

# **(Neuroimmunological) Lessons From Acute Disseminated Encephalomyelitis (ADEM)**

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# Major Inflammatory Demyelinating Disorders of the CNS

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- 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

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## Clinical

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

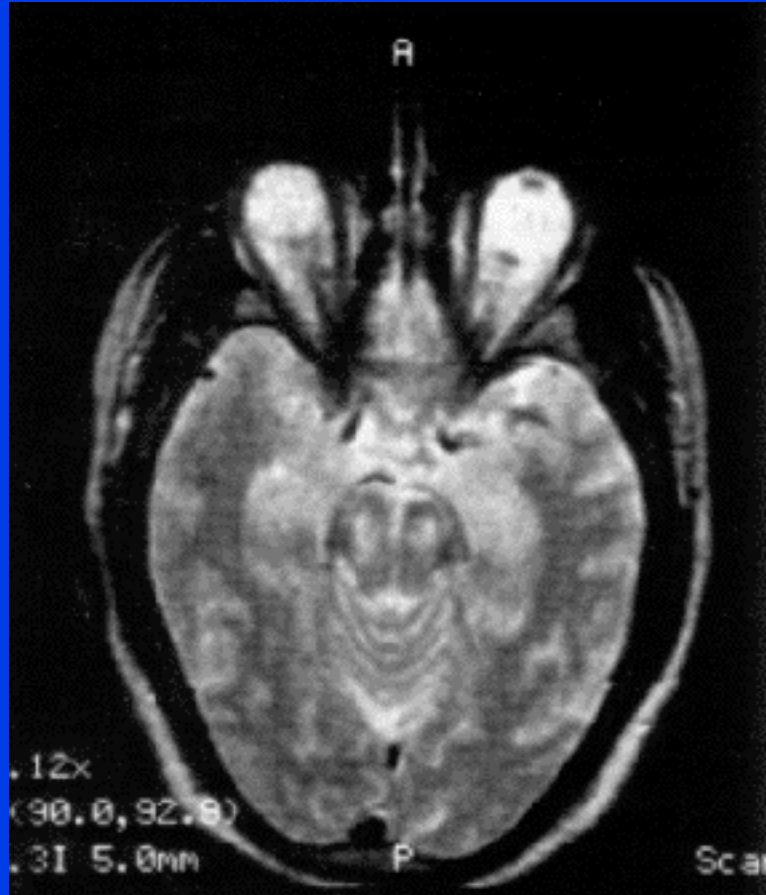
## Pathological

- perivascular inflammation, demyelination

## **ADEM: Diagnosis**

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- **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

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	<b>Acute Disseminated Encephalomyelitis</b>	<b>Multiple Sclerosis</b>
<b>Presentation</b>	Fever, meningism, seizures, coma; monophasic, pleomorphic	Lesions are separated in time and space; first attack usually occurs without fever or viral ailment
<b>Magnetic resonance imaging</b>	Lesions are large and symmetric; basal ganglia and thalamic involvement	More than four lesions; brainstem involvement
<b>Cerebrospinal fluid</b>	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
<b>Human lymphocyte antigen allele</b>	No association	Human lymphocyte antigen-DR and DQ regions

# ADEM: Precipitating Events

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## 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?

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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)

