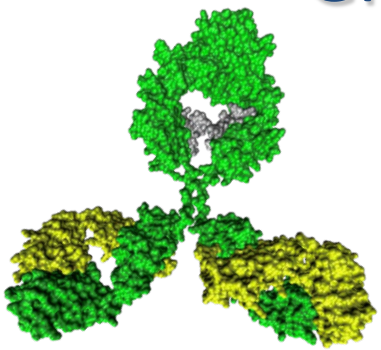
Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

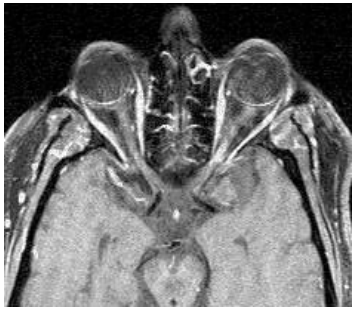
The child first and always

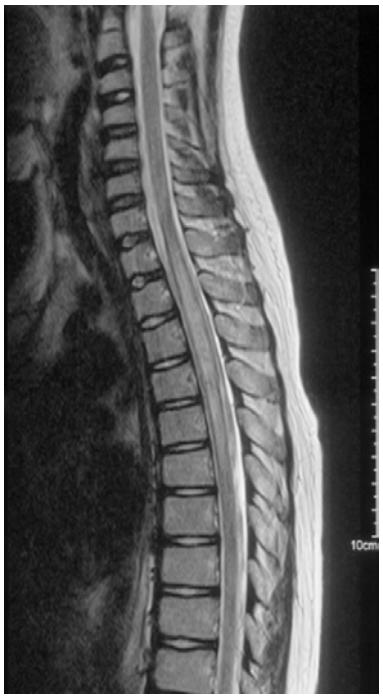
Development of drugs for Paediatric NMO

Cheryl Hemingway

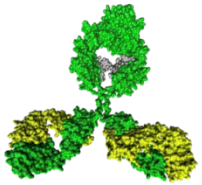
Great Ormond Street Hospital for Children





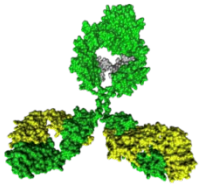


Talk outline



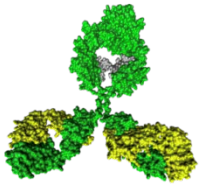
- Background
- Epidemiology
  - Surveillance study
  - NMO study
- Differences from adults
- Future

Background



- Children (<16y) account for 11 million of the 60 million UK population
- Not little adults
  - Differ in many ways: metabolism, immunity, endocrine
- Extrapolated data limited relevance and harmful
- Right to be protected BUT also a right to the highest standard of healthcare
- Europe: 65% commercial medicines not licensed for children and >90% not licensed in newborns

EU Regulation: "Better medicines for children"

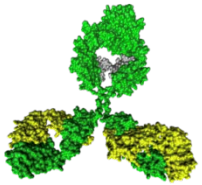


- Became law across EU on 26 January 2007
- Incentives and requirements for industry to undertake paediatric studies
- Paediatric Committee
  - Based in European Medicines Agency
- Paediatric Investigation Plan (PIP)
  - Development agreed with Paediatric Committee
- Coordinated European Paediatric Trials Network

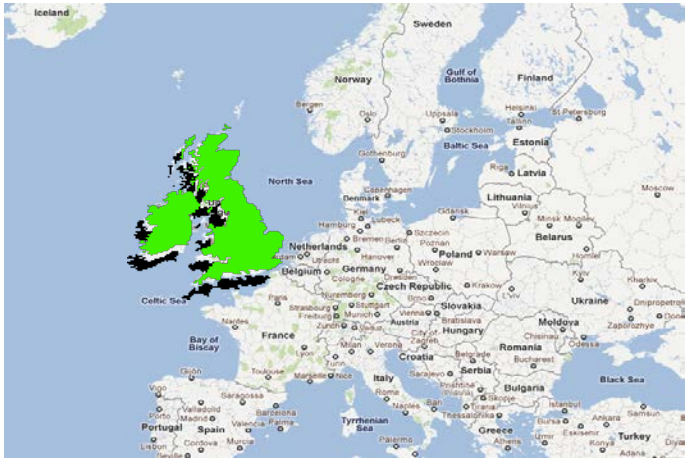
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EnprEMA

Incidence of IDE



- Paucity of population data
  - Canada 0.9/100 000/y[1]
  - Dutch 0.66/100 000/y[2]
  - UK 1.1/100 000/y[3]



- Surveillance study in UK 2009-2010
  - first onset CNS Inflammatory Demyelination <16y
  - 4095 clinicians surveyed; 90% return; 222+ notifications
- 2007 IPMSSG consensus definitions allow uniformity in research and 2010 McDonald MRI criteria

1: Banwell et al. **Neurology. 2009 Jan 20;72(3):232-9**
2: Ketelslegers et al. **J Neurol 2012 259;1929-1935**
3: Absoud et al **Mult Scler. 2012**

