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Review Article

Early-Onset Epileptic Encephalopathies: Ohtahara Syndrome and Early Myoclonic Encephalopathy

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ARTICLE INFORMATION

ABSTRACT

Ohtahara syndrome and early myoclonic encephalopathy are the earliest presenting of the epileptic encephalopathies. They are typically distinguished from each other according to specific clinical and etiologic criteria. Nonetheless, considerable overlap exists between the two syndromes in terms of clinical presentation, prognosis, and electroencephalographic signature. Newer understandings of underlying etiologies of these conditions may support the previously suggested concept that they represent a single spectrum of disease rather than two distinct disorders. We review both syndromes, with particular focus on the underlying genetics and pathophysiology and implications regarding the classification of these conditions.

Introduction

Early myoclonic epilepsy and early infantile epileptic encephalopathy (or Ohtahara syndrome) constitute the earliest presenting of the age-dependent epileptic encephalopathy syndromes. They are electroclinical syndromes, defined by their clinical features and electroencephalographic findings. They are classically distinguished from each other according to their presentations and differing etiologies, but they do share certain clinical, electroencephalographic, and prognostic features. This review will discuss the presentation, diagnosis, and pathogenesis of these syndromes, with special consideration for new understandings of pathophysiology and genetics, as well as difficulties in differentiating between the two disorders.

Historic background and classification

In 1976, Ohtahara et al. described an epilepsy syndrome affecting very young infants with characteristic electro-encephalographic changes, and termed it "early infantile epileptic encephalopathy with suppression-burst" [1]. Ohtahara further observed that this condition frequently evolved into West syndrome and Lennox-Gastaut syndrome [2]. The eponym Ohtahara syndrome, which is synonymous with early infantile epileptic encephalopathy, came into prominent use in the mid-1980s [3].

What came to be known as early myoclonic encephalopathy was first described 2 years after Ohtahara syndrome, in 1978, in neonates with erratic myoclonus and other seizure types [4]. Numerous terms have been applied to this condition, including myoclonic epilepsy with neonatal onset, neonatal epileptic encephalopathy with periodic electroencephalogram bursts, and early myoclonic epileptic encephalopathy [5].

In 2001, the Task Force on Classification and Terminology of the International League Against Epilepsy included both "Ohtahara syndrome" and "early myoclonic encephalopathy" within the category of epileptic encephalopathies [6]. This term describes epilepsy syndromes in which seizures and epileptiform electroencephalographic abnormalities are thought to contribute to progressive cerebral dysfunction. Other syndromes in this group include West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and electrical status epilepticus during sleep.

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More recently, the proposed organization by the Classification Commission of the International League Against Epilepsy termed both Ohtahara syndrome and early myoclonic encephalopathy as "electroclinical syndromes," characterized by their clinical and electroencephalographic characteristics [7].

Clinical presentation

Ohtahara syndrome

Ohtahara syndrome presents in early infancy, within the first 3 months of age, and often within the first 2 weeks [8]. Infants acutely develop tonic spasms that can be either generalized or lateralized, can occur both singly or in clusters, and are independent of the sleep cycle. Spasms typically last up to 10 seconds, and can occur hundreds of times per day [9]. Approximately one third of patients with Ohtahara syndrome will also develop other seizure types, most commonly focal motor seizures, hemiconvulsions, or generalized tonic-clonic seizures [10].

Electroencephalograms in Ohtahara syndrome indicate a suppression burst pattern, comprising bursts of high-amplitude spikes and polyspikes that alternate at a regular rate with periods of electric suppression (Fig 1). The bursts coincide with the tonic spasms [11]. The pattern typically remains unchanged during both wakefulness and sleep.

The prognosis is generally poor. Patients with Ohtahara syndrome frequently die during infancy [10], and survivors invariably manifest psychomotor impairments, whether or not the seizures are ultimately controlled [5].

In some cases, Ohtahara syndrome can transition into West syndrome over time, and can further evolve into Lennox-Gastaut syndrome. In the series of Yamatogi and Ohtahara, 75% of patients developed West syndrome between 2 and 6 months of age, and 12% subsequently developed Lennox-Gastaut syndrome [10]. The transition is accompanied by changes in electroencephalographic pattern. The evolution to West syndrome is marked by a transition from suppression burst to hypsarrhythmia, and further progression to Lennox-Gastaut syndrome is accompanied by the development of a generalized, slow spike-wave pattern. The close relationship among these three syndromes has led to the theory that they represent age-specific reactions in the brain to similar exogenous influences, and to the proposal that they be classified together as the age-dependent epileptic encephalopathies [2,8].