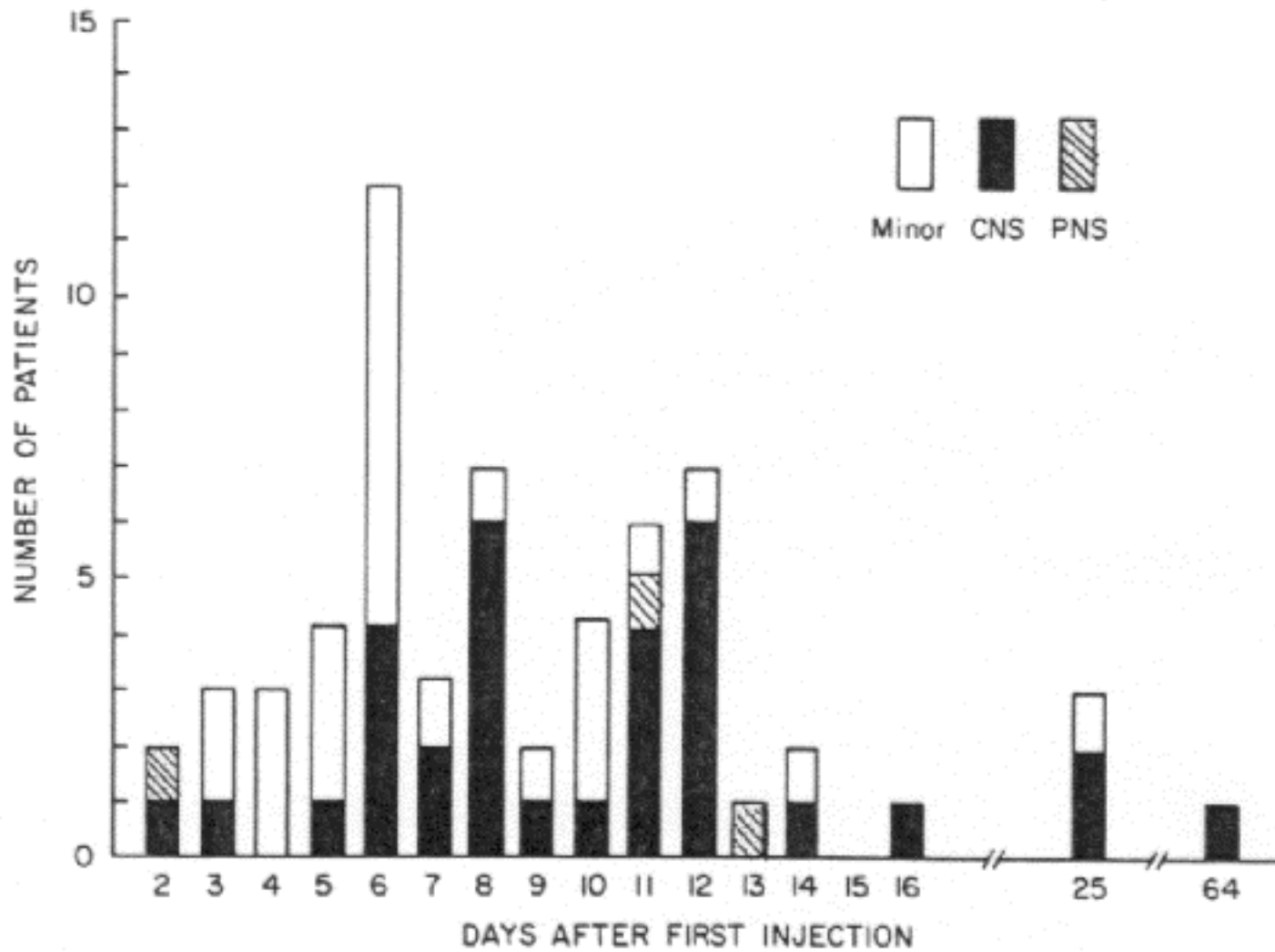
1920-present: “neuromyolytic accidents” occur in ~1:400 Semple rabies vaccine recipients

## **“SAE”: Semple vaccine-induced Autoimmune Encephalomyelitis**

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- **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**

