and Lennox-Gastaut syndrome are clinical manifestations of the same underlying encephalopathic process and expressing different features depending on brain maturation levels, clinical reports indicate that estimate of 15–54% evolution of West syndrome into Lennox-Gastaut syndrome (Ohtahara, Ishida & Oka 1976, Beaumanoir 1982, Lombroso 1983, Rantala & Putkonen 1999, Rantala & Putkonen 1999, Trevathan, Murphy & Yeargin-Allsopp 1999, Hrachovy & Frost 2003, You, Kim & Kang 2009, Galanopoulou 2013). 70–80% of the patients with Lennox-Gastaut syndrome, in turn, have preceding history other than West syndrome (Chevrie & Aicardi 1972, Markand 1977, Heiskala 1997).

The putative antiepileptic mechanisms such as inhibition of inflammation and modification of mitochondrial metabolism, as well as their correction with hormonal therapy or ketogenic diet respectively have been suspected to play key roles in preventing encephalopathy evolution to LGS in patients with WS (Bough & Rho 2007, Choi & Koh 2008, Choi & Koh 2008, You, Kim & Kang 2009). However, there is no proof-of-concept evidence about the impact of these mechanisms on WS evolution to LGS. Animal models of Lennox-Gastaut syndrome would be greatly useful in elucidating these questions.

8. Are there any lead candidates or unexplored targets for future therapy development for WS targeting inflammation?

To date, ACTH and corticosteroids remain among the first-line treatment options for WS (Mackay, Weiss, Adams-Webber, Ashwal, Stephens, Ballaban-Gill et al. 2004, Yamamoto, Fukuda, Miyamoto, Murakami & Kamiyama 2007). Previous studies have suggested immunosuppressive effect of ACTH and corticosteroids, together with anti-inflammatory properties, as well as direct inhibitory impact on CNS excitability and possible inhibition of endogenous proconvulsant factor synthesis (Baram & Hatalski 1998, Riikonen 2000, Brunson, Khan, Eghbal-Ahmadi & Baram 2001, Joels & Baram 2009, Vezzani, French, Bartfai & Baram 2011), although ACTH has been reported to be more efficient (Snead 2001). In addition, therapy with immune-modulatory agents such as ACTH and corticosteroids or high-dose immunoglobulin has shown efficacy on spasms cessation in

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some patients with IS of infectious etiology, however it was suggested that steroid therapy should be avoided in patients with a history of CMV and herpes simplex in the past (Ariizumi, Shiihara, Hibio, Ryo, Baba, Ogawa et al. 1983, Ariizumi, Baba, Hibio, Shiihara, Michihiro, Ogawa et al. 1987, Riikonen 1993, Wise, Rutledge & Kuzniecky 1996, Hattori 2001).

Insights from the multiple-hit rat model of IS further support evidence about focal lesion in the etiology of IS and provides proof-of-concept evidence that inflammatory processes are among the key triggers of IS of structural/metabolic origin (Scantlebury, Galanopoulou, Chudomelova, Raffo, Betancourth & Moshe 2010, Raffo, Coppola, Ono, Briggs & Galanopoulou 2011), due to efficacy of the tested therapeutic compounds. An mTOR inhibitor rapamycin has been shown to be a potential disease modifying therapeutic candidate, which promotes cessation of spasms and partial improvement of memory in multiple-hit model rats, although better analogues are necessary for testing due to transient weight loss as a side effect (Raffo, Coppola, Ono, Briggs & Galanopoulou 2011). Our recent findings about NF-κB activation in the cortex of the multiple-hit model rats and successful spasm cessation with NF-κB inhibitor celastrol (Shandra, Wang, Mowrey, Moshé & Galanopoulou 2015) provide additional evidence on the effectiveness of anti-inflammatory therapy on spasms.

Together, immune status alterations, activated inflammatory pathways, infectious etiology of IS, as well as efficacy of the anti-inflammatory and immune-regulatory therapy on spasms indicate the importance of these processes in the pathogenesis of WS and the promising strategy and targets for potential new therapy development. However, a detailed study of related links between epilepsy and neuroinflammation in WS will contribute to the isolation of the key “nodes” of dysregulation, and thus determine the new targets for potential pharmacological corrections.

9. Concluding remarks

Recent studies of epileptogenesis in infantile EE, such as WS, lead to findings of various processes involved in EE pathogenesis, including neuroinflammation, immune status alteration, and neuroendocrine system recruitment. Neuro-immunomodulation has been suggested to be among the key pathogenic mechanisms engaged in the epileptogenesis of WS.

Current interest in neuroinflammation research has provided certain knowledge of its pathways, targets and mechanisms involved in epilepsy development, progression and recurrence of seizures and development of pharmacorefractoriness. Nevertheless, there is an urge in continuous and extensive studies in neuroinflammation for better understanding of its role and implications in developing brain and EEs. Studies of animal models of early life epilepsies have provided researchers with invaluable tools for studying specific pathogenic processes, testing known and novel therapeutic candidates for better understanding of mechanisms of action and/or for identification of potential new therapies and molecular targets. Genetic advances have further advanced the research in neuroinflammatory genes and shown their relevance to several epilepsy syndromes. Animal models of eary life

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epilepsies and epileptic encephalopathies have started to generate an increasing amount of evidence for new therapy targets, candidate therapy targets and putative mechanisms incolved in epileptogenesis and comorbidogenesis of these early life epilepsies. Already few of these candidate drugs tested in animal models have entered clinical trials with promising results, lending value to the hope that the horizon of new pediatric therapy discovery will change to include not only extrapolation trials, but also novel pediatric preclinical therapy discovery using age-specific animal models of epileptic encephalopathies (Galanopoulou & Mowrey 2016).

