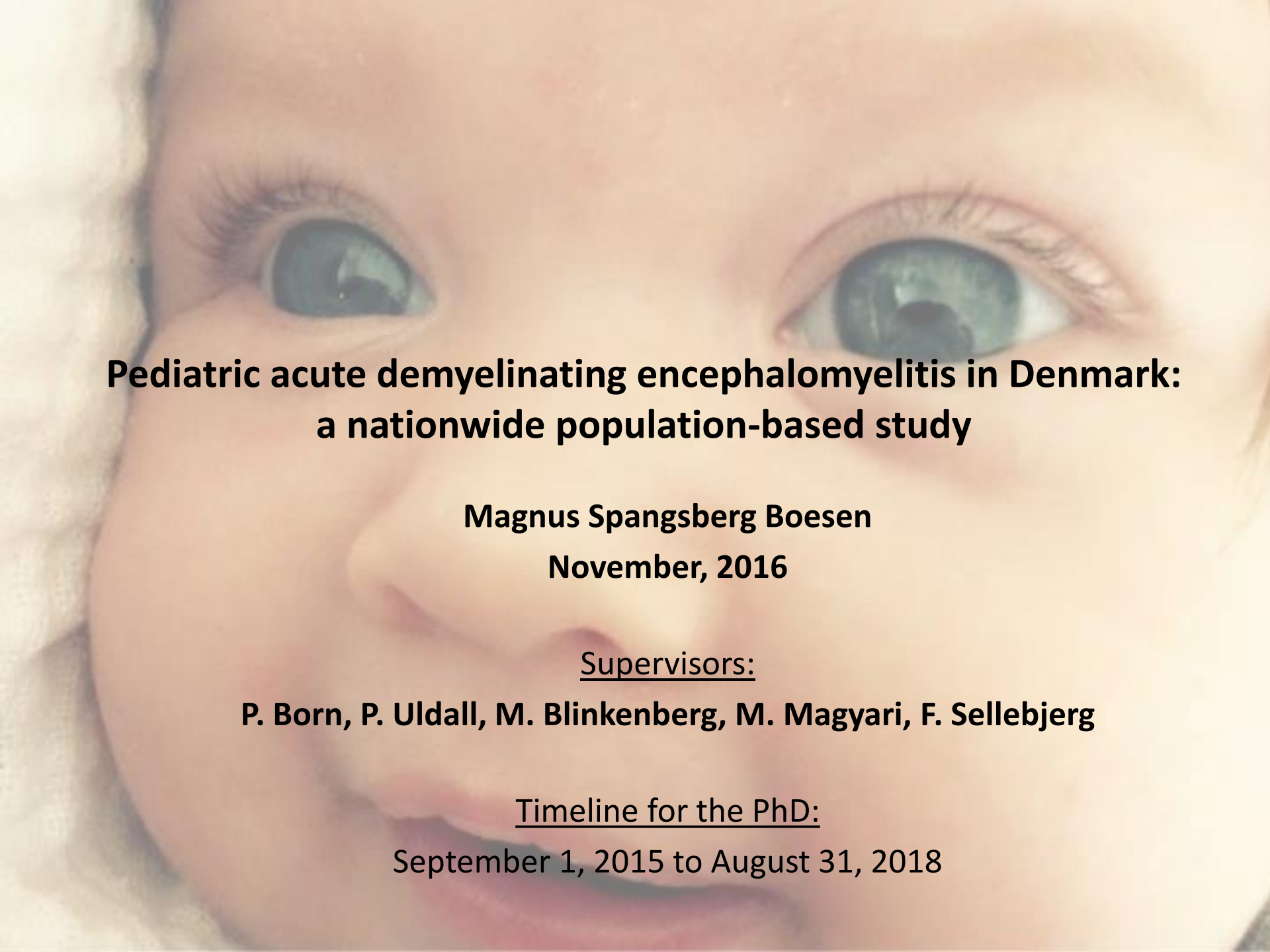

Pediatric acute demyelinating encephalomyelitis in Denmark: a nationwide population-based study

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Supervisors:

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Timeline for the PhD:

September 1, 2015 to August 31, 2018

Magnus Spangsberg Boesen

Medical doctor, University of Copenhagen (2012)

Pediatrics (1 year)

Neurology (1.5 years)

Now: PhD student

Paper:

Onset symptoms in paediatric multiple sclerosis. DMJ. 2014

Agenda

Background :

-Definition of acute disseminated encephalomyelitis (ADEM) and MS?