### Onset of First Symptoms



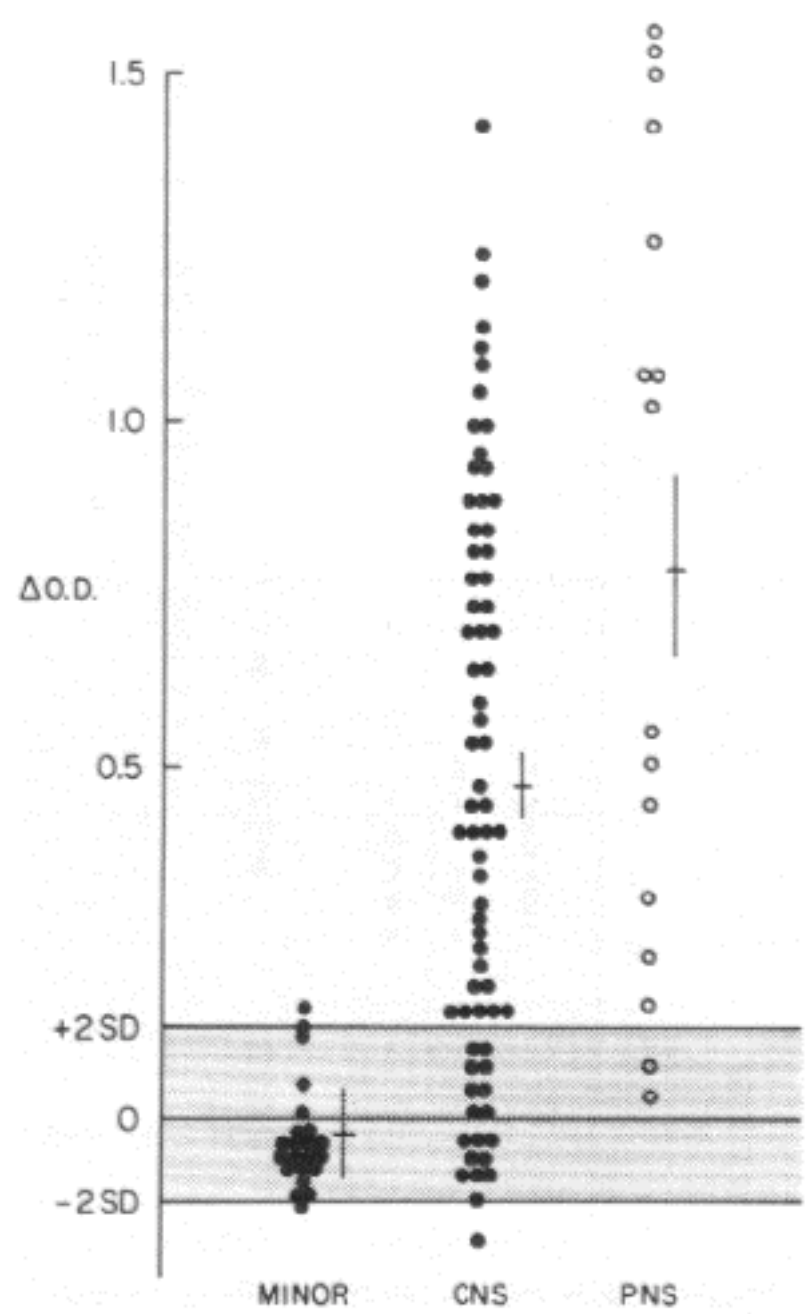
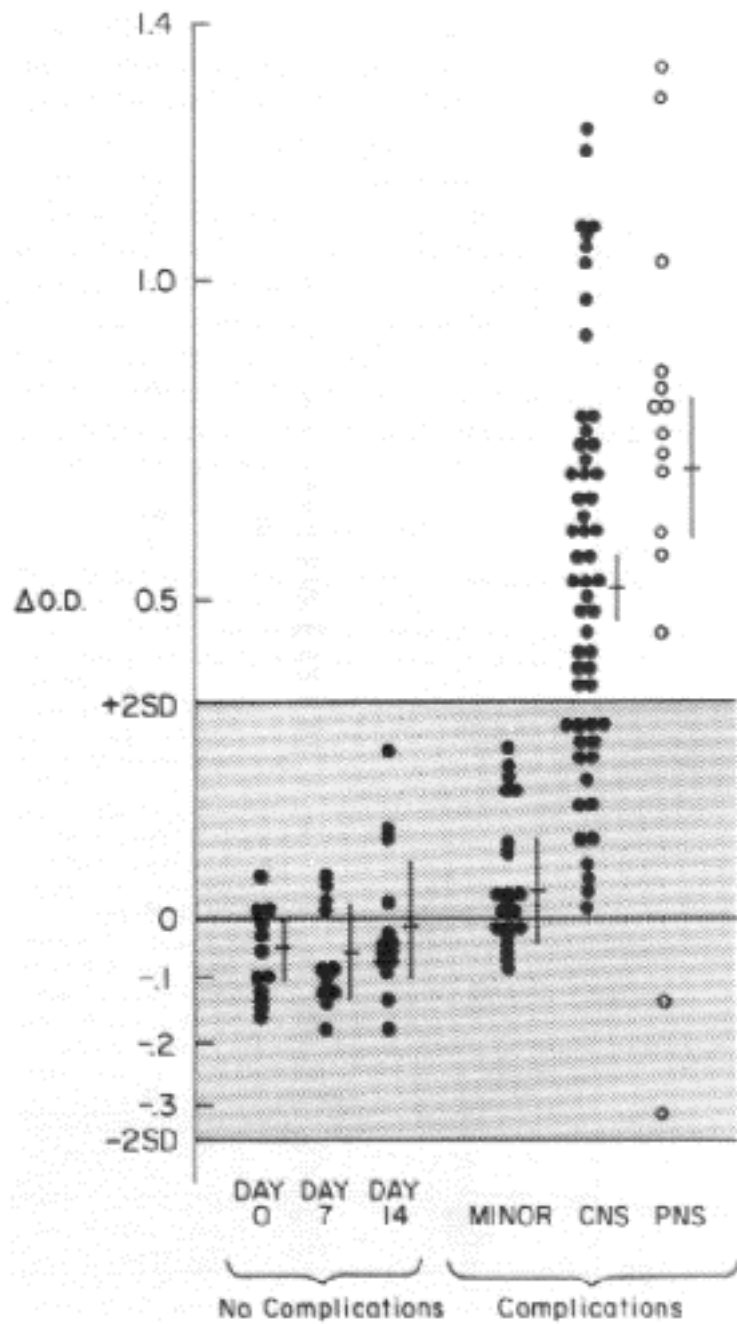
	CNS	PNS	Meningitis	Total (%)
<b>Clinical course</b>				
<b>Recovery</b>				
Complete	17	—	13	30 (83.3)
Incomplete	2	3	—	5 (13.9)
Death	—	1	—	1 (2.8)
<b>Duration of disease</b>				
1 to 3 days	5	—	1	6 (16.6)
4 to 6 days	3	—	8	11 (30.6)
7 to 9 days	3	2	3	8 (22.2)
10 to 12 days	1	—	1	2 (5.6)
More than 12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

