

(Neuroimmunological) Lessons From Acute Disseminated Encephalomyelitis (ADEM)

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Major Inflammatory Demyelinating Disorders of the CNS

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

ADEM: Definitions and Features

Clinical

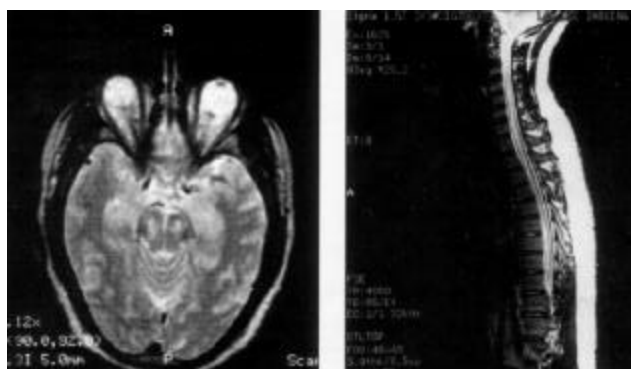
- rapid onset
- focal or multifocal neurologic dysfunction
- recent infection or immunization
- monophasic course

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



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 illness
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 the 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)

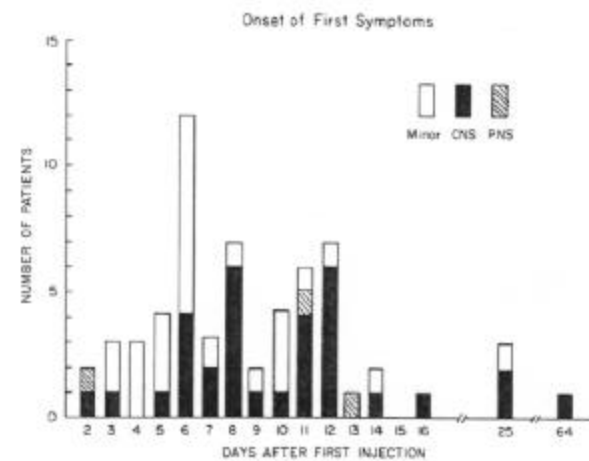
1920-present: "neuroparalytic accidents" occur in ~1:400 Semple rabies vaccine recipients

"SAE": Semple 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 study

•major complications (36) included encephalitis, myelitis, polyradiculitis, or meningitis; minor complications (25) included headache, fever, inflamed injection sites, and normal CSF

