

Neuroimmunological Lessons From Acute Disseminated Encephalomyelitis (ADEM)

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[disclosures: none]**

Major Inflammatory Demyelinating Disorders of the CNS

- **Multiple Sclerosis (MS)**
 - **Acute Disseminated Encephalomyelitis (ADEM)**
 - **Site-restricted disorders (transverse myelitis,
optic neuritis, cerebellitis, etc.)**
-
- **Experimental Autoimmune Encephalomyelitis
(EAE)**

ADEM: Definitions and Features

Clinical

- **rapid onset**
- **focal or multifocal neurologic dysfunction**
- **recent infection or immunization**
- **monophasic course**

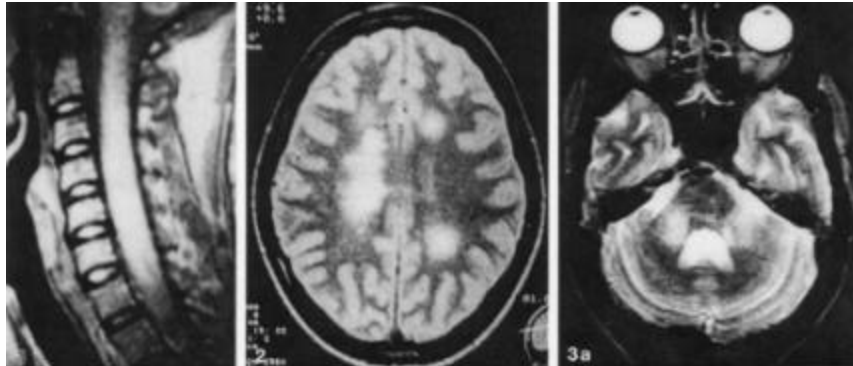
Pathological

- **perivascular inflammation, demyelination**

ADEM: Diagnosis

- **History (antecedent infection or immunization)**
- **Physical and neurological examination**
- **MRI imaging**
- **Cerebrospinal fluid (CSF) analysis**

- **Response to therapy**
- **Clinical and radiographic course over time**



Murthy JM. *Neuroradiology* 1998; 40:420-423

Differentiating ADEM From MS

	Acute Disseminated Encephalomyelitis	Multiple Sclerosis
Presentation	Fever, meningism, seizures, coma; monophasic, pleomorphic	Lesions are separated in time and space; first attack usually occurs without fever or viral ailment
Magnetic resonance imaging	Lesions are large and symmetric; basal ganglia and thalamic involvement	More than four lesions; brainstem involvement
Cerebrospinal fluid	Leukocytosis in 80% of patients; protein level is usually >100 mg/dL, usually no oligoclonal bands are present	Leukocytosis in 33% of patients; protein level is normal in 60% of patients, oligoclonal bands are present
Human lymphocyte antigen allele	No association	Human lymphocyte antigen-DR and DQ regions

ADEM: Precipitating Events

- **Postvaccination encephalomyelitis**
 - rabies
 - others? (influenza, DPT, hepatitis B, etc.)
- **Postinfectious encephalomyelitis**
 - measles
 - others (rubella, mumps, herpesviruses, influenza, mycoplasma, etc.)
- **Drug-induced**
- **Idiopathic**

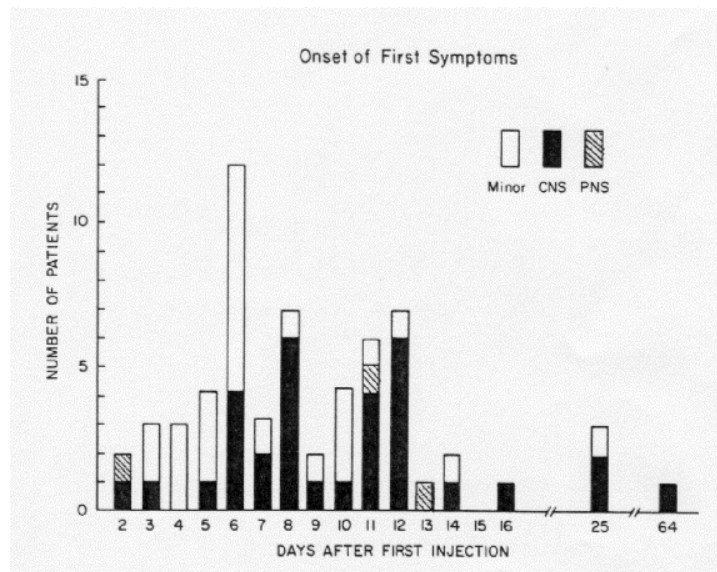
Neurologic Complications of Semple Rabies

Vaccine: Human EAE?