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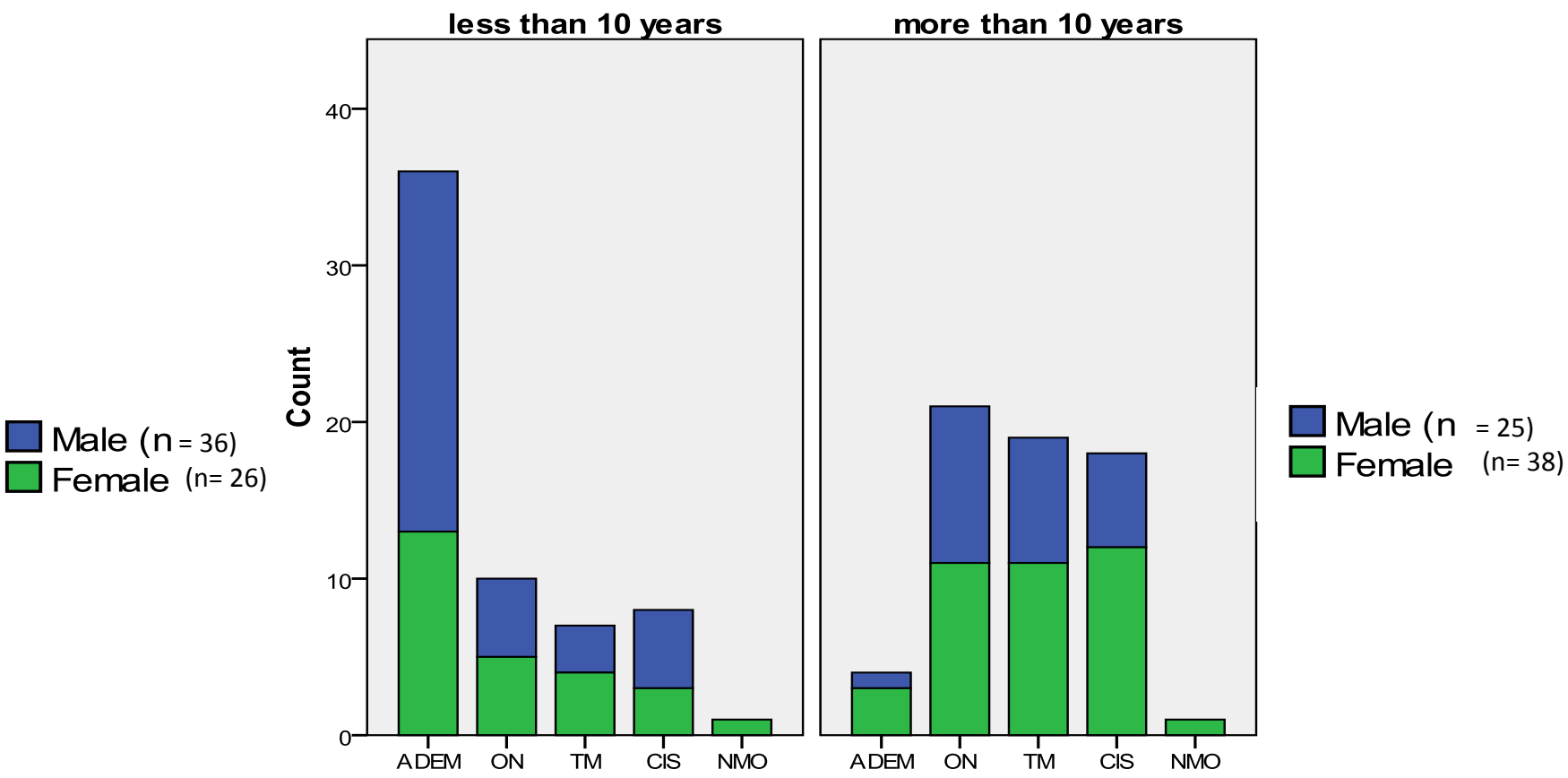
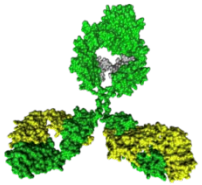
IDE – Age and presentation

n= 125

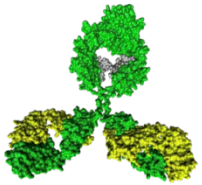


Paediatric UK NMO study



- Retrospective case ascertainment and note review of paediatric (<17 years) cases
- 4 UK demyelination clinics & UK national NMO service
- Inclusion criteria:
  - Wingerchuk 2006 criteria
  - or AQP4 antibody positive