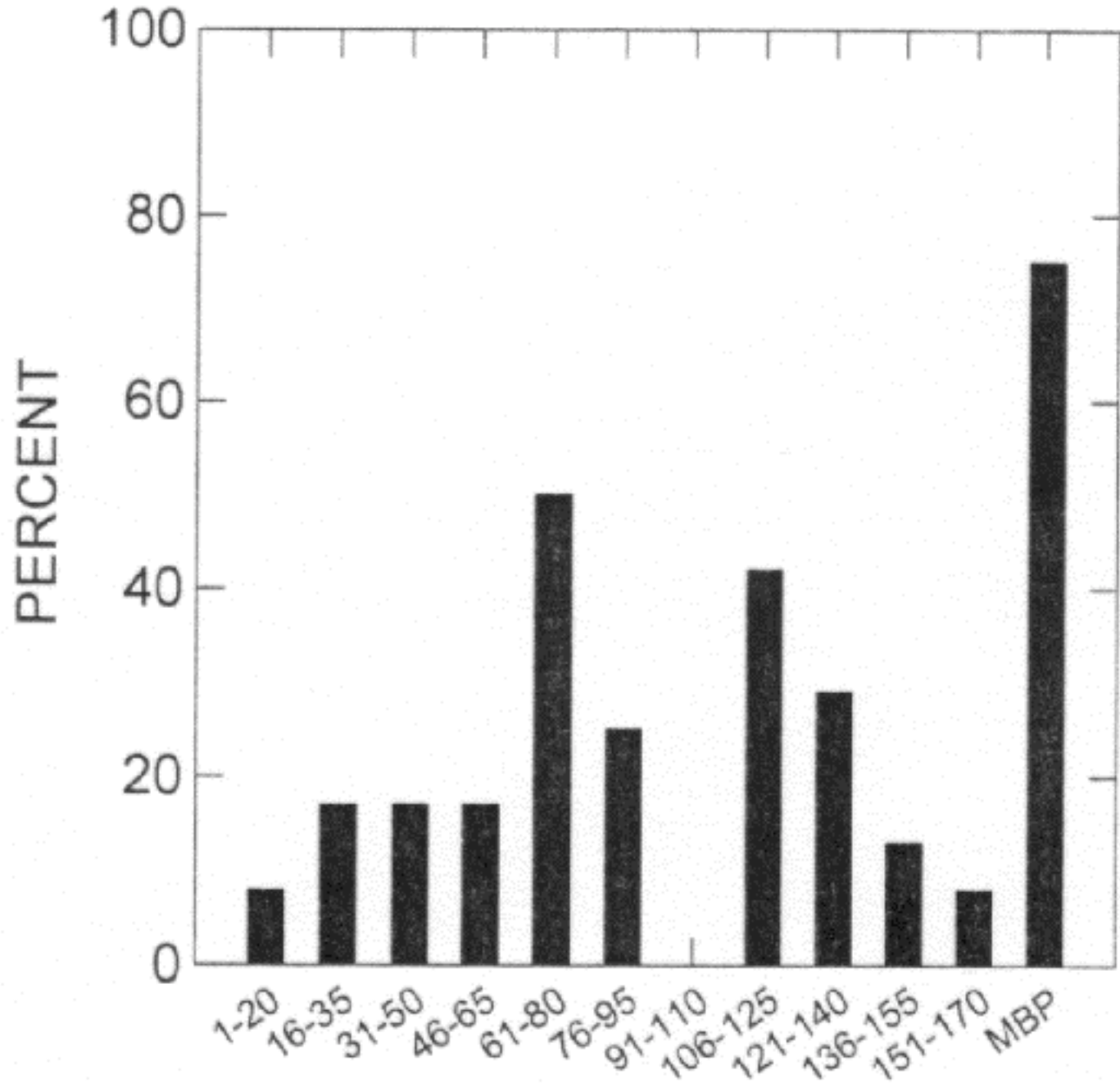
CNS, PNS = Patients with central nervous and peripheral nervous system (polyradiculitis) complications, respectively.