-Literature review: How many children with ADEM progress to MS?

My study:

-Pediatric acute demyelinating encephalomyelitis in Denmark: a nationwide population-based study

Diagnostic criteria for pediatric ADEM

The International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed the following criteria (2011) - all are required:

1) A first **polyfocal**, clinical CNS event with presumed inflammatory **demyelinating** cause

2) **Encephalopathy** that cannot be explained by fever:

- alteration in **consciousness** (e.g. stupor, lethargy) or **behavioral change** unexplained by fever, systemic illness or postictal symptoms

3) **No new clinical and MRI findings** emerge **three months** or more after the onset

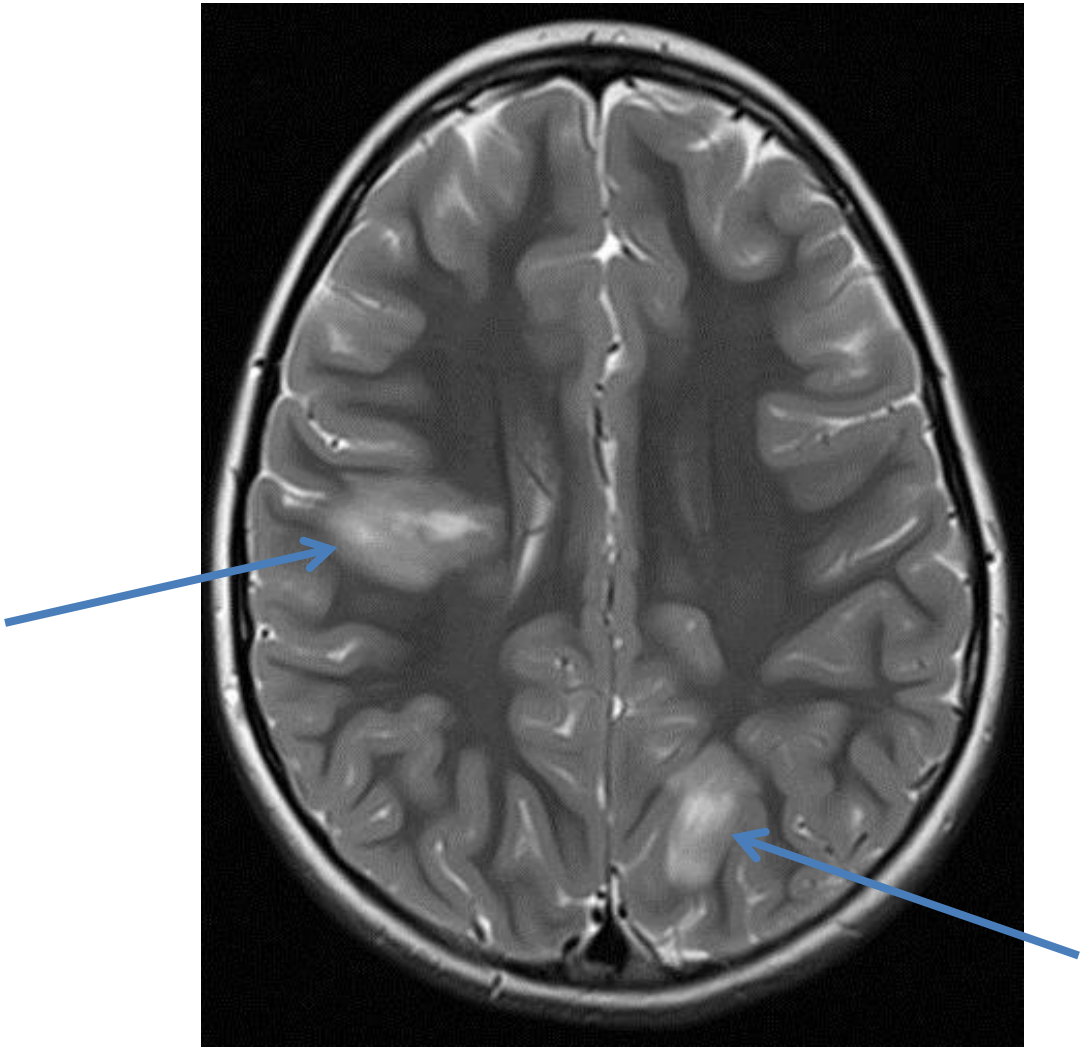
4) Brain **MRI** is **abnormal** during the acute (three-month) phase

5) Typically on brain MRI:

- **Diffuse, poorly demarcated**, large (>1–2 cm) lesions involving predominantly the cerebral **white matter**
- T1 hypointense lesions in the white matter are rare
- Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

Krupp et al. Mult Scler. 2013

MR cerebrum



What is required for a diagnosis of MS after ADEM?