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References

Akira S, et al. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001; 2(8):675–680. [PubMed: 11477402]

Akira S, et al. Pathogen recognition and innate immunity. Cell. 2006; 124(4):783–801. [PubMed: 16497588]

Ariizumi M, et al. Immunoglobulin therapy in the West syndrome. Brain and Development. 1987; 9(4): 422–425. [PubMed: 3124656]

Ariizumi M, et al. Originally published as Volume 2, Issue 8342HIGH DOSE GAMMAGLOBULIN FOR INTRACTABLE CHILDHOOD EPILEPSY. The Lancet. 1983; 322(8342):162–163.

Aronica E, et al. Complement activation in experimental and human temporal lobe epilepsy. Neurobiol Dis. 2007; 26(3):497–511. [PubMed: 17412602]

Autry AR, et al. Increased risk of death among children with Lennox-Gastaut syndrome and infantile spasms. J Child Neurol. 2010; 25(4):441–447. [PubMed: 20023065]

Auvin S, et al. Current understanding and neurobiology of epileptic encephalopathies. Neurobiol Dis. 2016; 92(Pt A):72–89. [PubMed: 26992889]

Balosso S, et al. The dual role of TNF-alpha and its receptors in seizures. Exp Neurol. 2013; 247:267–271. [PubMed: 23707217]

Bar-Klein G, et al. Losartan prevents acquired epilepsy via TGF-beta signaling suppression. Ann Neurol. 2014; 75(6):864–875. [PubMed: 24659129]

Baram TZ. Pathophysiology of massive infantile spasms: perspective on the putative role of the brain adrenal axis. Ann Neurol. 1993; 33(3):231–236. [PubMed: 8388675]

Baram TZ, Hatalski CG. Neuropeptide-mediated excitability: a key triggering mechanism for seizure generation in the developing brain. Trends Neurosci. 1998; 21(11):471–476. [PubMed: 9829688]

Baram TZ, et al. Brain-adrenal axis hormones are altered in the CSF of infants with massive infantile spasms. Neurology. 1992; 42(6):1171–1175. [PubMed: 1318521]

Baram TZ, Schultz L. Corticotropin-releasing hormone is a rapid and potent convulsant in the infant rat. Brain Res Dev Brain Res. 1991; 61(1):97–101. [PubMed: 1914160]

Baybis M, et al. mTOR cascade activation distinguishes tubers from focal cortical dysplasia. Ann Neurol. 2004; 56(4):478–487. [PubMed: 15455405]

Beaumanoir A. The Lennox-Gastaut syndrome: a personal study. Electroencephalogr Clin Neurophysiol. 1982; (Suppl 35):85–99.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Berg AT, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010; 51(4): 676–685. [PubMed: 20196795]

Bough KJ, Rho JM. Anticonvulsant mechanisms of the ketogenic diet. Epilepsia. 2007; 48(1):43–58. [PubMed: 17241207]

Briggs SW, et al. CPP-115, a vigabatrin analogue, decreases spasms in the multiple-hit rat model of infantile spasms. Epilepsia. 2014; 55(1):94–102. [PubMed: 24321005]

Brunson KL, et al. Corticotropin (ACTH) acts directly on amygdala neurons to down-regulate corticotropin-releasing hormone gene expression. Ann Neurol. 2001; 49(3):304–312. [PubMed: 11261504]

Catania A. The melanocortin system in leukocyte biology. J Leukoc Biol. 2007; 81(2):383–392. [PubMed: 17041004]

Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage." Nature reviews. Immunology. 2010; 10(12):826–837. [PubMed: 21088683]

Chevrie JJ, Aicardi J. Childhood Epileptic Encephalopathy with Slow Spike-Wave A Statistical Study of 80 Cases. Epilepsia. 1972; 13(2):259–271. [PubMed: 4217690]

Choi J, Koh S. Role of brain inflammation in epileptogenesis. Yonsei Med J. 2008; 49(1):1–18. [PubMed: 18306464]

Choi J, Koh S. Role of brain inflammation in epileptogenesis. Yonsei Medical Journal. 2008; 49(1):1–18. [PubMed: 18306464]

Chu-Shore CJ, et al. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010; 51(7):1236–1241. [PubMed: 20041940]

Chudomelova L, et al. Modeling new therapies for infantile spasms. Epilepsia. 2010; 51(Suppl 3):27–33.

Crespel A, et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. Brain Res. 2002; 952(2):159–169. [PubMed: 12376176]

Crino PB. The pathophysiology of tuberous sclerosis complex. Epilepsia. 2010; 51(Suppl 1):27–29.