- **1885**: Pasteur uses a spinal cord extract from a rabies-infected rabbit as post-exposure rabies prophylaxis in humans
- **1911**: Semple develops the phenol-inactivated rabies vaccine (sheep or goat brain tissue)
- **1920-present**: “neuroparalytic accidents” occur in ~1:400 Semple rabies vaccine recipients

“SAE”: Simple Vaccine-Induced Autoimmune Encephalomyelitis

- 156 cases out of 59,597 vaccinees in Bangkok, Thailand between 1961 and 1970 (~1:400)
- 61 cases prospectively identified between 4/84 and 6/85 for further clinical and immunological study
- major complications (n=36) included encephalitis, myelitis, polyradiculitis, or meningitis; minor complications (n=25) included headache, fever, inflamed injection sites, and normal CSF



Hemachuda et al. *Neurology* 1987; 37:550-556

	CNS	PNS	Meningitis	Total (%)
Clinical course				
Recovery				
Complete	17	—	13	30 (83.3)
Incomplete	2	3	—	5 (13.9)
Death	—	1	—	1 (2.8)
Duration of disease				
1 to 3 days	5	—	1	6 (16.6)
4 to 6 days	3	—	8	11 (30.6)
7 to 9 days	3	2	3	8 (22.2)
10 to 12 days	1	—	1	2 (5.6)
More than 12 days	7	2	—	9 (25.0)

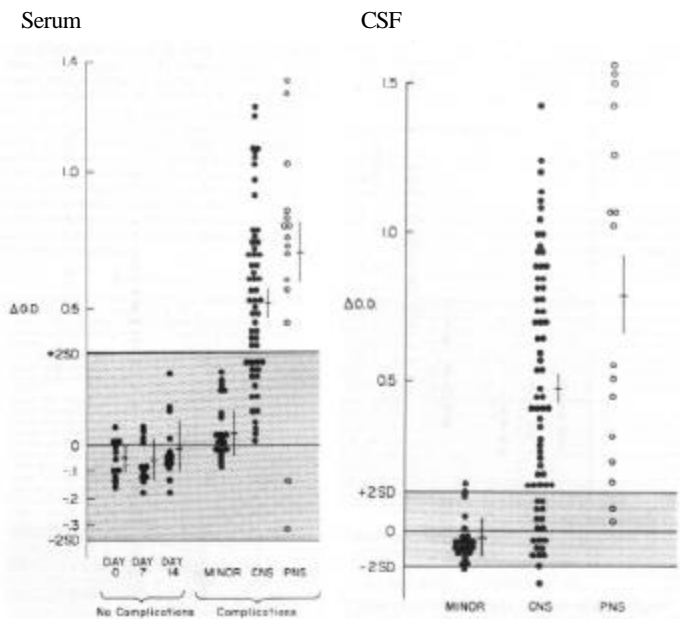
CNS, PNS = Patients with central nervous and peripheral nervous system (polyradiculitis) complications, respectively.

Hemachuda et al. *Neurology* 1987; 37:550-556

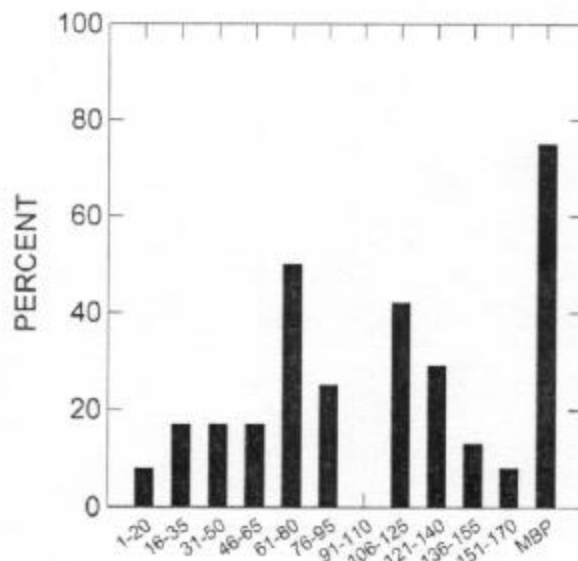
Lymphoproliferation to Purified Myelin Basic Protein (MBP) in Simple Vaccine Recipients

Group	SI	SI >2.0
• uncomplicated vaccine		
– Day 0	1.3 ± 0.1	0/13
– Day 7	0.9 ± 0.2	0/10
– Day 14	1.1 ± 0.2	0/16
• minor complications	1.2 ± 0.1	0/3
• major complications	2.4 ± 0.4	4/6

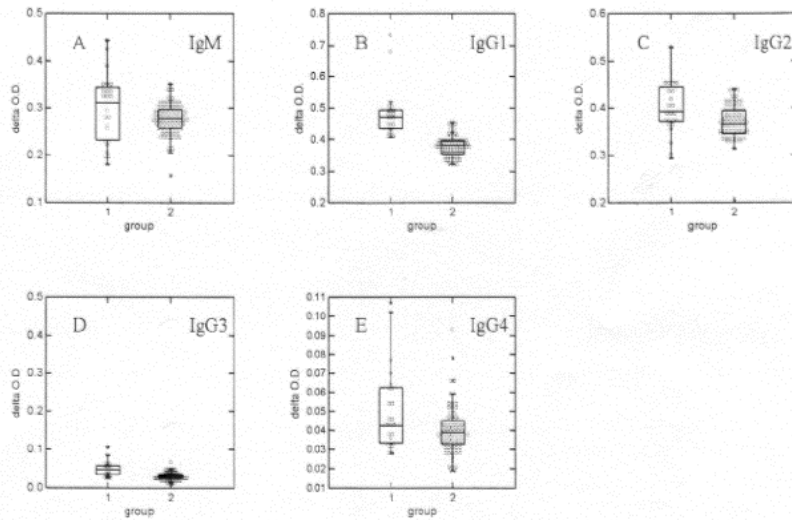
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Hemachuda et al. *New Engl J Med* 1987; 316:369-374