Early myoclonic encephalopathy

Considerable similarities characterize the clinical presentations of Ohtahara syndrome and early myoclonic encephalopathy. Like Ohtahara syndrome, early myoclonic encephalopathy presents during the neonatal period, usually within the first 3 months of age, and sometimes as early as a few hours after birth. The initial presentation typically involves the onset of focal myoclonus, usually of the face or extremities and or of only a small area, such as a finger or eyelid. The jerks are often described as erratic or fragmentary because they can shift from one area of the body to another in an asynchronous, seemingly random pattern.

Focal seizures are also very common, and occur in more than 80% of cases [12]. These seizures may be overt, involving deviation of an eye or tonic posturing, or they may be subtle, sometimes involving only autonomic signs such as facial flushing or apnea. Tonic spasms are also frequent, occurring both singly and in clusters.

The key electroencephalographic feature in early myoclonic encephalopathy comprises a suppression burst pattern, much like that in Ohtahara syndrome (Fig 1). In the case of early myoclonic encephalopathy, however, this pattern is not continuous, and is often more distinct during sleep. It was reported exclusively during sleep in 33% of cases in one study [12]. The suppression burst pattern in early myoclonic encephalopathy may not be appreciated at disease onset, and follow-up electroencephalograms may be necessary to arrive at the diagnosis [13]. The myoclonic movements themselves are not associated with electrographic changes.

The suppression burst pattern can evolve into an atypical pattern of hypsarrhythmia in up to 50% of patients, typically occurring at 3-5 months of age [12]. This change is generally transient, lasting months, with a subsequent return to burst suppression, which can last throughout childhood [14].
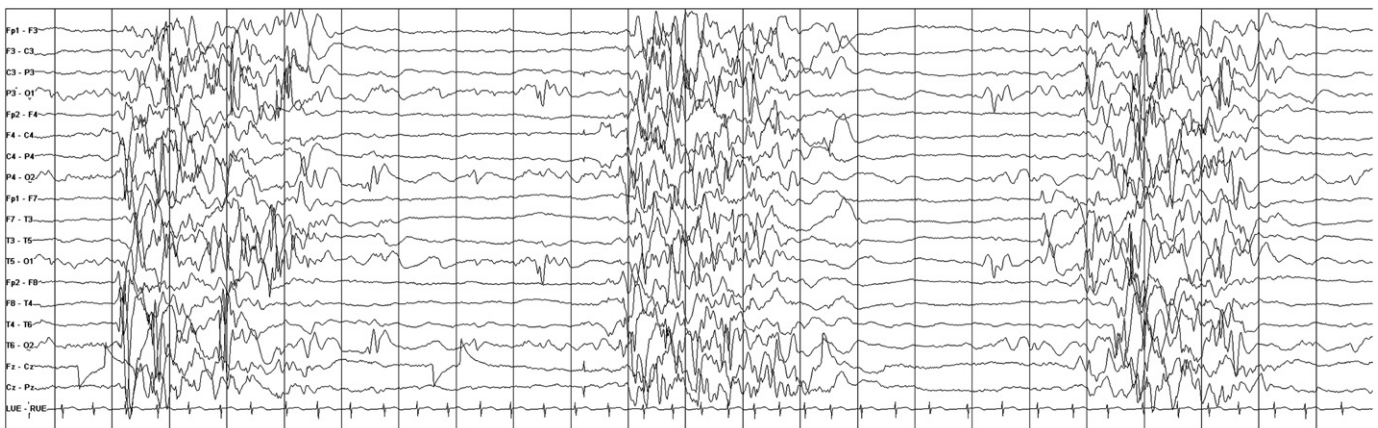

Figure 1. Electroencephalogram indicates typical suppression burst pattern that can be observed in both Ohtahara syndrome and early myoclonic encephalopathy. This recording is of a 3-month-old girl with Ohtahara syndrome. Time base, 30 mm/second; sensitivity, 10 μV/mm.