Curatolo P, et al. Infantile spasms in tuberous sclerosis complex. Brain Dev. 2001; 23(7):502–507. [PubMed: 11701245]

Dey A, et al. Anti-Inflammatory Small Molecules To Treat Seizures and Epilepsy: From Bench to Bedside. Trends Pharmacol Sci. 2016; 37(6):463–484. [PubMed: 27062228]

Donat JF, Wright FS. Seizures in series: similarities between seizures of the west and Lennox-Gastaut syndromes. Epilepsia. 1991; 32(4):504–509. [PubMed: 1868807]

Doumlele K, et al. A case report on the efficacy of vigabatrin analogue (1S, 3S)-3-amino-4-difluoromethylenyl-1-cyclopentanoic acid (CPP-115) in a patient with infantile spasms. Epilepsy Behav Case Rep. 2016; 6:67–69. [PubMed: 27668180]

Dube C, et al. Interleukin-1beta contributes to the generation of experimental febrile seizures. Ann Neurol. 2005; 57(1):152–155. [PubMed: 15622539]

Dube CM, et al. Hyper-excitability and epilepsy generated by chronic early-life stress. Neurobiol Stress. 2015; 2:10–19. [PubMed: 25884016]

Dube CM, et al. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. J Neurosci. 2010; 30(22):7484–7494. [PubMed: 20519523]

Dulac O. What is West syndrome? Brain Dev. 2001; 23(7):447–452. [PubMed: 11701238]

Dussaix E, et al. Intrathecal synthesis of different alpha-interferons in patients with various neurological diseases. Acta Neurol Scand. 1985; 71(6):504–509. [PubMed: 4024861]

Epi4K. Consortium. et al. De novo mutations in epileptic encephalopathies. Nature. 2013; 501(7466): 217–221. [PubMed: 23934111]

Esposito P, et al. Corticotropin-releasing hormone and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. J Pharmacol Exp Ther. 2002; 303(3):1061–1066. [PubMed: 12438528]

Fabene PF, et al. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nat Med. 2008; 14(12):1377–1383. [PubMed: 19029985]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Friedman A, et al. Should losartan be administered following brain injury? Expert Rev Neurother. 2014; 14(12):1365–1375. [PubMed: 25346269]

Frost JD Jr, Hrachovy RA. Pathogenesis of infantile spasms: a model based on developmental desynchronization. J Clin Neurophysiol. 2005; 22(1):25–36. [PubMed: 15689710]

Fukuyama Y. A special note on terminology of West syndrome and infantile spasms. Brain Dev. 2001; 23(7):442. [PubMed: 11701236]

Galanopoulou AS. Basic mechanisms of catastrophic epilepsy – overview from animal models. Brain Dev. 2013; 35(8):748–756. [PubMed: 23312951]

Galanopoulou AS, et al. Finding a better drug for epilepsy: the mTOR pathway as an antiepileptogenic target. Epilepsia. 2012; 53(7):1119–1130. [PubMed: 22578218]

Galanopoulou AS, Moshe SL. Neonatal and Infantile Epilepsy: Acquired and Genetic Models. Cold Spring Harb Perspect Med. 2015; 6(1)

Galanopoulou AS, Moshe SL. Pathogenesis and new candidate treatments for infantile spasms and early life epileptic encephalopathies: A view from preclinical studies. Neurobiol Dis. 2015; 79:135–149. [PubMed: 25968935]

Galanopoulou AS, Moshe SL. Neonatal and Infantile Epilepsy: Acquired and Genetic Models. Cold Spring Harb Perspect Med. 2016; 6(1):a022707.

Galanopoulou AS, Mowrey W. Not all that glitters is gold: a guide to critical appraisal of animal drug trials in epilepsy. Epilepsia Open. 2016; 1(3–4):86–101. [PubMed: 28497130]

Galic MA, et al. Postnatal Inflammation Increases Seizure Susceptibility in Adult Rats. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2008; 28(27):6904–6913. [PubMed: 18596165]

Go CY, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2012; 78(24):1974–1980. [PubMed: 22689735]

Graeber MB, et al. Role of microglia in CNS inflammation. FEBS Lett. 2011; 585(23):3798–3805. [PubMed: 21889505]

Haginoya K, et al. Reduced levels of interleukin-1 receptor antagonist in the cerebrospinal fluid in patients with West syndrome. Epilepsy Res. 2009; 85(2–3):314–317. [PubMed: 19375283]

Hattori H. Spontaneous remission of spasms in West syndrome – implications of viral infection. Brain and Development. 2001; 23(7):705–707. [PubMed: 11701282]

He JJ, et al. The interleukin 17 system in cortical lesions in focal cortical dysplasias. J Neuropathol Exp Neurol. 2013; 72(2):152–163. [PubMed: 23334598]

Heiskala H. Community-based study of Lennox-Gastaut syndrome. Epilepsia. 1997; 38(5):526–531. [PubMed: 9184597]

Hong AM, et al. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia. 2010; 51(8):1403–1407. [PubMed: 20477843]

Hrachovy RA, Frost JDJ. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). J Clin Neurophysiol. 2003; 20(6):408–425. [PubMed: 14734931]

Hunt A, Dennis J. Psychiatric disorder among children with tuberous sclerosis. Dev Med Child Neurol. 1987; 29(2):190–198. [PubMed: 3582788]

Iori V, et al. Receptor for Advanced Glycation Endproducts is upregulated in temporal lobe epilepsy and contributes to experimental seizures. Neurobiology of Disease. 2013; 58:102–114. [PubMed: 23523633]

Jequier Gygax M, et al. Efficacy and tolerability of the galanin analog NAX 5055 in the multiple-hit rat model of symptomatic infantile spasms. Epilepsy Res. 2014; 108(1):98–108. [PubMed: 24252685]