Cohort characteristics

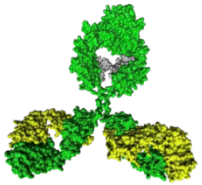


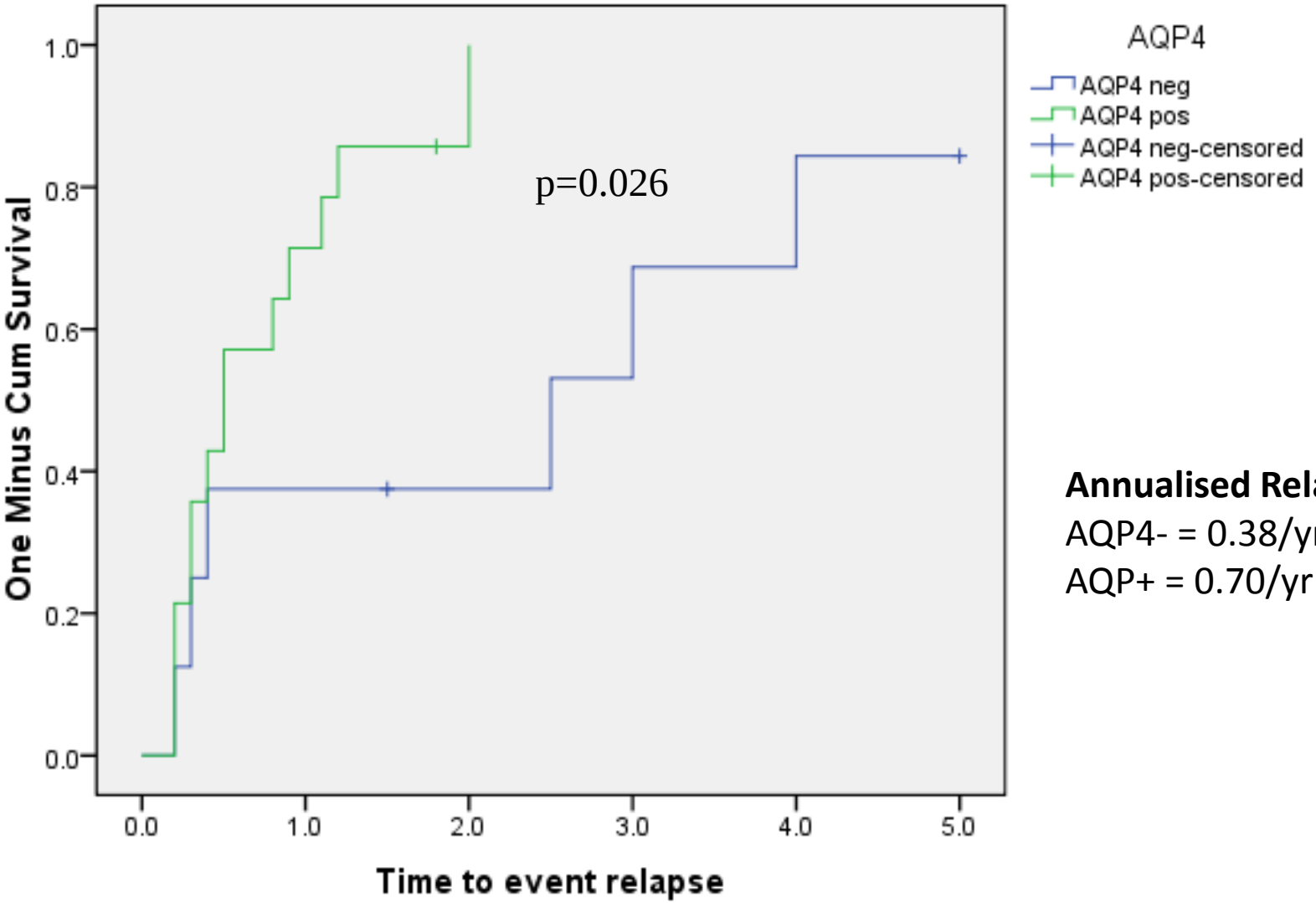
Characteristic		AQP4-AB		Significance	TOTAL n=22
		AQP4 neg	AQP4 pos		
Sex	**Male: Female**	0:8	3:11	p=0.17	3:19 (86%)
Age at onset	**Median** **Range**	10.9 (5.4-16.8)	9.3 (2.9-15.0)	p=0.50	
Follow up duration (years)	**Median** **Range**	5.4 (1.5-12.0)	6.1 (1.8-17.8)	p=0.92	
Wingerchuck 2006		8/8	12/14		20/22
First presentation	**unilateral ON** **bilateral ON** **TM** **TM and ON** **ADEM**	2 2 2 2 0	7 2 2 1 2	p=0.38 (for unilat ON)	9 (41%) 4 (18%) 4 (18%) 3 2
MRI brain changes present	**1**	5/8 (63%)	10/14 (71%)	p=0.67	15/22 (65%)
CSF OCB- positive		0/7	2/11	p=0.25	2/18 (11%)
Relapsing		6/8 ARR 0.38	13/14 ARR 0.7	P=0.25	19/22 (86%)

ADEM= Acute disseminated encephalomyelitis; AQP4-Ab= Aquaporin 4 antibody; CSF OCB= cerebrospinal fluid oligoclonal bands; ON= optic neuritis; TM= transverse myelitis