The prognosis is generally very poor. Up to half of patients die by 2 years of age [5]. The remainder manifest severe psychomotor impairments, including some patients who remain in a persistent vegetative state [15].

Etiology and pathogenesis

Ohtahara syndrome

Ohtahara syndrome can result from a variety of etiologies, but the majority of cases have been associated with structural brain abnormalities. Cases related to genetic mutations and metabolic abnormalities have also been described, although at least some of these cases also exhibited associated structural malformations. Even in some cases when no structural lesion was evident on cranial imaging, postmortem examinations demonstrated evidence of a migration disorder or dysgenesis that was not previously appreciated on neuroimaging [3,16].

A variety of structural malformations have been associated with Ohtahara syndrome, including hemimegalencephaly [11,17], agenesis of the corpus callosum [3,8], porencephaly [8], agenesis of the mamillary bodies [18], and dentato-olivary dysplasia [17]. Hypoxic injury [3], cortical dysplasias, and cerebral migration disorders are also frequently described [16,19,20].

Metabolic disorders that were reported to accompany Ohtahara syndrome include nonketotic hyperglycinemia [3], cytochrome C oxidase deficiency [21], pyridoxine dependency, carnitine palmitoyltransferase deficiency [11], and a case of Leigh encephalopathy [22]. More recently, a patient with biotinidase deficiency [23] and two patients with mitochondrial respiratory chain complex I deficiency were described [24,25]. One of the patients with respiratory chain complex I deficiency also manifested microcephaly, thinning of the corpus callosum, and cortical atrophy [24]. The other patient with a similar complex 1 deficiency demonstrated normal cranial imaging [25]. Deficiencies in cytochrome C oxidase or respiratory chain complex I may result in energy depletion during development, in turn leading to demyelination and abnormalities in neuronal migration [26].

Underlying genetic mutations have been increasingly reported with Ohtahara syndrome. Mutations in the syntaxin binding protein 1 (STXBP1) gene, for example, have been described in Ohtahara syndrome since 2008 [27]. A proportion of patients with known Ohtahara syndrome is now thought to manifest underlying STXBP1 mutations, although the exact number of such patients has varied from study to study, ranging from 10-13% [28,29] to 38% in the original report [27]. Similarly, mutations of the Aristaless-related homeobox (ARX) gene have also been associated with Ohtahara syndrome [30-32]. In keeping with the close relationship between the age-dependent epileptic encephalopathies, mutations in both ARX and STXBP1 have also been described in patients with West syndrome [28,29,31]. Finally, two reports described patients with Ohtahara syndrome who had mutations in the solute carrier family 25 (SLC25A22) gene. Both patients were born to consanguinous parents [33].

As with the metabolic disturbances, the mechanisms by which these genetic abnormalities cause Ohtahara syndrome are thought to be related to brain dysgenesis or neuronal dysfunction. The SLC2A22 gene is involved in mitochondrial glutamate transport. Mutations could lead to energy depletion during development, or to neuronal dysfunction and cell death [26]. The ARX gene plays a role in regulating neuronal differentiation and proliferation, as well as the migration of neuron progenitors to the developing cortex [26,34,35]. Mutations of the ARX gene have been associated with structural abnormalities such as hypoplastic corpus callosum, small basal ganglia and hippocampi, a defect of the cavum septum pellucidum, and cerebral atrophy [30-32]. Dysfunctional differentiation may also lead to a deficiency of inhibitory interneurons, partly accounting for the intractable seizures observed in these patients [34]. The STXBP1 gene is involved in the regulation of synaptic vesicle release, and thus, like ARX, also plays a role in neuronal progenitor cell differentiation and migration, because the release of γ-aminobutyric acid and glutamate are important for these functions [26,35].

Moreover, mutations of STXBP1 may lead to brainstem abnormalities. Widespread cell death in the brainstem has been observed in STXBP1 null mice [34]. Brainstem dysfunction was previously implicated in Ohtahara syndrome because the tonic seizures that are prevalent in the syndrome are thought to be generated in the brainstem, and brainstem abnormalities are frequently reported in autopsies of patients with Ohtahara syndrome [36]. Interestingly, brainstem dysfunction is also thought to contribute to the development of hypsarrhythmia in infantile spasms [37], and may play a role in the transition from Ohtahara syndrome to West syndrome.

