17  Acute Disseminated Encephalomyelitis

Stefan Schwarz and Michael Knauth

CONTENTS

17.1 Introduction 255
17.2 Epidemiology 256
17.3 Etiology 256
17.4 Pathophysiological Hypotheses 256
17.5 Pathological Findings 257
17.6 Clinical Symptoms 257
17.7 Cerebrospinal Fluid 258
17.8 Therapeutic Options and Prognosis 258
17.9 The Problem of Relapsing or Multiphasic ADEM 259
17.10 Differential Diagnosis 259
17.11 Neuroradiology 260
17.11.1 Computed Tomography 260
17.11.2 Magnetic Resonance Imaging 260
17.11.3 New MRI Techniques 265
17.12 Variant of MS or Distinct Disease Entity? 265
References 266

17.1 Introduction

The first clinical descriptions of patients with “acute disseminated encephalomyelitis” (ADEM) originate from the begin of the 20th century. In a summary of these early case reports, McAlpine concluded in 1931 that ADEM typically occurs after an infection or immunization, but may also arise spontaneously. He further pointed out that the course of the disease is short, the mortality low, and, in contrast to the “disseminated sclerosis”, the disease is monophasic (McAlpine 1931). Unfortunately, today, more than 70 years after McAlpine’s landmark publication, a more detailed and precise definition of ADEM is still not available.

Although the number of case reports and small case series has increased to date, generally accepted diagnostic criteria for the diagnosis ADEM have not been established. It remains debatable whether ADEM is a distinct disease entity or a subform of multiple sclerosis (MS). Because many neurologists, encouraged from the results of the CHAMPS (Jacobs et al. 2000) and ETOMS (Comi et al. 2001) trials, now tend to treat patients with a suspected MS already after the first clinical manifestation, it is of particular importance to identify those patients with a monophasic disease who would not need an improper, expensive and potentially hazardous preventive immunomodulatory medication. Applying the novel McDonald diagnostic criteria for MS (McDonald et al. 2001), in many of the patients previously diagnosed with ADEM, the diagnosis of MS could be made already during the first episode of symptoms using the clinical and MRI findings usually present in these patients. To complicate these diagnostic qualms even further, the discrimination of ADEM from other acute demyelinating syndromes such as “acute MS of the Marburg type”, Schilder’s diffuse sclerosis, Devic’s neuromyelitis optica, or Hurst syndrome frequently is elusive. Because there have been no large systematic studies, the previous attempts for a classification of these syndromes depended on hypotheses and empirical clinical evidence only. Most authors agree that “Marburg disease” should be subsumed under ADEM, and the Hurst syndrome constitutes the most severe variant of ADEM.

The aim of this chapter is to give an overview of the neuroradiological features of ADEM. Because ADEM and its complex diagnostic problems cannot be understood on radiological grounds only, we also briefly review the clinical symptoms, pathological and laboratory findings. We will show that during the initial presentation of the patients there is a wide range of overlapping clinical symptoms and radiological findings with MS, and today, the diagnosis of ADEM can only be established with certainty after a long symptom-free follow-up.
17.2 Epidemiology

ADEM is an uncommon disease. Accurate epidemiological figures do not exist. Miller et al. (1956) estimated the incidence of a parainfectious ADEM after acute measles infection to be 1:1000. However, these and other results from studies originating from the pre-MRI era must be interpreted with caution because, at this time, the diagnostic possibilities were hardly adequate. Before the introduction of MRI, an acute demyelinating disease could only be presumed from the patients’ history and clinical findings; a definite diagnosis was only possible after a brain biopsy or autopsy. Because mild or transient symptoms rarely justify a brain biopsy, it can be presumed that severe or even lethal courses are overrepresented in the studies from the pre-MRI era. This is also the reason for the previously frequently held opinion that ADEM is a severe disease with a high mortality.

Supposedly, the incidence of ADEM is higher than previously assumed because the disease may be clinically completely asymptomatic or the symptoms are mild and transient, and further diagnostic procedures are not performed.

The incidence of ADEM is probably highest in children and declines with increasing age. In patients older than 40 years, ADEM is rare (Wang et al. 1996). However, few single patients with ADEM over 70 years have been described. As a rule of thumb, in patients over 40 years, the diagnosis of ADEM should be established only with great caution.

The occurrence of postinfectious and postvaccinal ADEM is not confined to populations with a high incidence of MS (Modi et al. 2001; Murthy et al. 1999). Unfortunately, there are no systematic studies comparing the incidence of ADEM between countries with a high incidence of MS and countries where indigenous MS is virtually absent. However, the rate of “idiopathic” ADEM without preceding infection or vaccination seems to be higher in the European and North American countries than in Brazil (Reis et al. 1999) and India (Murthy et al. 1999). The development of MS after the diagnosis of ADEM is also uncommon in these countries.

17.3 Etiology

In the majority of patients, an infection, or, rarely, a vaccination, precedes the onset of symptoms. This is particularly true for children: in 62 of 84 children an infection or vaccination preceded the onset of ADEM (Tenembaum et al. 2002). In contrast, in adults ADEM occurs more often spontaneously. The interval between infection and onset of symptoms is variable. Typically, the time interval is between 2 days and 4 weeks.

ADEM is associated with a large number of different, in particular viral, infections. The most common trigger is an unspecified upper respiratory tract infection. Many other viral infections have been reported: Coxsackie, HHV-6, EBV, HSV, CMV, HIV, HTLV-1, varicella, measles, mumps, and rubella. Arguably, the non-viral encephalomyelitis in HIV-infected patients with the “common variable immunodeficiency syndrome (CVID)” is a variant of ADEM (Happe and Husstedt 2000).

Compared with the reports on viral infections and ADEM, associations with bacterial or parasitic infections are much more infrequent. Fairly often, an association with intracellular bacteria has been described, above all with Mycoplasma. Anecdotally, ADEM has been reported after infections with Chlamydia, Leptospira, Legionella, Rickettsia, Streptococcus and Salmonella.

Given the enormous number of vaccinations, ADEM should be considered as a very rare complication [for an overview, see Stratton et al. (1994)]. Although the association between vaccination and ADEM may be purely coincidental in some patients, especially in children, in single patients, a causal association is obvious. A high rate of postvaccinal ADEM (0.83%) has been reported after vaccinations against rabies with Semple rabies vaccine produced on neural cell cultures. In developing countries, these sera are still in use due to lower production costs.

Apart from vaccinations and infections, ADEM has been associated with gold therapy, live lamb cell injection, parenteral therapy with herbal extracts (Schwarz et al. 2000), transplantation, bee sting and after accidental inoculation with guinea pig brain tissue.

17.4 Pathophysiological Hypotheses

The pathophysiology of ADEM has not yet been fully elucidated. There is only the general agreement that autoimmune mechanisms may play a key role in postvaccinal and parainfectious ADEM. In idio-