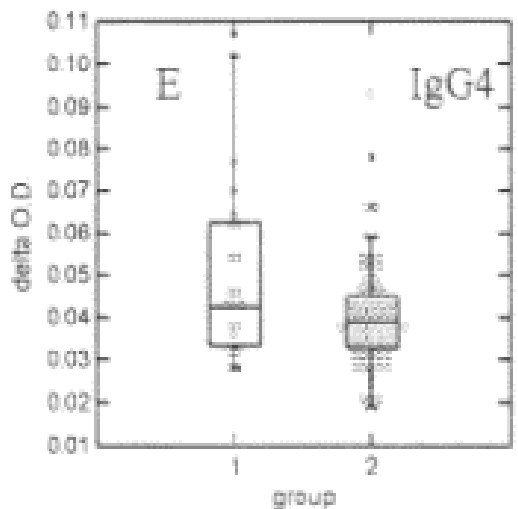
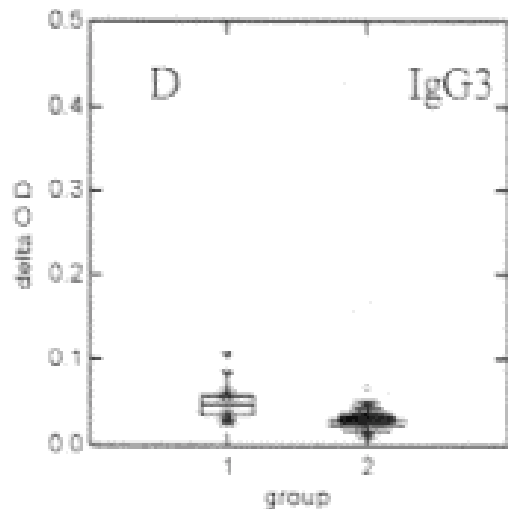
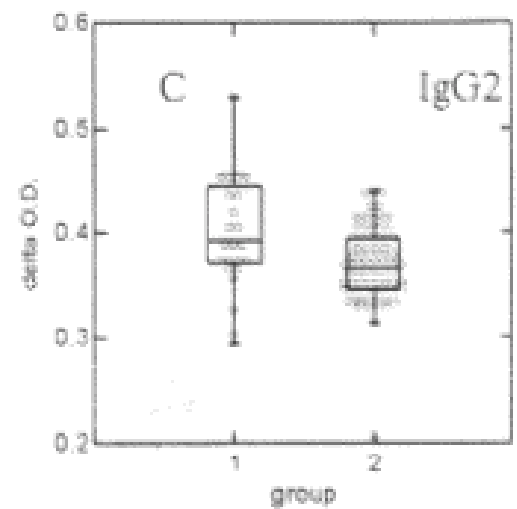
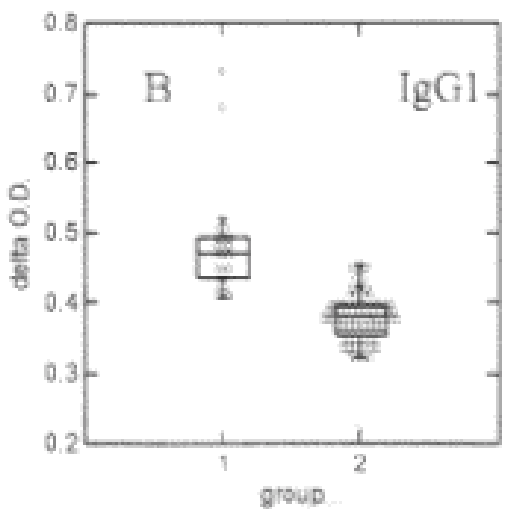
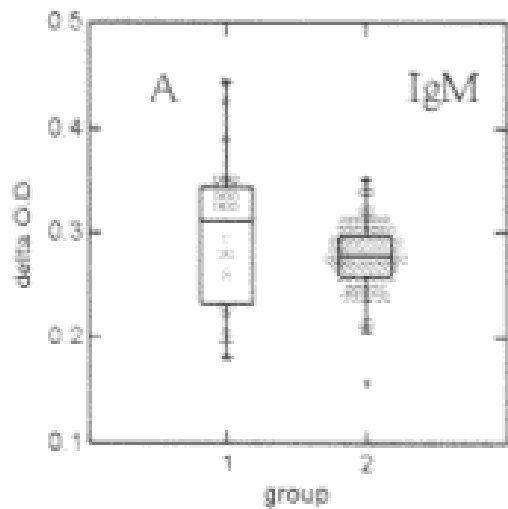
## Lymphoproliferation to Purified Myelin Basic Protein (MBP) in Simple Vaccine Recipients