Early myoclonic encephalopathy

Similar to Ohtahara syndrome, the pathogenesis of early myoclonic encephalopathy is variable, with structural, metabolic, and genetic abnormalities all playing a role. The overall picture in early myoclonic encephalopathy seems to involve a diffuse process particularly involving the brainstem and white matter, possibly leading to deafferentation and hyperexcitability of the cortex.

Unlike Ohtahara syndrome, focal structural abnormalities are not frequently observed in early myoclonic encephalopathy. However, progressive, diffuse cortical atrophy has been reported in most cases [12]. Once again, this finding is suggestive of an underlying metabolic or degenerative disorder [9].

Associated metabolic abnormalities are frequently described. In particular, nonketotic hyperglycinemia has been associated with a large number of cases [38-40], and this entity was suggested to constitute the most common etiology of early myoclonic encephalopathy [41]. Cases have also been reported in association with D-glyceric acidemia, propionic aciduria, molybdenum cofactor deficiency, pyridoxine deficiency, methylmalonic acidemia, sulfite oxidase deficiency, Menkes disease, and Zellweger syndrome [39-44].

Pathologic findings in early myoclonic encephalopathy include demyelination, multifocal spongy changes in the white matter, imperfect lamination of the deep cortical layers, perivascular concentric bodies, and astrocytic proliferation [45]. Autopsy reports described prevalent white matter abnormalities and brainstem pathology [36].

The presence of numerous spiny neurons dispersed in the white matter has also been reported, which is suggestive of impaired neuronal migration and apoptosis [20].

Using functional neuroimaging techniques in a patient with early myoclonic encephalopathy, Hirose et al. [46] demonstrated hypoperfusion and hypometabolism in the basal ganglia and thalami interictally, with ictal hyperperfusion of the basal ganglia, thalami, brainstem, and deep front-parietal cortex. This finding was indicative of dysfunction in these regions, and was thought to suggest a functional deafferentation of the cortex from subcortical structures [46].

A number of familial cases of early myoclonic encephalopathy have been reported [14,40], raising the question of whether the disease involves a genetic component. A likely genetically mediated case was reported in association with Schinzel-Giedion syndrome, a rare genetic multiple malformation disorder [47]. In 2009, early myoclonic encephalopathy was reported in association with a mutation of the v-erb-a erythroblastic leukemia viral oncogene homologue 4 (ErbB4 gene), which is involved in the migration of interneurons to the cortex [48]. This genetic abnormality is consistent with the persistence of spiny neurons in the white matter on pathologic examination, and of the functional deafferentation described by Hirose et al. [46], both of which seem to indicate impaired neuronal migration to the cortex, suggesting a degree of "cortical isolation" in the brains of these patients [20,46,48].

Assessment and treatment

The diagnosis of both Ohtahara syndrome and early myoclonic encephalopathy is based on a typical clinical picture and associated electroencephalographic findings, as already described. The prognosis is universally poor. Neuroimaging to assess for structural brain abnormalities is generally recommended in cases of Ohtahara syndrome. Brainstem evoked potentials are occasionally abnormal in both conditions, but normal studies do not exclude the possibility of disease [36].

Only anecdotal evidence supports the use of specific antiepileptic drugs in these conditions. Phenobarbital, valproate, pyridoxine, zonisamide, and benzodiazepines have all demonstrated limited effectiveness in seizure control in Ohtahara syndrome [10,49]. Adrenocorticotropic hormone therapy also exerts limited efficacy, and may be particularly beneficial in cases of Ohtahara syndrome that progress to West syndrome [3,9]. None of the antiepileptic medications has been effective in treating early myoclonic encephalopathy, nor have alternative methods of seizure management such as adrenocorticotropic hormone therapy, corticosteroids, and pyridoxine. Cases have been reported in which the early myoclonic encephalopathy worsened after an administration of vigabatrin [50]. Some success in controlling seizures has been reported with the ketogenic diet in Ohtahara syndrome, but not in early myoclonic encephalopathy [3,51].