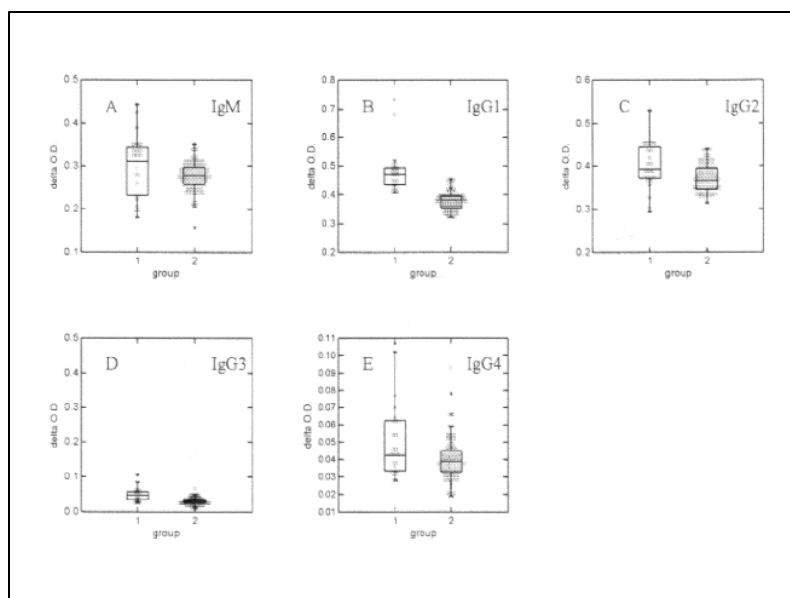
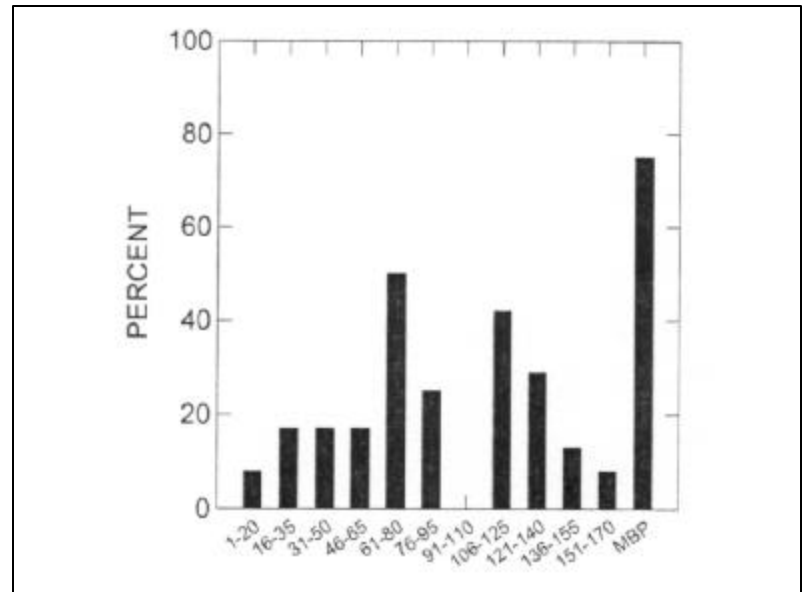
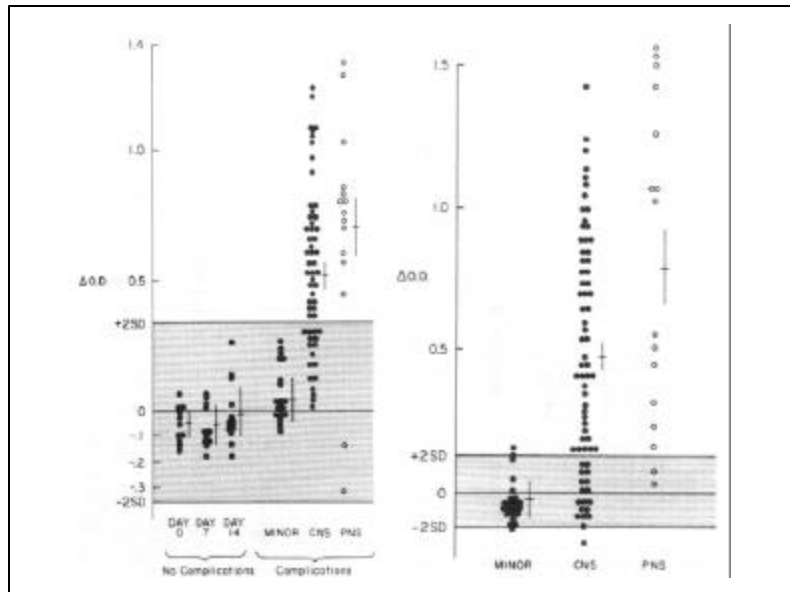


	CNS	PNS	Meningitis	Total (%)
Clinical course				
Recovery				
Complete	17	—	13	30 (83.3)
Incomplete	2	3	—	5 (13.9)
Death	—	1	—	1 (2.5)
Duration of disease				
1 to 3 days	5	—	1	6 (16.6)
4 to 6 days	3	—	8	11 (30.6)
7 to 9 days	3	2	3	8 (22.2)
10 to 12 days	1	—	1	2 (5.6)
More than 12 days	7	2	—	9 (25.0)

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

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

Group	SI ± SEM	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	2.1 ± 0.4	4/6