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<u>Group</u>	<u>SI <math>\pm</math> SEM</u>	<u>SI &gt;2.0</u>
<b>uncomplicated vaccine</b>		
Day 0	1.3 $\pm$ 0.1	0/13
Day 7	0.9 $\pm$ 0.2	0/10
Day 14	1.1 $\pm$ 0.2	0/16
<b>minor complications</b>	1.2 $\pm$ 0.1	0/3
<b>major complications</b>	2.1 $\pm$ 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 <sup>a</sup>	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) <sup>a,b</sup>	14.0	5.8	4.3
Total	100	100	100

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

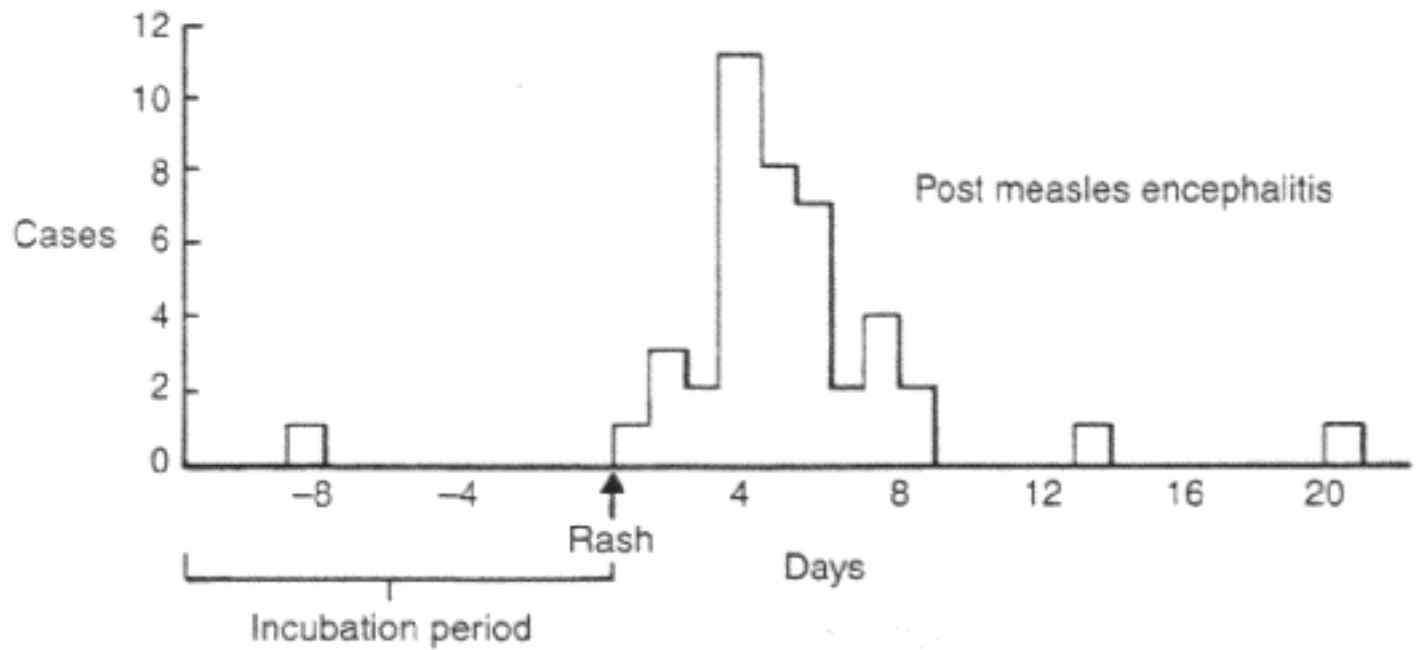
<sup>a</sup>The odds ratios of having DR9 (DRB1\*0901) and DR17 (DRB1\*0301) in SAE patients compared with unvaccinated controls were 3.0 ( $p = 0.018$ ) and 3.6 ( $p = 0.032$ ), respectively.