Absoud et al. JNNP 2014

Time to first relapse: AQP4 - vs +



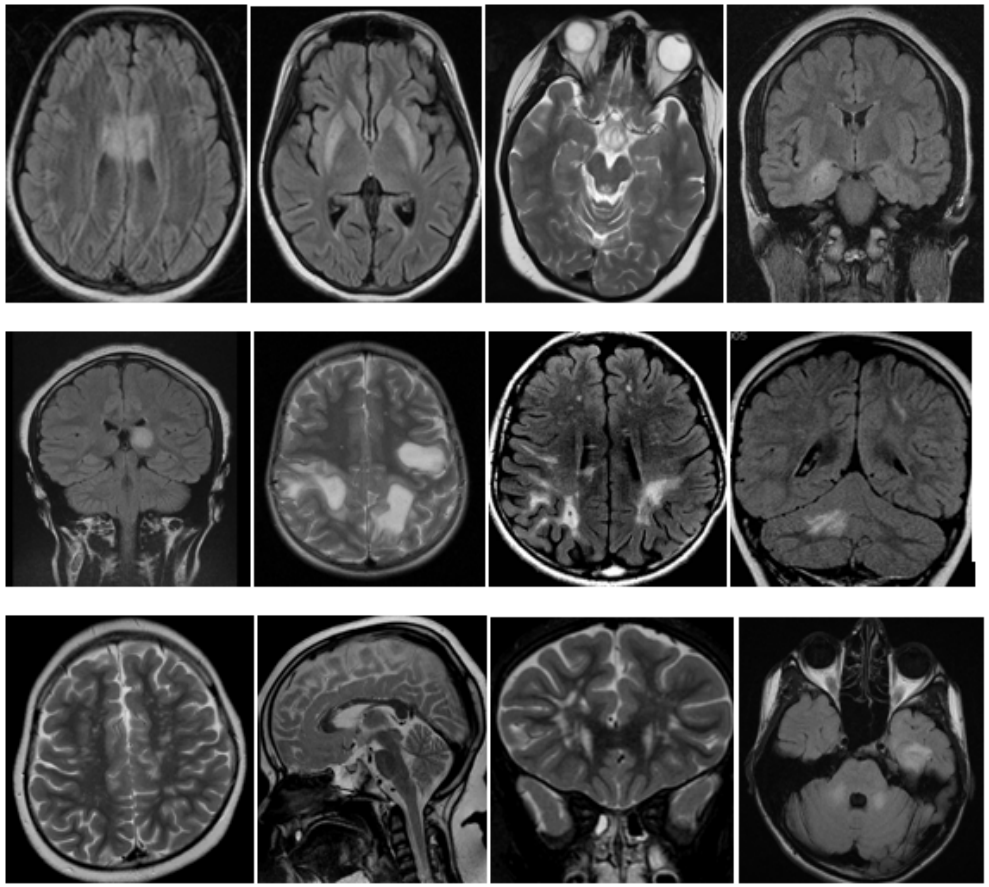


Annualised Relapse Rate

AQP4- = 0.38/yr

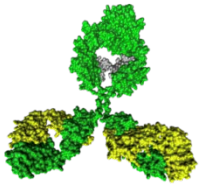
AQP+ = 0.70/yr

MRI Brain data

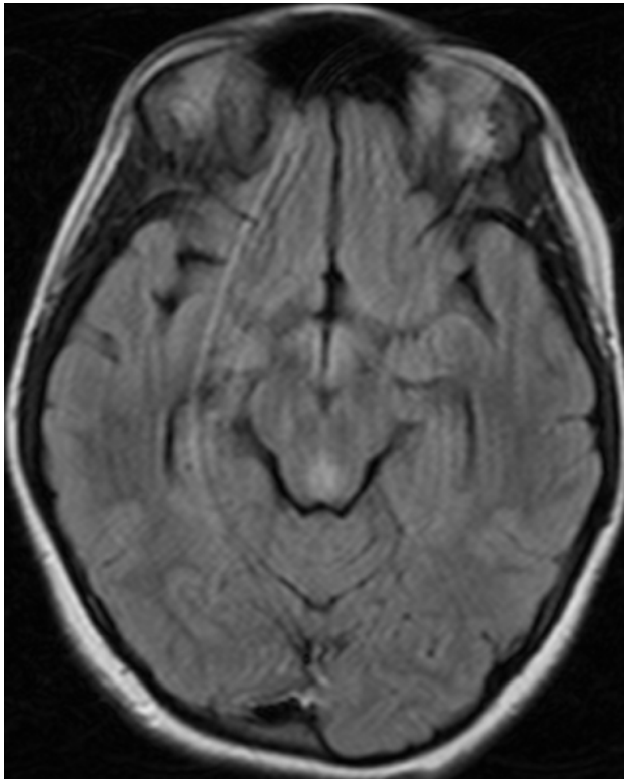


Data from 19 scans	Count	%
Centrum semiovale / DWM	6	31.60%
Periventricular	6	31.60%
Brainstem	5	26.30%
Periaqueductal grey	5	26.30%
Juxtacortical	4	21.10%
Cerebellar	4	21.10%
Corpus Callosum	3	15.80%
Thalamic	3	15.80%
Hypothalamic	3	15.80%
Cortical	2	10.50%
Basal ganglia	2	10.50%

Differential diagnosis prior to diagnosis



- Osmotic myelinolysis
- Mitochondrial
- Metabolic
- ADEM
- Multiple Sclerosis
- Isolated Optic Neuritis
- Isolated TM
- Tumour-brain/cord



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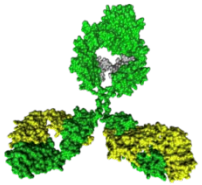

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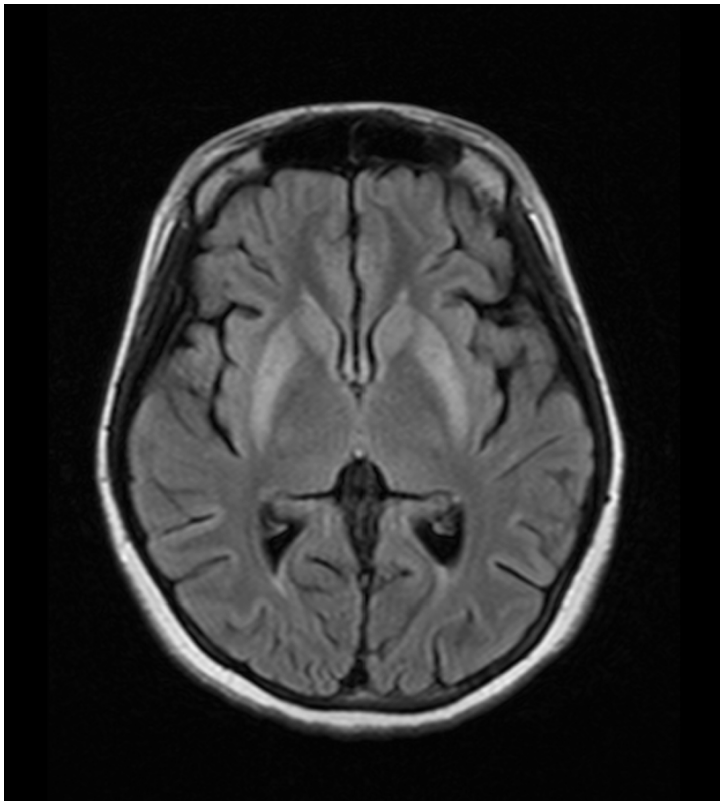