Jiang J, Dingledine R. Prostaglandin receptor EP2 in the crosshairs of anti-inflammation, anti-cancer, and neuroprotection. Trends Pharmacol Sci. 2013; 34(7):413–423. [PubMed: 23796953]

Joels M, Baram TZ. The neuro-symphony of stress. Nat Rev Neurosci. 2009; 10(6):459–466. [PubMed: 19339973]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010; 11(5):373–384. [PubMed: 20404851]

Kim JV, et al. Myelomonocytic cell recruitment causes fatal CNS vascular injury during acute viral meningitis. Nature. 2009; 457(7226):191–195. [PubMed: 19011611]

Koo B, et al. Infantile spasms: outcome and prognostic factors of cryptogenic and symptomatic groups. Neurology. 1993; 43(11):2322–2327. [PubMed: 8232950]

Lado FA, Moshe SL. Role of subcortical structures in the pathogenesis of infantile spasms: what are possible subcortical mediators? Int Rev Neurobiol. 2002; 49:115–140. [PubMed: 12040889]

Langlais PJ, et al. Changes in CSF neurotransmitters in infantile spasms. Pediatr Neurol. 1991; 7(6): 440–445. [PubMed: 1724602]

Lawrence T. The Nuclear Factor NF-κB Pathway in Inflammation. Cold Spring Harbor Perspectives in Biology. 2009; 1(6):a001651. [PubMed: 20457564]

Lehtimaki KA, et al. Regulation of IL-6 system in cerebrospinal fluid and serum compartments by seizures: the effect of seizure type and duration. J Neuroimmunol. 2004; 152(1–2):121–125. [PubMed: 15223244]

Lehtimaki KA, et al. Levels of IL-1beta and IL-1ra in cerebrospinal fluid of human patients after single and prolonged seizures. Neuroimmunomodulation. 2010; 17(1):19–22. [PubMed: 19816053]

Li N, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010; 329(5994):959–964. [PubMed: 20724638]

Lim KC, Crino PB. Focal malformations of cortical development: new vistas for molecular pathogenesis. Neuroscience. 2013; 252:262–276. [PubMed: 23892008]

Liu ZS, et al. Serum cytokine levels are altered in patients with West syndrome. Brain Dev. 2001; 23(7):548–551. [PubMed: 11701253]

Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. Epilepsia. 1983; 24(2):135–158. [PubMed: 6299719]

Lubin FD, et al. Nuclear factor-kappa B regulates seizure threshold and gene transcription following convulsant stimulation. J Neurochem. 2007; 103(4):1381–1395. [PubMed: 17727632]

Mackay MT, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004; 62(10):1668–1681. [PubMed: 15159460]

Mackay MT, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004; 62(10):1668–1681. [PubMed: 15159460]

Marcon J, et al. Age-dependent vascular changes induced by status epilepticus in rat forebrain: implications for epileptogenesis. Neurobiol Dis. 2009; 34(1):121–132. [PubMed: 19320047]

Mares P, Velisek L. N-methyl-D-aspartate (NMDA)-induced seizures in developing rats. Brain Res Dev Brain Res. 1992; 65(2):185–189. [PubMed: 1572063]

Markand ON. Slow spike-wave activity in EEG and associated clinical features: often called ‘Lennox’ or “Lennox-Gastaut’ syndrome. Neurology. 1977; 27(8):746–757. [PubMed: 407485]

Markand ON. Lennox-Gastaut syndrome (childhood epileptic encephalopathy). J Clin Neurophysiol. 2003; 20(6):426–441. [PubMed: 14734932]

Maroso M, et al. Interleukin-1beta biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice. Neurotherapeutics. 2011; 8(2):304–315. [PubMed: 21431948]

Maroso M, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. Nat Med. 2010; 16(4):413–419. [PubMed: 20348922]

Maroso M, et al. Interleukin-1 type 1 receptor/Toll-like receptor signalling in epilepsy: the importance of IL-1beta and high-mobility group box 1. J Intern Med. 2011; 270(4):319–326. [PubMed: 21793950]

Mazarati A, et al. High-mobility group box-1 impairs memory in mice through both toll-like receptor 4 and Receptor for Advanced Glycation End Products. Exp Neurol. 2011; 232(2):143–148. [PubMed: 21884699]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Montelli TCB, et al. Immunologic aspects of West syndrome and evidence of plasma inhibitory effects on T cell function. Arquivos de Neuro-Psiquiatria. 2003; 61:731–737. [PubMed: 14595474]

Mota NG, et al. Demonstration of antibody and cellular immune response to brain extract in West and Lennox-Gastaut syndromes. Arq Neuropsiquiatr. 1984; 42(2):126–131. [PubMed: 6466144]

Moustafa M, et al. Inhibition of tumor necrosis factor-alpha stimulated NFkappaB/p65 in human keratinocytes by alpha-melanocyte stimulating hormone and adrenocorticotropic hormone peptides. J Invest Dermatol. 2002; 119(6):1244–1253. [PubMed: 12485424]

Ohtahara S, et al. On the specific age dependent epileptic syndrome: the early infantile epileptic encephalopathy with suppression burst (Japanese). No To Hattatsu. 1976; 8(4):270–280.