<sup>b</sup>There were no DR18 (3) alleles in these three groups.

## Measles Encephalomyelitis

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- 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)

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

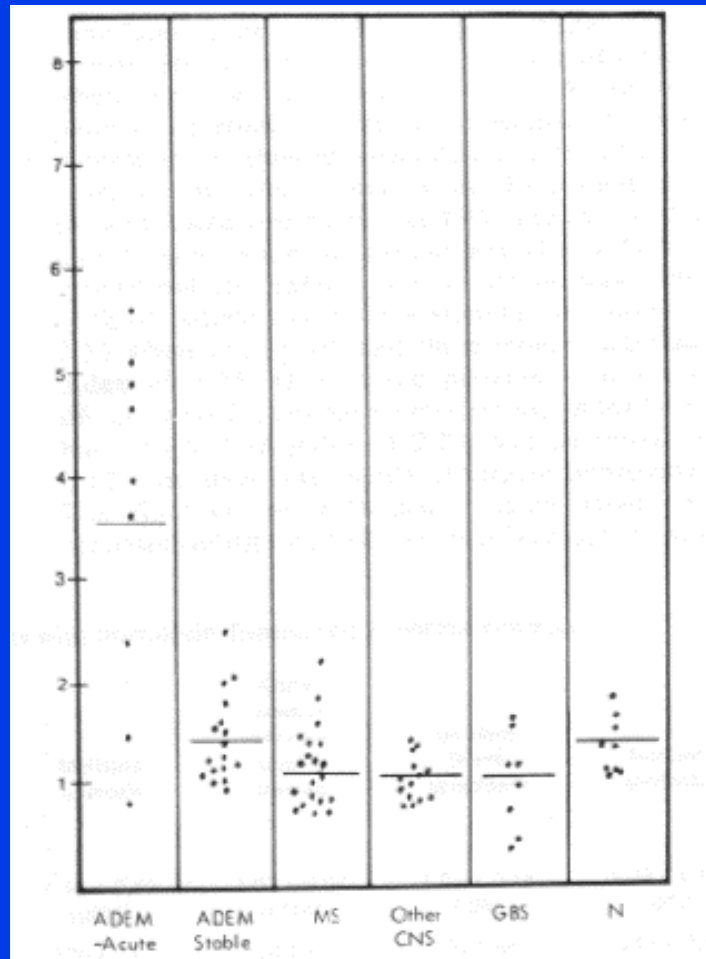
## **Pathogenesis of Measles (Postinfectious) Encephalomyelitis: Molecular Mimicry?**

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- 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

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	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 <sup>a</sup>
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	+	+	-

<sup>a</sup>From the beginning of the incubation periods.

# Subtle Immunologic Differences in the Human CNS Inflammatory/Demyelinating Disorders

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	<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

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- **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?**

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### **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?**