Piyasirisilp S, et al. *J Neuroimmunol* 1999; 98:96-104



Piyasirisilp S, et al. *J Neuroimmunol* 1999; 98:96-104

DR	SAE Patients (n = 18)	Vaccinated Controls (n = 43)	Unvaccinated Controls (n = 140)
1	0	1.2	0.4
4	16.7	9.3	11.4
7	8.3	8.1	14.3
8	2.8	4.7	2.8
9 ^a	22.2	12.8	8.6
10	5.5	9.3	2.9
11 (5)	5.6	5.8	6.4
12 (5)	5.5	11.6	19.6
13 (6)	0	2.3	4.3
14 (6)	8.3	7.0	4.3
15 (2)	8.3	16.3	17.9
16 (2)	2.8	5.8	2.8
17 (3) ^{a,b}	14.0	5.8	4.3
Total	100	100	100

The serological split terminologies of DR alleles are indicated in parentheses.

^aThe odds ratios of having DR9 (DRB1*0901) and DR17 (DRB1*0301) in SAE patients compared with unvaccinated controls were 3.0 ($p = 0.018$) and 3.6 ($p = 0.032$), respectively.

^bThere were no DR18 (3) alleles in these three groups.

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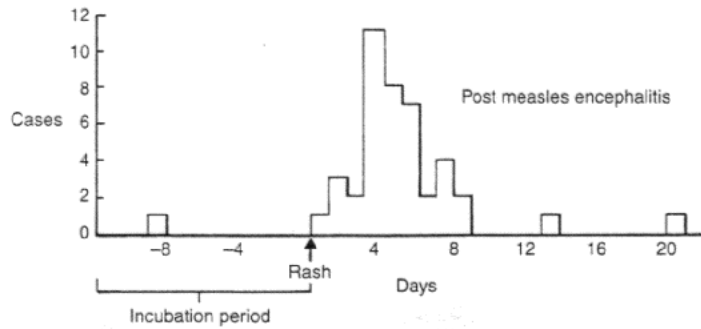
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Measles Encephalomyelitis

- complicates 1:1000 cases of acute measles in children > 2 years of age
- distinct from both SSPE and inclusion-body encephalitis seen in immunocompromised hosts
- 10-20% acute mortality; long-term neurologic sequelae are common in survivors
- EAE-like pathology
- no evidence of direct virus infection within the CNS or virus-specific antibody in the CSF



Measles Encephalomyelitis: Circulating T Cells React to MBP

<u>Group</u>	<u>SI >2.0</u>
• Measles	
– encephalomyelitis	11/17*
– uncomplicated disease	5/42
• Controls	
– other demyelinating diseases	3/3
– other neurological diseases	1/27
– normal children	0/6

Pathogenesis of Measles Encephalomyelitis: Molecular Mimicry?

- antigen-specific T cells generated against viral peptides cross-react to myelin epitopes,
AND/OR
- infection activates pre-existing myelin-specific T cells in the periphery
- activated, myelin-specific T cells enter the CNS
- immune-mediated destruction of myelin (and axons?)

	Experimental autoimmune encephalomyelitis	Postrabies vaccine encephalomyelitis	Postinfectious encephalomyelitis
Inducing event	Inoculation with CNS tissue or myelin basic protein	Inoculation with CNS tissue	Infection with enveloped viruses
Latent period (days)	10–21	7–42	10–40 ^a
Clinical forms			
Acute onset	+	+	+
Monophasic disease	+	+	+
Occasional chronic or relapsing forms	+	+	+
Pathologic findings			
Perivenular lymphocytes	+	+	+
Perivenular demyelination	+	+	+
Immunologic studies			
Lymphocytes stimulated <i>in vitro</i> by myelin basic protein	+	+	+
<i>In vitro</i> demyelination by lymphocytes	+	?	+
Antimyelin protein antibodies	+	+	-

^aFrom the beginning of the incubation periods.

Immunologic Differences in Human CNS Inflammatory/Demyelinating Disorders

	<u>MS</u>	<u>SAE</u>	<u>ADEM</u>
• HLA linkages	-DR2	-DR9 -DR17	-DR4 -DR5
• Primary MBP Ab epitope	84-96	61-80	N/A

Conclusions

- **ADEM is an inflammatory/demyelinating CNS disorder, usually having a monophasic course**
- **it often occurs on the heels of a vaccination or infection**
- **many ADEM patients show enhanced immune responses against myelin antigens (MBP)**