When a **second clinical event** meets the following **three requirements**:

1) Is **non-encephalopathic**

2) Occurs **three or more months** after the incident neurologic illness

3) Is associated with new **MRI findings consistent with revised radiologic criteria for dissemination in space** (DIS)

Krupp et al. Mult Scler. 2013

8–28% progress from ADEM to MS (follow-up 0.5-6.6 years)

However, **definitions of ADEM and progression to MS differ!**

One or two other non-ADEM events necessary for disease progression to MS?

Encephalopathy or polyfocal neurological deficits required for ADEM?

Studies:
Banwell et al. Lancet Neurol 2011
Dale et al, Dev Med Child Neurol. 2007
Tenembaum et al, Neurology. 2002
Suppeij et al, Pediatric Neurology. 2008
Neutoboom et al, Neurology. 2008
Mikaeloff et al, J Eur Paediatr Neurol Soc. 2007
Mikaeloff et al, The Journal of Paediatrics. 2004

Our ADEM study

Methods:

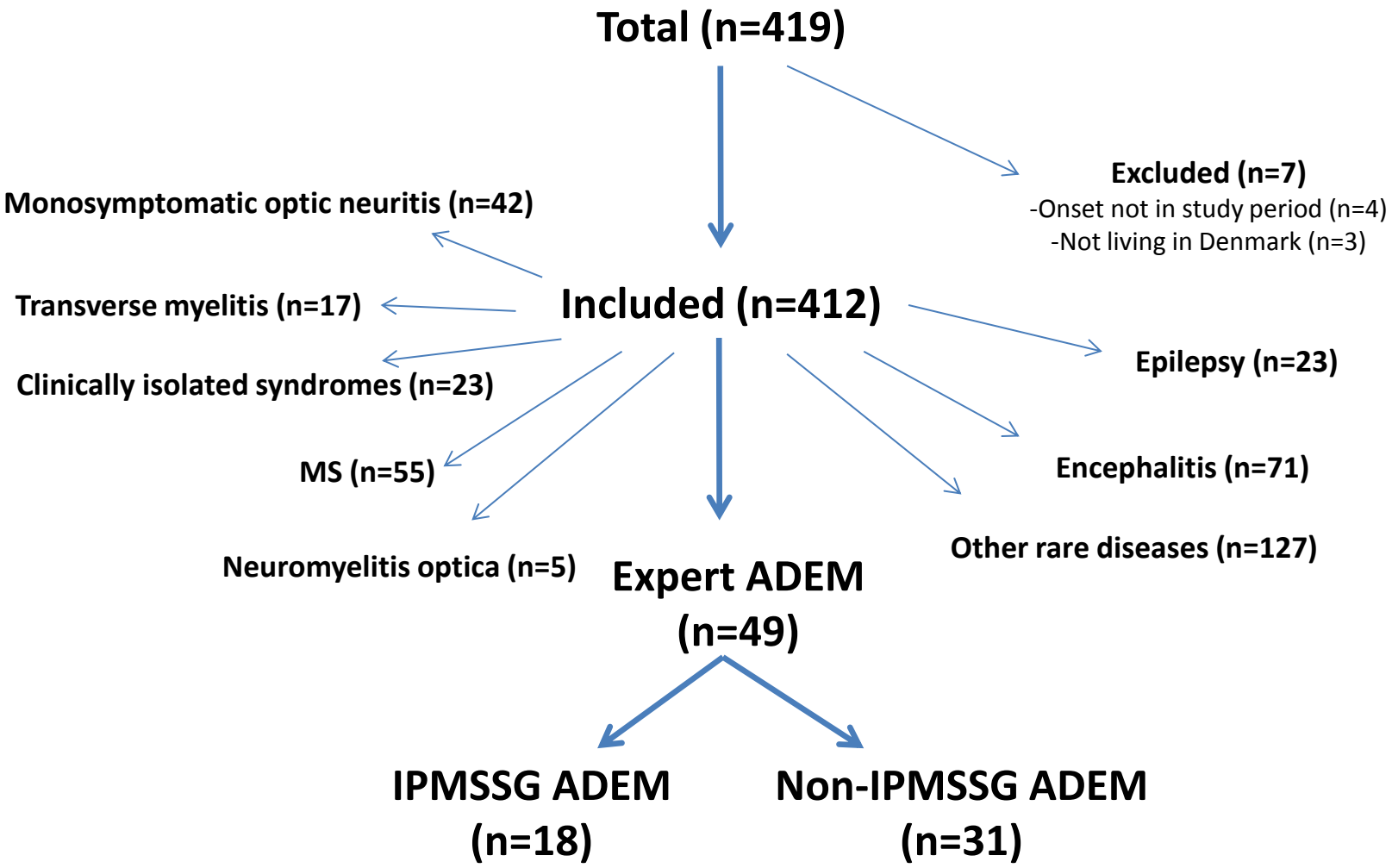
Nationwide population-based cohort study in **Denmark** from **2008–2015**