Ohya T, et al. A pilot study on the changes in immunity after ACTH therapy in patients with West syndrome. Brain Dev. 2009; 31(10):739–743. [PubMed: 19118960]

Ono T, et al. Intracortical injection of lipopolysaccharide induces epileptic spasms in neonatal rats: another animal model of symptomatic infantile spasms. Epilepsy Currents. 2011; 12(1)

Ono T, et al. Carisbamate acutely suppresses spasms in a rat model of symptomatic infantile spasms. Epilepsia. 2011; 52(9):1678–1684. [PubMed: 21770922]

Orlova KA, et al. STRADalpha deficiency results in aberrant mTORC1 signaling during corticogenesis in humans and mice. J Clin Invest. 2010; 120(5):1591–1602. [PubMed: 20424326]

Osborne JP, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. Epilepsia. 2010; 51(10):2168–2174. [PubMed: 20726878]

Paciorkowski AR, et al. Copy number variants and infantile spasms: evidence for abnormalities in ventral forebrain development and pathways of synaptic function. Eur J Hum Genet. 2011; 19(12): 1238–1245. [PubMed: 21694734]

Pardo CA, et al. Mechanisms of epileptogenesis in pediatric epileptic syndromes: Rasmussen encephalitis, infantile spasms, and febrile infection-related epilepsy syndrome (FIRES). Neurotherapeutics. 2014; 11(2):297–310. [PubMed: 24639375]

Parker WE, et al. Rapamycin prevents seizures after depletion of STRADA in a rare neurodevelopmental disorder. Sci Transl Med. 2013; 5(182):182ra153.

Pellock JM, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010; 51(10):2175–2189. [PubMed: 20608959]

Peltola J, et al. Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels. Seizure. 2002; 11(1):44–46. [PubMed: 11888259]

Pernhorst K, et al. TLR4, ATF-3 and IL8 inflammation mediator expression correlates with seizure frequency in human epileptic brain tissue. Seizure. 2013; 22(8):675–678. [PubMed: 23706953]

Pintaudi M, et al. Can fever treat epileptic encephalopathies? Epilepsy Res. 2007; 77(1):44–61. [PubMed: 17875384]

Pires ME, et al. Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study. Epilepsy Res. 2013; 105(1–2):189–194. [PubMed: 23357723]

Pirone A, et al. APC conditional knock-out mouse is a model of infantile spasms with elevated neuronal beta-catenin levels, neonatal spasms, and chronic seizures. Neurobiol Dis. 2016; 98:149–157. [PubMed: 27852007]

Qian L, et al. Interleukin-10 protects lipopolysaccharide-induced neurotoxicity in primary midbrain cultures by inhibiting the function of NADPH oxidase. J Pharmacol Exp Ther. 2006; 319(1):44–52. [PubMed: 16807359]

Raffo E, et al. A pulse rapamycin therapy for infantile spasms and associated cognitive decline. Neurobiol Dis. 2011; 43(2):322–329. [PubMed: 21504792]

Ransohoff RM. Immunology: Barrier to electrical storms. Nature. 2009; 457(7226):155–156. [PubMed: 19129836]

Rantala H, Putkonen T. Occurrence, Outcome, and Prognostic Factors of Infantile Spasms and Lennox-Gastaut Syndrome. Epilepsia. 1999; 40(3):286–289. [PubMed: 10080506]

Rantala H, Putkonen T. Occurrence, Outcome, and Prognostic Factors of Infantile Spasms and Lennox-Gastaut Syndrome. Epilepsia. 1999; 40(3):286–289. [PubMed: 10080506]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Rao JK, Willis J. Hypothalamo-pituitary-adrenal function in infantile spasms: effects of ACTH therapy. J Child Neurol. 1987; 2(3):220–223. [PubMed: 3038989]

Ravizza T, et al. The IL-1beta system in epilepsy-associated malformations of cortical development. Neurobiol Dis. 2006; 24(1):128–143. [PubMed: 16860990]

Ravizza T, et al. Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. Neurobiol Dis. 2008; 29(1):142–160. [PubMed: 17931873]

Ravizza T, et al. Immunity activation in brain cells in epilepsy: mechanistic insights and pathological consequences. Neuropediatrics. 2013; 44(6):330–335. [PubMed: 24166145]

Riazi K, et al. Contributions of peripheral inflammation to seizure susceptibility: cytokines and brain excitability. Epilepsy Res. 2010; 89(1):34–42. [PubMed: 19804959]

Riazi K, et al. Contributions of peripheral inflammation to seizure susceptibility: Cytokines and brain excitability. Epilepsy Research. 2010; 89(1):34–42. [PubMed: 19804959]

Rigau V, et al. Angiogenesis is associated with blood-brain barrier permeability in temporal lobe epilepsy. Brain. 2007; 130(Pt 7):1942–1956. [PubMed: 17533168]

Riikonen R. Infantile spasms: infectious disorders. Neuropediatrics. 1993; 24(5):274–280. [PubMed: 8309517]

Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev. 2001; 23(7):683–687. [PubMed: 11701277]

Riikonen R. Recent advances in the pharmacotherapy of infantile spasms. CNS Drugs. 2014; 28(4): 279–290. [PubMed: 24504827]

Riikonen R, Amnell G. Psychiatric disorders in children with earlier infantile spasms. Dev Med Child Neurol. 1981; 23(6):747–760. [PubMed: 7319142]