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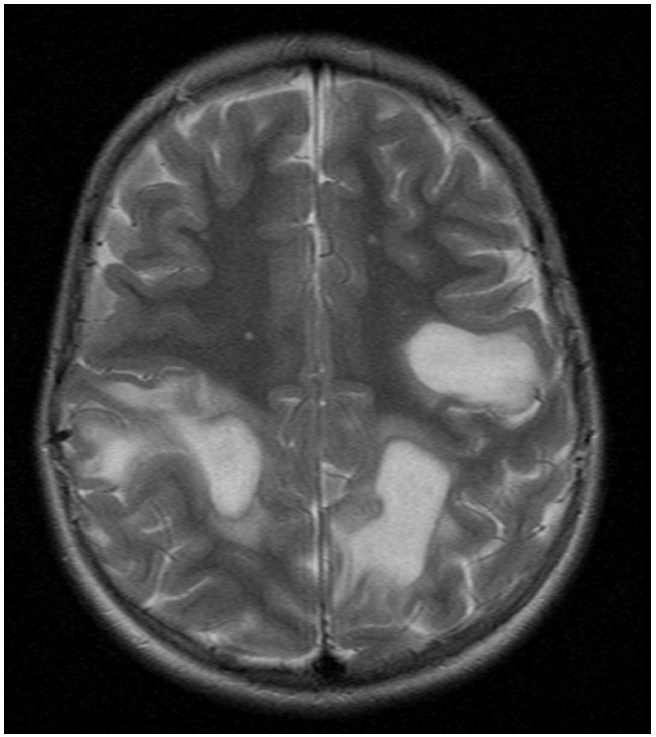
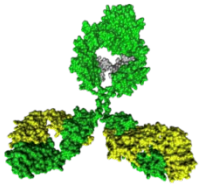
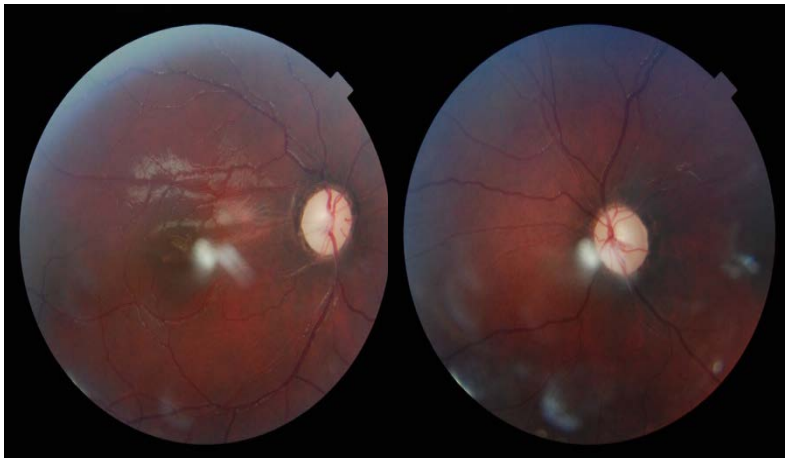


Disability



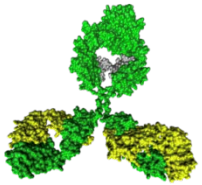
- Permanent disability is attack-related in NMO
- Visual impairment common in AQP4+

	AQP4 status	
	AQP4 neg	**AQP4 pos**
At least one eye 6/60 or worse	0/8	11/14 (79%)
Severe VI	0/8	7/14 (50%)



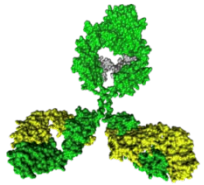
- Three (14%) were wheelchair dependent on follow up

Treatment



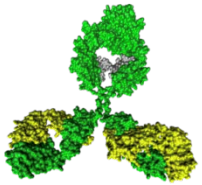
- No RCTs - all practise based on adult studies
- Acute attacks treated with 5 days of IV steroids ± IV immunoglobulin.
- Severe exacerbations treated with plasmapheresis
- A wide variety of disease modifying drugs used including AZA, Pred, MMF, Rituximab

Similar studies



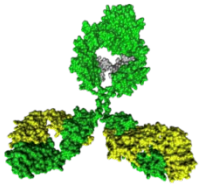
	Incidence ADS	F:M	Age(y)	AQP4+	ARR	MRI abN	Outcome	
							SVI	EDSS >6
Absoud (22) 2014	2%	9:1	10.5y	60%	0.7	75%	50%	14%
Banwell (17) 2008	3.2%	3.2:1	10.4y	47%	1.27	53%	25%	6.3%
Lotze (9) 2008		girls	14y	77%	-	100%		
McKeon (88) 2008	5%	9:1	12y	n/a	-	60%	54%	Worse than MS
Collongues (12) 2011		3:1	14.5y	66.7%	0.6	50%	-	Better than adults
Fragoso (29) 2013		2.6:1	13y	76%	0.75			40%