Children under 18 years of age at onset

Identification of patients in the National Patient Registry with a ***possible*** **ADEM diagnosis code in ICD-10**

All medical records were subsequently **reviewed** by an expert group consisting of a fellow neurologist (M.S.B) and a senior pediatric neurologist (A.P.B)

Results – Flow diagram



Results – Diagnostic criteria

"Expert ADEM" vs "IPMSSG ADEM"

The expert group diagnosed 49 children with ADEM. All had an abnormal MRI.

However, only 18/49=**37%** of patients diagnosed with ADEM fulfilled the IPMSSG diagnostic criteria

Encephalopathy			
No		Yes	
12		37	
Polyfocal		**Polyfocal**	
No	Yes	No	Yes
7	5	19	18

Clinical data

"Expert ADEM" vs "IPMSSG ADEM"

	Expert ADEM (n=49)	IPMSSG ADEM (n=18)	NON-IPMSSG ADEM (n=31)
Demographical features			
Age at onset, y, median (range)	5.4 (0.8-17.2)	3.9 (1.0-15.0)	7.8 (0.8-17.2)
Age at the end of FU, y, median	10.0 (2.0-24.3)	8.3 (5.7-23.2)	11.6 (2.0-24.3)
Male gender, (%)	61%	56%	64%
Antecedent vaccination	4%	6%	3%
Onset symptoms, (%)			
Infection/feber	82%	83%	81%
Seizures	16%	28%	9%
Degree of symptom remission			
Complete	69%	56%	77%

No patients progressed to MS; however three patients deserve further explanation:

1) 8 yrs boy with encephalopathy, diplopia, paresis, urinary retention. His CSF revealed pleocytosis (61 leucocytes), increased protein (0.69 gram/liter), negative oligoclonal band, and positivity for myelin oligodendrocyte glycoprotein. MRI with white matter lesions in cerebrum, brain stem and spinal cord. **2 months later ON**; treated with interferon beta-1a.

2) 8 yrs boy with encephalopathic ADEM. Previous history with **TM**

3) One patients with "IPMSSG ADEM" had **accrual of MRI white matter lesions**, but **no clinical** relapse; treated with interferon beta-1a

None had relapse of ADEM

Cerebrospinal fluid

"Expert ADEM" vs "IPMSSG ADEM"

	Expert ADEM (n=49)	IPMSSG ADEM (n=18)	NON-IPMSSG ADEM (n=31)
CSF data, (%)			
Leucocytosis (>5)	80%	73%	83%
Protein increased	26%	18%	30%
IgG index positive	37%	50%	31%
Oligoclonal bands present	5%	20%	0

80% had **pleocytosis**

26% had increased **protein**

"IPMSSG ADEM" was more likely to have **positive IgG index** and **oligoclonal bands**

MRI features

"Expert ADEM" vs "IPMSSG ADEM"

	Expert ADEM (n=49)	IPMSSG ADEM" (n=18)	NON-IPMSSG ADEM (n=31)
MRIs performed, n, median (range)	3 (1-11)	3 (1-11)	3 (1-5)
Lesions on initial MRI, (%)			
White matter lesions	98%	100%	97%
Bilaterale lesions	90%	89%	87%
Basal ganglia lesions	59%	53%	62%
Gadolinium enhancement	27%	27%	27%
Features on most recent MRI, (%)			
Complete resolution	39%	22%	48%