Riikonen RS. Steroids or vigabatrin in the treatment of infantile spasms? Pediatr Neurol. 2000; 23(5): 403–408. [PubMed: 11118795]

Rizzi M, et al. Glia activation and cytokine increase in rat hippocampus by kainic acid-induced status epilepticus during postnatal development. Neurobiol Dis. 2003; 14(3):494–503. [PubMed: 14678765]

Saemundsen E, et al. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. Epilepsia. 2008; 49(11):1865–1870. [PubMed: 18557779]

Salar S, et al. Synaptic plasticity in area CA1 of rat hippocampal slices following intraventricular application of albumin. Neurobiol Dis. 2016; 91:155–165. [PubMed: 26972679]

Sankar R, et al. Inflammation contributes to seizure-induced hippocampal injury in the neonatal rat brain. Acta Neurol Scand Suppl. 2007; 186:16–20. [PubMed: 17784532]

Sankar R, et al. Inflammation contributes to seizure-induced hippocampal injury in the neonatal rat brain. Acta Neurol Scand. 2007; 115(4 Suppl):16–20. [PubMed: 17362271]

Sayyah M, et al. The bacterial endotoxin lipopolysaccharide enhances seizure susceptibility in mice: involvement of proinflammatory factors: nitric oxide and prostaglandins. Neuroscience. 2003; 122(4):1073–1080. [PubMed: 14643773]

Scantlebury MH, et al. A model of symptomatic infantile spasms syndrome. Neurobiol Dis. 2010; 37(3):604–612. [PubMed: 19945533]

Shandra, O., et al. American Epilepsy Society annual meeting. Philadelphia, PA: American Epilepsy Society; 2015. Effects of celastrol and edaravone in the multiple-hit rat model of infantile spasms. #2.048

Sharma A, et al. Dysregulation of mTOR signaling in fragile X syndrome. J Neurosci. 2010; 30(2): 694–702. [PubMed: 20071534]

Sheng JG, et al. Increased neuronal beta-amyloid precursor protein expression in human temporal lobe epilepsy: association with interleukin-1 alpha immunoreactivity. J Neurochem. 1994; 63(5): 1872–1879. [PubMed: 7931344]

Shiihara T, et al. Peripheral lymphocyte subset and serum cytokine profiles of patients with West syndrome. Brain Dev. 2010; 32(9):695–702. [PubMed: 19954907]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sidenvall R, Eeg-Olofsson O. Epidemiology of infantile spasms in Sweden. Epilepsia. 1995; 36(6): 572–574. [PubMed: 7555969]

Silanpaa M, et al. Long-term mortality of patients with West syndrome. Epilepsia Open. 2016; 1(1–2): 61–66.

Silverstein F, Johnston MV. Cerebrospinal fluid monoamine metabolites in patients with infantile spasms. Neurology. 1984; 34(1):102–105. [PubMed: 6197678]

Snead OC 3rd. How does ACTH work against infantile spasms? Bedside to bench. Ann Neurol. 2001; 49(3):288–289. [PubMed: 11261501]

Steele SU, et al. Electroencephalographic and seizure manifestations in two patients with folate receptor autoimmune antibody-mediated primary cerebral folate deficiency. Epilepsy Behav. 2012; 24(4):507–512. [PubMed: 22749608]

Takaki J, et al. L-glutamate released from activated microglia downregulates astrocytic L-glutamate transporter expression in neuroinflammation: the 'collusion' hypothesis for increased extracellular L-glutamate concentration in neuroinflammation. J Neuroinflammation. 2012; 9:275. [PubMed: 23259598]

Takeda K, Akira S. TLR signaling pathways. Semin Immunol. 2004; 16(1):3–9. [PubMed: 14751757]

Talos DM, et al. Cell-specific alterations of glutamate receptor expression in tuberous sclerosis complex cortical tubers. Ann Neurol. 2008; 63(4):454–465. [PubMed: 18350576]

Tekgul H, et al. Cerebrospinal fluid interleukin-6 levels in patients with West syndrome. Brain Dev. 2006; 28(1):19–23. [PubMed: 15967615]

Theoharides TC. Mast cells: the immune gate to the brain. Life Sci. 1990; 46(9):607–617. [PubMed: 2407920]

Theoharides TC, Konstantinidou AD. Corticotropin-releasing hormone and the blood-brain-barrier. Front Biosci. 2007; 12:1615–1628. [PubMed: 17127408]

Trevathan E, et al. The descriptive epidemiology of infantile spasms among Atlanta children. Epilepsia. 1999; 40(6):748–751. [PubMed: 10368073]

Velisek L, et al. Model of infantile spasms induced by N-methyl-D-aspartic acid in prenatally impaired brain. Ann Neurol. 2007; 61(2):109–119. [PubMed: 17315208]

Vezzani A, et al. Epilepsy and brain inflammation. Exp Neurol. 2013; 244:11–21. [PubMed: 21985866]

Vezzani, A., et al. Glia-neuronal interactions in ictogenesis and epileptogenesis: role of inflammatory mediators. In: Noebels, JL.Avoli, M.Rogawski, MA.Olsen, RW., Delgado-Escueta, AV., editors. Jasper's Basic Mechanisms of the Epilepsies. Bethesda (MD): 2012.