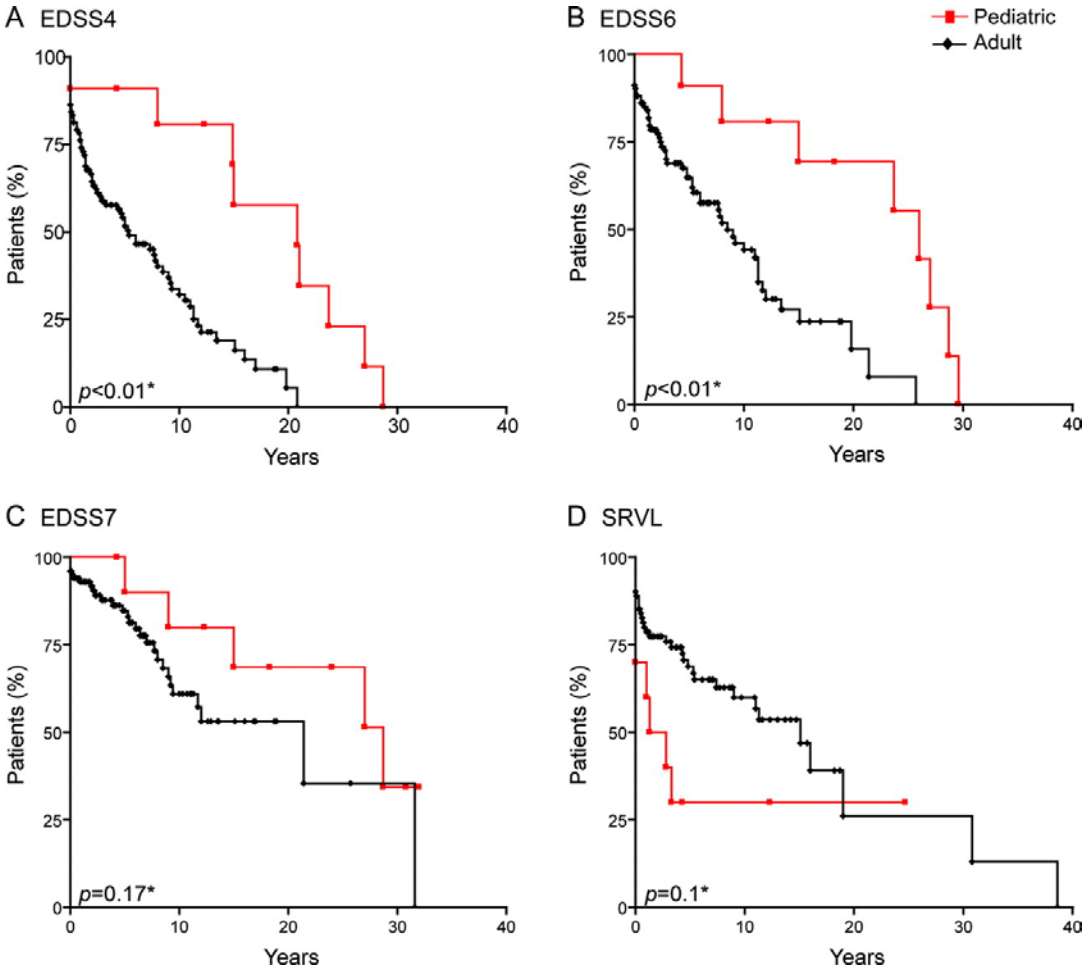
Differences from adult NMO



- Paediatric onset NMO rarer than in adults
- Monophasic illness in about 20%
- Clinical presentation similar BUT some age dependent anatomical susceptibility differences
  - Optic neuritis and secondary SVI more common
  - Brain spectrum wider
  - MRI lesions larger, in areas not AQP4 rich, and often symptomatic
  - LETM is less specific – 10% MS spinal lesions LE