The correction of underlying metabolic disorders may lead to more favorable outcomes. In particular, patients with Ohtahara syndrome have been reported to do relatively well after the correction of underlying pyridoxine deficiencies [11] or biotinidase deficiencies [23]. In cases of early myoclonic encephalopathy associated with non-ketotic hyperglycinemia, treatment with sodium benzoate, ketamine, and dextromethorphan has been used, sometimes in combination with tryptophan, strychnine, or imipramine [41,52,53]. These treatments can improve the neonatal course, but do not seem to affect long-term outcomes [53].

Cases with operable structural abnormalities such as hemimegalencephaly or cortical dysplasia can benefit from neurosurgical intervention with focal resection or hemispherectomy [54].

Differentiation

Early myoclonic encephalopathy and Ohtahara syndrome share many features, including age at presentation, a similar electroencephalographic pattern, intractable seizures, and poor prognosis. Tonic seizures and focal motor seizures are frequently observed in both syndromes. Thus differentiating between the two conditions can be difficult, especially early in their course, and they have been conceptualized by some as part of the same continuum of disease [34,36].

In 2006, Ohtahara and Yamatogi [9] highlighted the differences between the syndromes, indicating that they were separate and distinguishable diseases (Table 1). Specifically, they pointed out the prevalence of structural abnormalities in Ohtahara syndrome vs metabolic disease in early myoclonic encephalopathy, and emphasized that the suppression burst pattern is present equally in wakefulness and sleep in Ohtahara syndrome, whereas it is either exclusively present during sleep or more distinct during sleep in early myoclonic encephalopathy. Furthermore, the evolution of disease can differ. Ohtahara syndrome can progress to West syndrome and then to Lennox-Gastaut

Table 1. Classic differentiation between Ohtahara syndrome and early myoclonic epilepsy

	Ohtahara Syndrome	Early Myoclonic Encephalopathy
EEG pattern	Continuous suppression burst	Discontinuous pattern, suppression burst not always evident at first, and often more distinct during sleep
Primary seizure type	Tonic spasms	Myoclonus
Other seizure types	Focal motor seizures	Focal motor seizures
	Hemiconvulsions	Tonic spasms
	Generalized tonic-clonic seizures	
Major etiology	Structural lesions	Metabolic abnormalities
Evolution of disease	75% progress to West syndrome, 12% progress to Lennox-Gastaut syndrome	Up to 50% develop transient atypical hypsarrhythmia, with subsequent return to the suppression burst pattern

Abbreviation:
EEG = Electroencephalogram

syndrome, or can transition to severe focal epilepsy. Early myoclonic encephalopathy typically remains unchanged for years or transiently evolves to an atypical hypsarrhythmia pattern, which is thought to differ significantly from typical West syndrome in terms of seizure type and atypical electroencephalographic findings. Finally, Ohtahara and Yamatogi [9] emphasized that although some seizure types do overlap between the two syndromes, tonic spasms are the first seizure type observed in Ohtahara syndrome, whereas focal seizures and erratic myoclonus occur first in early myoclonic encephalopathy [9].

Although these differences are helpful in differentiating between the two conditions in their purest forms, considerable clinical overlap may still occur in practice. As already described, Ohtahara syndrome has been associated with multiple metabolic disturbances in addition to structural abnormalities. Furthermore, Schlumberger et al. reported on several patients with Ohtahara syndrome in whom the suppression burst pattern was not present equally in sleep and wakefulness as expected, but was present only during sleep or more marked during sleep [17]. The evolution of disease can also be misleading, because the transient hypsarrhythmia sometimes observed in early myoclonic encephalopathy may be interpreted as indicating a transition to West syndrome. Persistence of the suppression burst pattern has been reported in Ohtahara syndrome, although this persistence is generally thought to be more consistent with the natural history of early myoclonic encephalopathy [55]. Differences in seizure type may not help to differentiate the two diseases, because tonic spasms and focal motor seizures are a prominent feature of both.

Some authors proposed that the two syndromes may actually involve one spectrum of disease, and that differences in seizure pattern reflect the differing progression of pathology. In reviewing autopsy reports of patients with Ohtahara syndrome and early myoclonic encephalopathy, Djukic et al. [36] observed that brainstem pathology was the only consistent finding in every reported case. Brainstem dysfunction was presumed to be the source of the tonic seizures in these syndromes. Djukic et al. [36] hypothesized that the brainstem dysfunction may occur earlier in Ohtahara syndrome, leading to early tonic seizures at presentation. Brainstem involvement in early myoclonic encephalopathy may be less severe initially but may progress over time, possibly as a result of a kindling process or a release of the brainstem from cortical inhibitory control, leading to the emergence of tonic seizures later in the course of disease. Thus the differences between the two syndromes may reflect disease burden in the brain, rather than an indication that they are two separate entities [36].