Vezzani A, et al. The role of inflammation in epilepsy. Nat Rev Neurol. 2011; 7(1):31–40. [PubMed: 21135885]

Vezzani A, et al. Immunity and Inflammation in Epilepsy. Cold Spring Harb Perspect Med. 2016; 6(2):a022699.

Vitaliti G, et al. Targeting inflammation as a therapeutic strategy for drug-resistant epilepsies: an update of new immune-modulating approaches. Hum Vaccin Immunother. 2014; 10(4):868–875. [PubMed: 24609096]

Wang Y, et al. A role for the mTOR pathway in surface expression of AMPA receptors. Neurosci Lett. 2006; 401(1–2):35–39. [PubMed: 16677760]

Wang YC, et al. Toll-like receptors in cerebral ischemic inflammatory injury. J Neuroinflammation. 2011; 8:134. [PubMed: 21982558]

Wang YJ, et al. Effects of adrenal dysfunction and high-dose adrenocorticotropic hormone on NMDA-induced spasm seizures in young Wistar rats. Epilepsy Res. 2012; 100(1–2):125–131. [PubMed: 22584030]

Wilson J. Proceedings: Neurological complications of DPT inoculation in infancy. Arch Dis Child. 1973; 48(10):829–830.

Wise MS, et al. Rasmussen syndrome and long-term response to gamma globulin. Pediatric Neurology. 1996; 14(2):149–152. [PubMed: 8703228]

Wu HM, Huang W-Y. Role of NOX2 in seizure susceptibility of mice following systemic inflammation (P4. 251). Neurology. 2015; 84(14 Supplement):P4.251.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Yamamoto H. Studies on CSF tryptophan metabolism in infantile spasms. Pediatr Neurol. 1991; 7(6): 411–414. [PubMed: 1724601]

Yamamoto H, et al. A new trial liposteroid (dexamethasone palmitate) therapy for intractable epileptic seizures in infancy. Brain Dev. 2007; 29(7):421–424. [PubMed: 17275235]

Yamanaka G, et al. Increased level of serum interleukin-1 receptor antagonist subsequent to resolution of clinical symptoms in patients with West syndrome. Journal of the Neurological Sciences. 2010; 298(1–2):106–109. [PubMed: 20807663]

Yang F, et al. Roles of astrocytes and microglia in seizure-induced aberrant neurogenesis in the hippocampus of adult rats. J Neurosci Res. 2010; 88(3):519–529. [PubMed: 19774666]

Ye ZC, Sontheimer H. Cytokine modulation of glial glutamate uptake: a possible involvement of nitric oxide. Neuroreport. 1996; 7(13):2181–2185. [PubMed: 8930985]

You SJ, et al. Factors influencing the evolution of West syndrome to Lennox-Gastaut syndrome. Pediatr Neurol. 2009; 41(2):111–113. [PubMed: 19589458]

Youn Y, et al. The role of cytokines in seizures: interleukin (IL)-1β, IL-1Ra, IL-8, and IL-10. Korean Journal of Pediatrics. 2013; 56(7):271–274. [PubMed: 23908665]

Yum MS, et al. Prenatal stress promotes development of spasms in infant rats. Epilepsia. 2012; 53(3):e46–49. [PubMed: 22191812]

Zakharova M, Ziegler HK. Paradoxical anti-inflammatory actions of TNF-alpha: inhibition of IL-12 and IL-23 via TNF receptor 1 in macrophages and dendritic cells. J Immunol. 2005; 175(8): 5024–5033. [PubMed: 16210605]

Zbytek B, et al. CRH inhibits NF-kappa B signaling in human melanocytes. Peptides. 2006; 27(12): 3276–3283. [PubMed: 16959375]

Zeng LH, et al. Modulation of astrocyte glutamate transporters decreases seizures in a mouse model of Tuberous Sclerosis Complex. Neurobiol Dis. 2010; 37(3):764–771. [PubMed: 20045054]

Zurolo E, et al. Activation of Toll-like receptor, RAGE and HMGB1 signalling in malformations of cortical development. Brain. 2011; 134(Pt 4):1015–1032. [PubMed: 21414994]

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Table 1

Association of pro-inflammatory cytokines with seizures in patients with epilepsy and seizures.

Condition	Specimen	Increase in:	Decrease in:	References
TLE	TL tissue	Beta-amyloid precursor, IL-1	NR	(Sheng, Boop, Mrak & Griffin 1994)
FCD type IA, IIA and IIB	FCD brain tissue	IL-17, IL-17r	NR	(He, Li, Shu, Yu, Liu, Yin et al. 2013)
Tonic-clonic seizures (24h following seizure)	Serum/CSF	IL-6, leukocyte counts, C-reactive protein	NR	(Peltola, Laaksonen, Haapala, Hurme, Rainesalo & Keranen 2002)
Drug-resistant epilepsy	Serum/CSF	IL-6	IL-1ra, IL-1ra:IL-1β ratio	(Lehtimaki, Keranen, Huhtala, Hurme, Ollikainen, Honkaniemi et al. 2004, Lehtimaki, Keranen, Palmio & Peltola 2010)

Abbreviations: CSF: cerebrospinal fluid; FCD: Focal cortical dysplasia; IL: Interleukin; IL-1ra: Interleukin-1 receptor antagonist; IL-17r: IL-17 receptor; NR: Not reported; TL: Temporal lobe; TLE: Temporal lobe epilepsy.