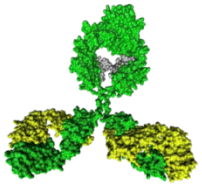
Ped NMO - Long term Outcome

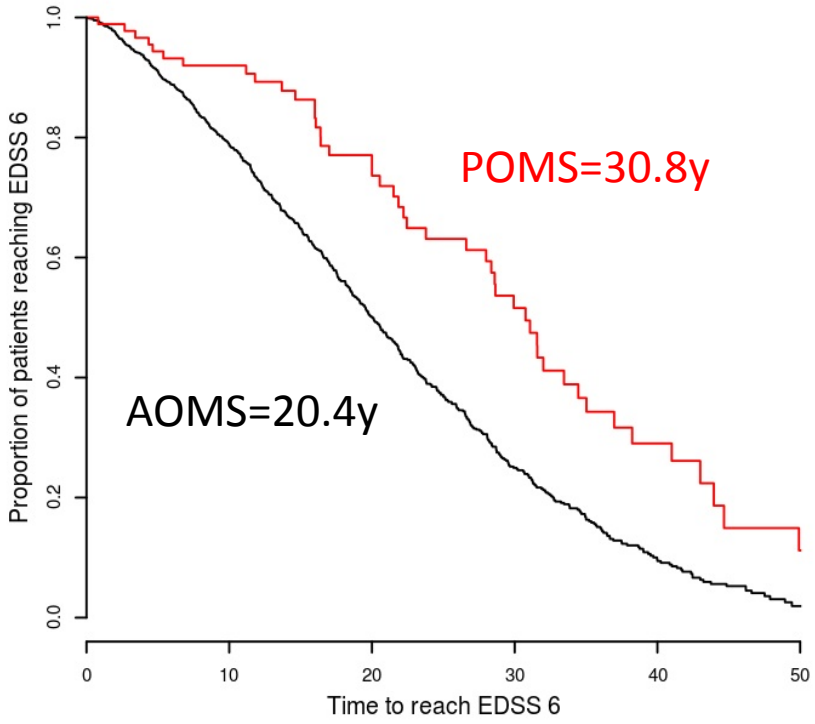




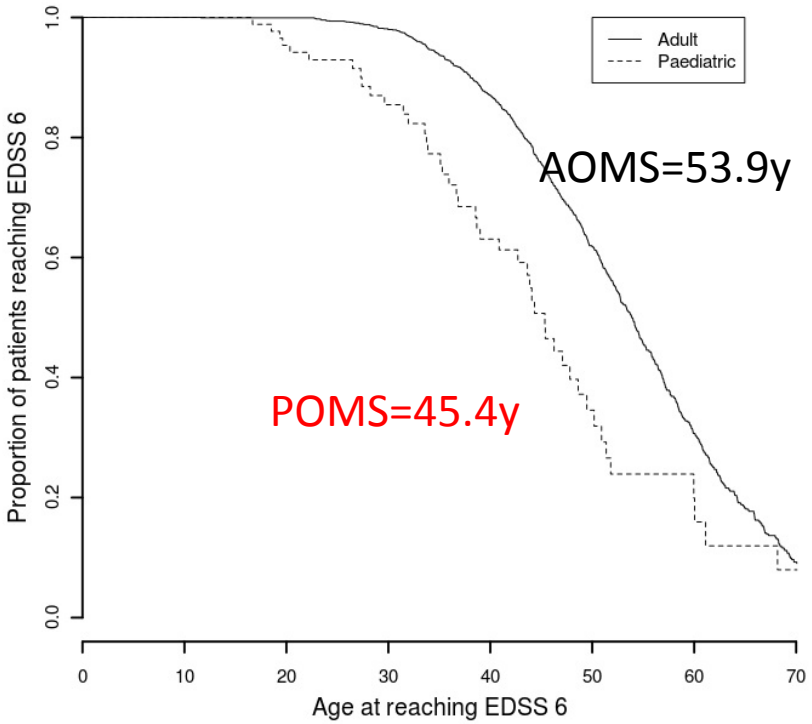
Collongues N et al. Neurology 2010;75:1084-1088

POMS –time to EDSS 6.0



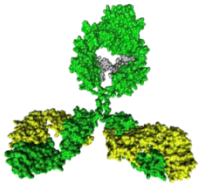


Welsh database



Harding et al **JNNP** 2013

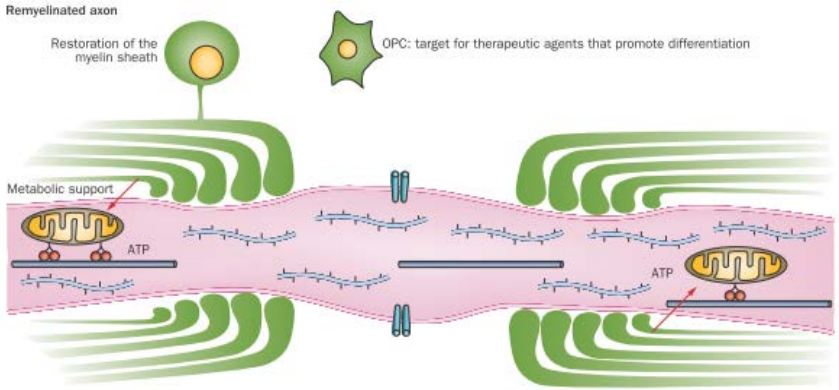
Age a determinant of remyelination?



Neuroprotection and repair in multiple sclerosis

Robin J. M. Franklin, Charles ffrench-Constant, Julia M. Edgar and Kenneth J. Smith

nature REVIEWS NEUROLOGY



The American Journal of Pathology, Vol. 180, No. 5, May 2012

DOI: 10.1016/j.ajpath.2012.01.018

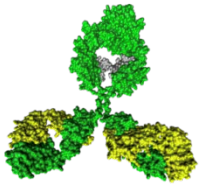
Cell Injury, Repair, Aging, and Apoptosis

Focal Immune-Mediated White Matter Demyelination Reveals an Age-Associated Increase in Axonal Vulnerability and Decreased Remyelination Efficiency

David W. Hampton,* Neill Innes,*
Doron Merkler,†‡§ Chao Zhao,¶
Robin J.M. Franklin,¶ and Siddharthan Chandran*

From the Euan MacDonald Centre for Motor Neurone Disease Research, Centre for Neuroregeneration, University of Edinburgh, Edinburgh, United Kingdom; the Division of Clinical*

Future trials in children



Negatives

- Rare - a trial to reduce ARR from 0.70 to 0.35: would need 84 patients/arm
- Large international studies

Positives

- Diagnostic criteria
- Biomarker
- Relapses important prognostic marker for disability