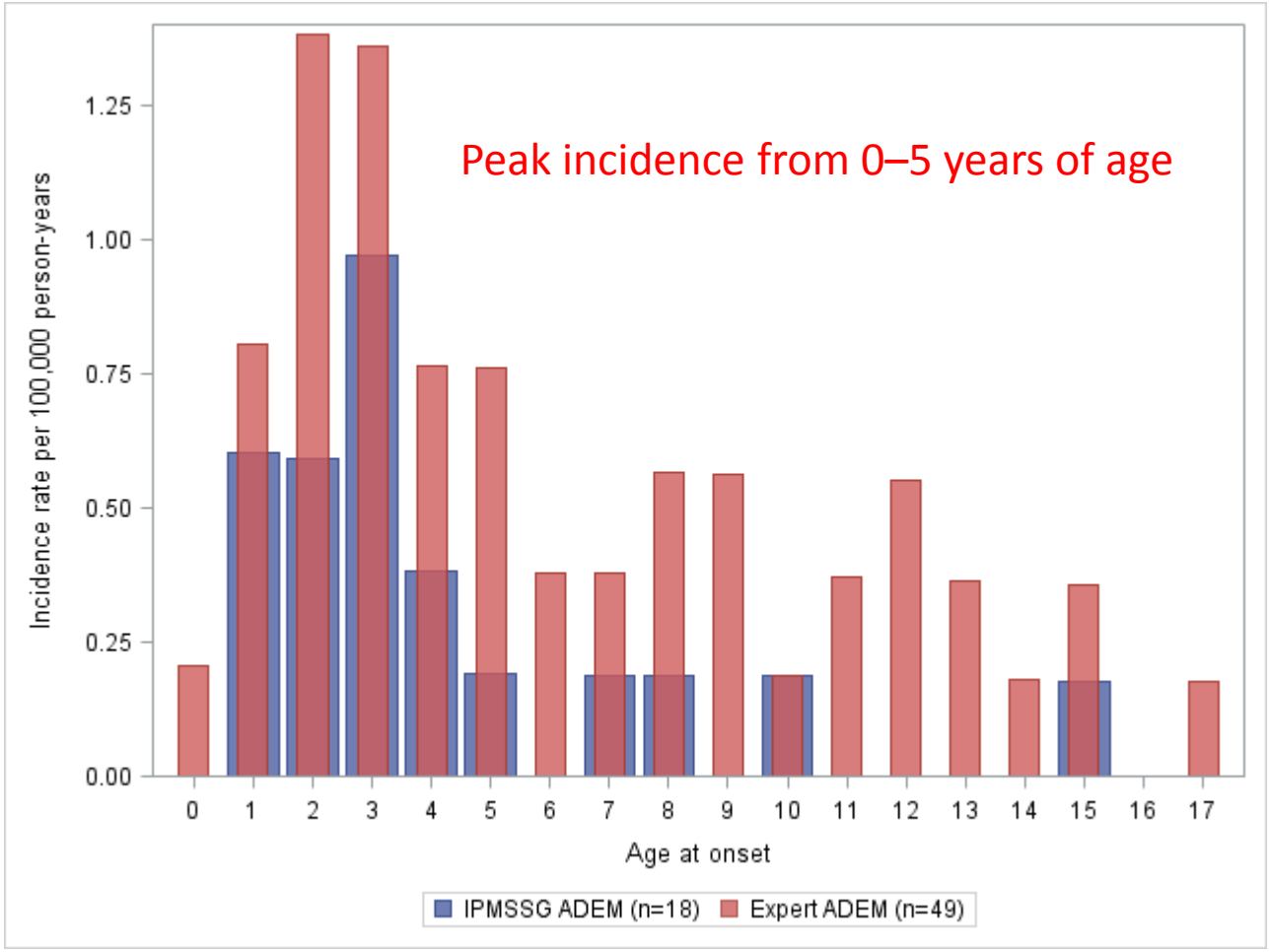
Virtually all had **white matter lesions** suggestive of ADEM in **both hemispheres**