Based on newer understandings of the genetics underlying these disorders, both syndromes were also postulated to represent a "phenotypic continuum" in which multiple underlying genetic abnormalities led to similar metabolic and structural defects, producing a clinical spectrum of disease [34]. Table 2 summarizes some prominent examples of genetic and phenotypic overlap among the epileptic encephalopathy syndromes. Many of these conditions can be caused by multiple different genetic mutations, and certain gene mutations can cause multiple syndromes. This finding would indicate that differing underlying abnormalities can lead to common pathophysiologic pathways,

Table 2. Genetic mutations associated with epileptic encephalopathies

Mutation Site	Ohtahara Syndrome	EME	West Syndrome	SMEI	Atypical RTT with Early Epilepsy	EFMR
ARX	Yes		Yes			
CDKL5			Yes		Yes	
ErbB4		Yes				
MAGI2			Yes			
PCDH19				Yes		Yes
PNKP	Yes		Yes			
SCN1A				Yes		
SLC25 A22	Yes					
STXBP1	Yes		Yes			

Abbreviations:
EFMR = Epilepsy and mental retardation limited to females
EME = Early myoclonic encephalopathy
RTT = Rett syndrome
SMEI = Severe myoclonic epilepsy of infancy (also known as Dravet syndrome)
Only epileptic encephalopathy syndromes presenting during infancy are included. Some mutations may also be associated with other conditions, e.g., the SCN1A mutation is associated with generalized epilepsy with febrile seizures.

resulting in a range of clinical phenotypes. In the case of Ohtahara syndrome and early myoclonic encephalopathy, both syndromes may result from processes leading to impaired neuronal differentiation and migration, as already described. Specifically, the ARX and STXBP1 mutations and complex I deficiency associated with Ohtahara syndrome, the ErbB4 mutation and multiple metabolic abnormalities correlated with early myoclonic encephalopathy, and the prominent brainstem pathology in both syndromes all suggest a common pathophysiologic pathway leading to abnormal neuronal migration and a functional isolation of the cortex from the brainstem. Thus, multiple underlying anomalies may lead to similar impairments in neuronal differentiation and migration, resulting in a spectrum of epileptic encephalopathies with clinical similarities that encompasses Ohtahara syndrome and early myoclonic encephalopathy.

Conclusion

Ohtahara syndrome and early myoclonic encephalopathy, as electroclinical syndromes, are defined by their clinical presentations and specific electroencephalographic findings. Based on these criteria, they are traditionally distinguished from each other according to differing seizure types, differences in their pattern of suppression burst, and differing etiologies. Specifically, in its purest form, Ohtahara syndrome is thought to result mostly from structural malformations, whereas early myoclonic encephalopathy is associated with metabolic abnormalities. However, considerable clinical overlap between these conditions can occur.

Newer understandings of the genetic and pathophysiologic mechanisms underlying these diseases have revealed further similarities between them. Broadly speaking, both syndromes frequently seem associated with conditions that lead to abnormal neuronal migration, possibly leading to both structural brain abnormalities and a functional disconnection between the cortex and the deep brain and brainstem [20,26,34,46,48]. The prominence of brainstem abnormalities in both syndromes similarly indicates a disconnect between the cortex and subcortical structures.

This so-called "cortical deafferentation" may play a role in the intractable nature of the seizures as well the prevalence of tonic seizures in both syndromes [34,36,46].

Thus, to think of Ohtahara syndrome and early myoclonic encephalopathy as part of a spectrum may be possible. The multiple etiologies identified in these conditions lead to similar pathophysiologic pathways. These pathways may result in a range of similar disease states involving tonic seizures, a suppression burst electroencephalographic pattern, onset during infancy, and progressive encephalopathy with psychomotor retardation. The two syndromes may therefore not involve two distinct diseases, but rather may form part of a continuum of disease.

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