CYP want trials and want EBM to be informing their care

Involving children

- Careful assessment of risks

Involving children

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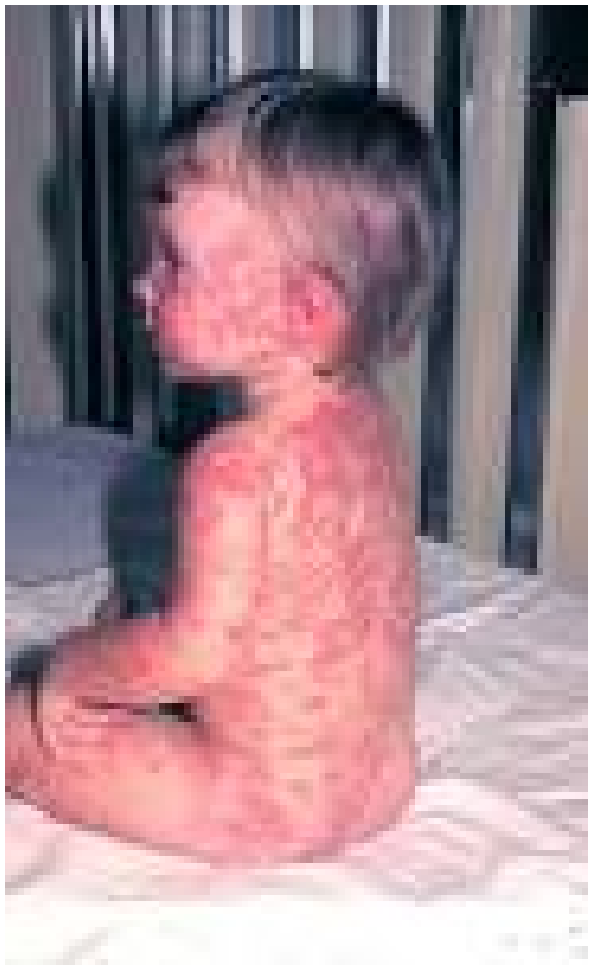

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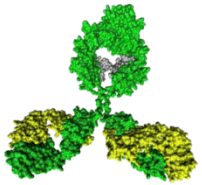
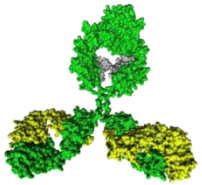


- Careful assessment of risks
- ↓ risks by good trial design, referral centres

Involving children



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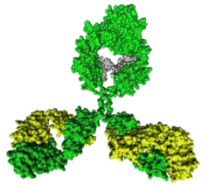
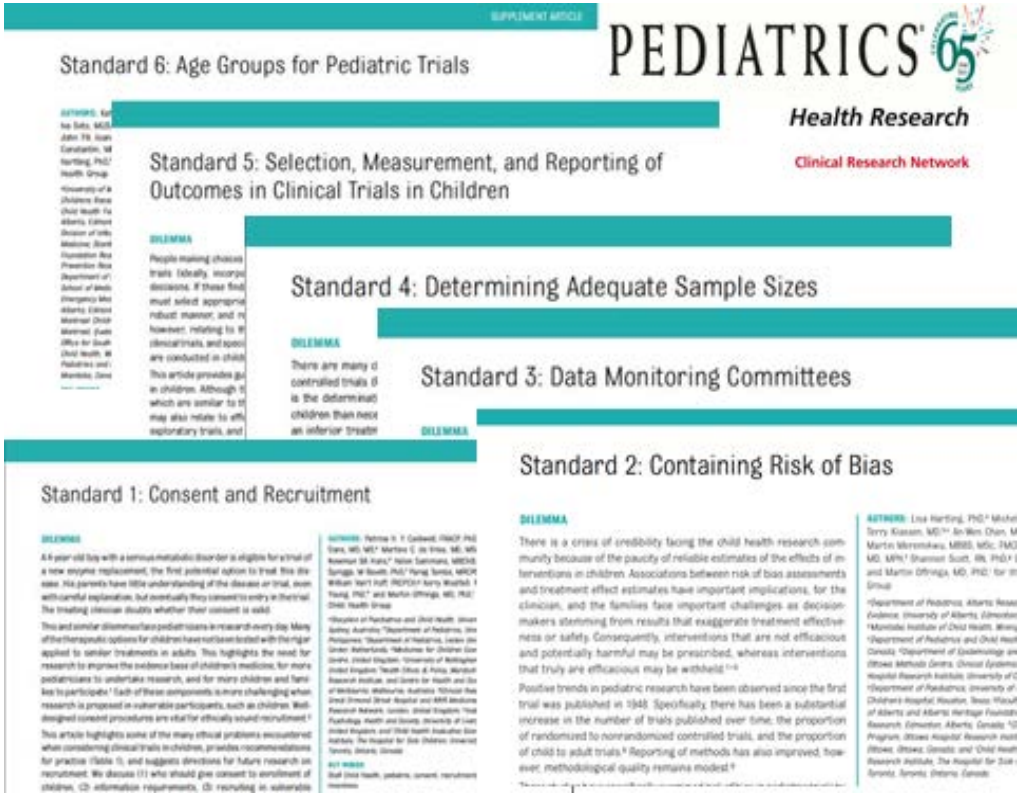


- Careful assessment of risks
- ↓ risks by good trial design, referral centres
- Trained personnel
- Adherence to well established paediatric research standards



To work towards this result..

- Start with a registry of all patients so we're not in this situation in 10 years time
- All children given therapy to be entered on a trial
- Trials in paediatrics to occur alongside the adult Phase 3 studies