50% had **basal ganglia lesions**

Approximately **30%** had **gadolinium enhancement**

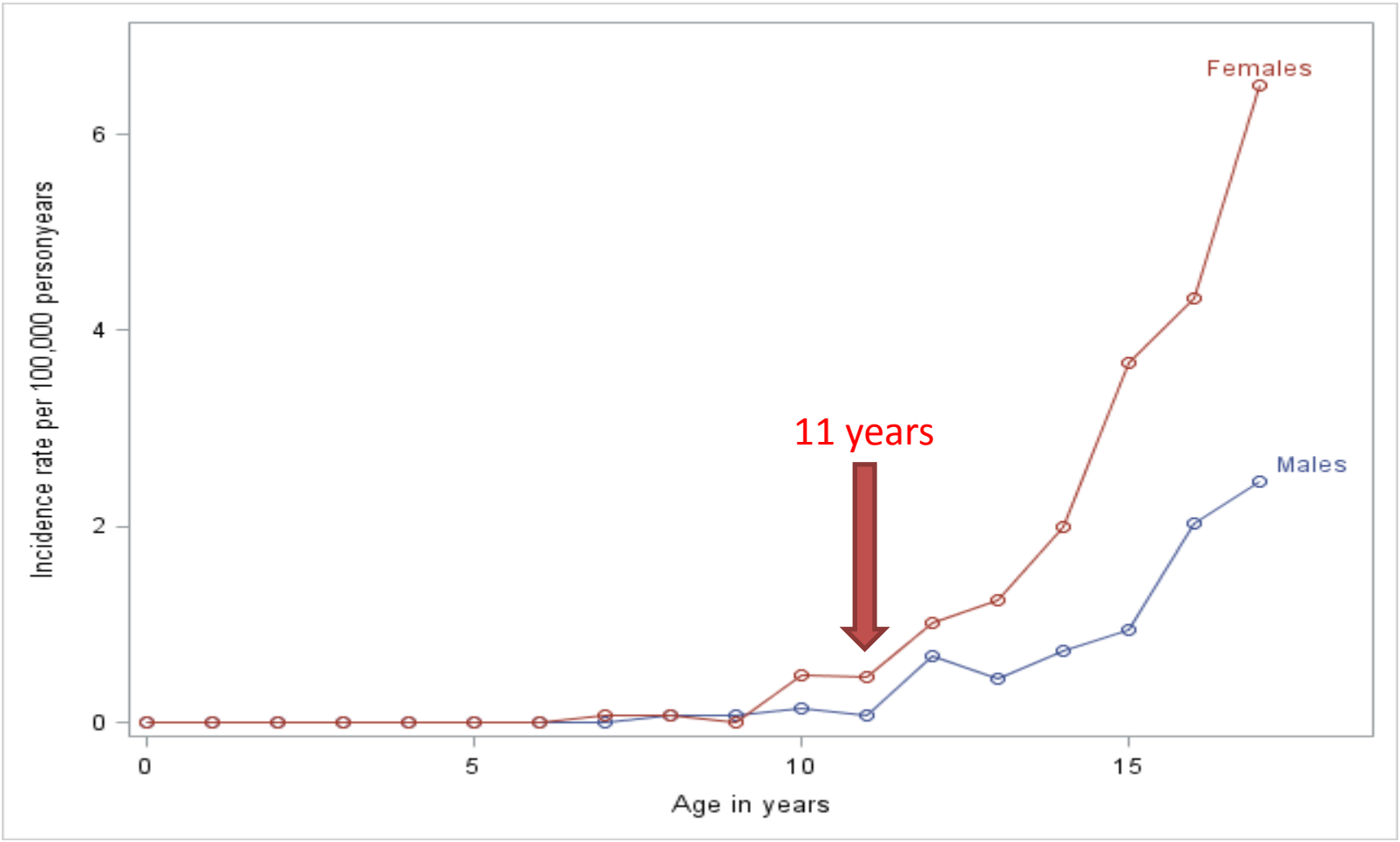
98% received methylprednisolone; few immunoglobulins or plasmaferesis

Incidence rate of pediatric ADEM in Denmark during 2008-15 by "Expert ADEM" and "IPMSSG ADEM"



MS is rare before 11 years of age; therefore, some children with ADEM may progress to MS with longer follow-up

Sex-specific incidence of pediatric-onset MS in Denmark by age at onset during 1977–2015



Conclusions

- ADEM is rare, but usually presents in children aged 0-5 years
- Children usually presents with encephalopathy, polyfocal neurological deficits, and are febrile
- The majority have pleocytosis, few have oligoclonal bands.
- Two-thirds have neurologic sequelae, but none of the children with ADEM progressed to MS. However, some children may progress to MS with longer follow-up as the age end-of-follow-up 11 years, and MS is rare in children younger than 11 years of age