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Table 2

Immunological findings in patients with WS

These findings indicate a possible role of the cytokines and immune status alteration in the pathogenesis of WS, although it is difficult to make a strong comparison due to variations in patient groups, specimens and parameters evaluated.

References	Total number of patients with WS	Treatment	Principal parameters investigated	Specimen	Time of specimen collection	Total number of control patients	Immunologic markers	
							WS before treatment vs controls	WS after treatment vs WS before treatment
(Tekgul, Polat, Tosun, Serdaroglu, Kutukculer & Gokben 2006)	12 (8 – symptomatic; 4 cryptogenic)	None (newly diagnosed)	IL-6	CSF	Before treatment	Patients with tonic-clonic seizures (CNS infection or trauma)	**Reduced:** IL-6	NR
(Dussaix, Lebon, Ponsot, Huault & Tardieu 1985)	12	NR	IFN-α	CSF	NR	Patients with acute encephalitis or meningitis or other chronic neurological disorders	No IFN-α in CSF detected	NR
(Liu, Wang, Wang & Yang 2001)	23 (13 – symptomatic; 10 – unknown)	ACTH (4–6 weeks), further CZP/VPA/TOP	IL-2, TNF-α, IFN-α	Blood	Before treatment	15 (healthy controls)	**Elevated:** IL-2, TNF-α, IFN-α	NR
(Montelli, Soares & Peraçoli 2003)	50 (including 17 post-WS@)	NR	Peripheral lymphocyte subsets; CD3+ cells, CD4+ cells, CD8+ cells, and CD4+/CD8+ ratio	Blood	Samples collected at infection-and ACTH-free period (not reflected if prior or after therapy)	20 (healthy controls)	**Elevated:** CD8+; **Reduced:** CD3+; CD4+; CD4/CD8 ratio *(not reported whether the data obtained before or after treatment)*	
(Ohya, Nagai, Araki, Yanagawa, Tanabe, Iyoda et al. 2009)	18 (8 – symptomatic; 10 – unknown)	ACTH (Cortrosyn Z^R); Other treatments: VPA (16/18), Vitamin B6 8/18), CZP, etc)	WBC counts; lymphocyte counts; T cell, B cell, CD4+ T cell, CD8+ T cell counts; CD 4/8 ratio, and the levels of IgA, IgM, and IgG	Blood	Before treatment; immediately after, 1, 3, 6 and 12 months after treatment	NR		**Reduced by ACTH:** CD4+; CD4/8 ratio; Lymphocyte counts **No change:** Ig
(Shiihara, Miyashita, Yoshizumi, Watanabe, Yamada & Kato 2010)	76 (44 – symptomatic; 32 – unknown)	ACTH	Peripheral lymphocyte subsets; IL-1β, IL-1ra, IL-5, IL-6, IL-12, IL-15; eotaxin; bFGF; IFN-γ-inducible protein-10;, MIP-1β; CD3+ CD25+, CD19+, CD19+	Blood	Before and after treatment	26 (healthy controls)	**Elevated:** IL-1ra; IL-5; IL-6; IL-15; eotaxin; bFGF; IFN-γ-IP-10;	**Elevated:** none **Reduced:** CD4+; CD3+; CD4+/8+

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References	Total number of patients with WS	Treatment	Principal parameters investigated	Specimen	Time of specimen collection	Total number of control patients	Immunologic markers	
							WS before treatment vs controls	WS after treatment vs WS before treatment
			CD95+, CD4+ cells and CD4+/8+ ratio				**Reduced:** CD3+ CD25+; CD19+; CD19+ CD95+	ratio; IL-1β; IL-12; MIP-1β
(Yamanaka, Kawashima, Oana, Ishida, Miyajima, Kashiwagi et al. 2010)	13 (9 – symptomatic; 4 – unknown)	ACTH Other treatments: Vitamin B6, VPA, ZNS	IL-1β, IL-1ra	Blood and CSF	Before or after ACTH	NR	**Before ACTH:** No group differences noted	**Elevated in responders:** serum IL-1ra
(Haginoya, Noguchi, Zhao, Munakata, Yokoyama, Tanaka et al. 2009)	24 (17 – symptomatic; 7 – unknown)	None (newly diagnosed)	IL-1β, IL-1ra, IL-6, TNF-α	CSF	Before ACTH treatment	15 (healthy controls) and 16 (aseptic meningitis)	**Reduced:** IL-1ra; **No change:** IL-1β; TNF-α; IL-6	NR

[@] – Post-WS designate patients initially diagnosed WS later evolving to other epilepsy such as Lennox–Gastaut syndrome;

[*] – Only in WS patients before treatment, no comparison with controls

[a] – Group of unknown origin compared to controls;

Abbreviations: ACTH: adrenocorticotropic hormone; ASD: Antiseizure drugs; bFGF: Basic fibroblast growth factor; CSF: cerebrospinal fluid; CZP: clonazepam; IFN: interferon; IFN-γ-IP-10: IFN-γ-inducible protein −10; Ig: Immunoglobulin; IL: interleukin; IL-1ra: Interleukin-1 receptor antagonist; MIP: Macrophage inflammatory protein; TNF: tumor necrosis factor; TOP: topiramate; VPA: valproate; WS: West syndrome; ZNS: zonisamide.