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*	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) [†]	14.0	5.8	4.3
Total	100	100	100

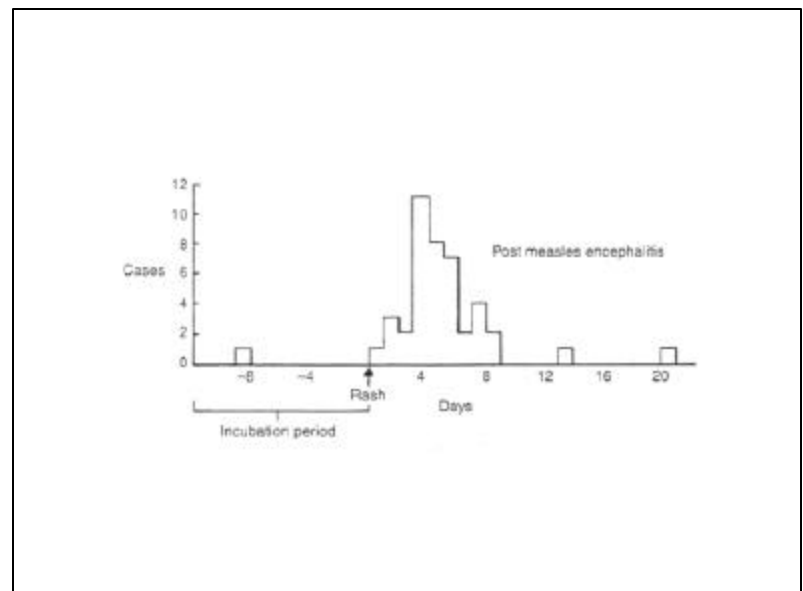
The serological split terminologies of DR alleles are indicated in parentheses.

*The 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.

[†]There were no DR18 (3) alleles in these three groups.

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 immunodeficient 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



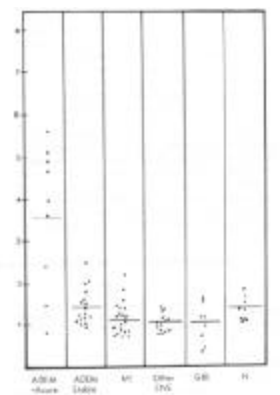
Measles Encephalomyelitis: Circulating T Cells Are Highly Reactive to Myelin Antigens (MBP)

Group	SI >2.0
Measles	
encephalomyelitis	11/17*
uncomplicated disease	5/42
Controls	
other demyelinating diseases	3/3
other neurologic diseases	2/17
normal children	0/6

Pathogenesis of Measles (Postinfectious) Encephalomyelitis: Molecular Mimicry?

- antigen-specific T cells generated against viral peptides cross-react to self (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?)

Lymphoproliferation To Human Myelin Basic Protein



	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*
Clinical forms			
Acute onset	+	+	+
Monophasic disease	+	+	+
Occasional chronic or relapsing forms	+	+	+
Pathologic findings			
Perivascular lymphocytes	+	+	+
Perivascular demyelination	+	+	+
Immunologic studies			
Lymphocytes stimulated in vitro by myelin basic protein	+	+	+
In vitro demyelination by lymphocytes	+	?	+
Antimyelin protein antibodies	+	+	-

*From the beginning of the incubation periods.

Subtle Immunologic Differences in the Human CNS Inflammatory/Demyelinating Disorders

	MS	SAE	ADEM
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 with a monophasic course
- it often occurs shortly after a vaccination or infection
- many ADEM patients show enhanced immune responses against myelin antigens (MBP)

**ADEM: Are There Immunologic Lessons Which
Can Be Applied to TM?**

Questions:

- Is acute TM associated with elevated cellular and/or humoral immune responses to myelin?
- Could there be other spinal cord-specific target antigens involved?
- Can any of these early immune responses be correlated with the clinical course of disease?
- How can the identification of such immune responses be translated into more rational therapy?