MS in Childhood –

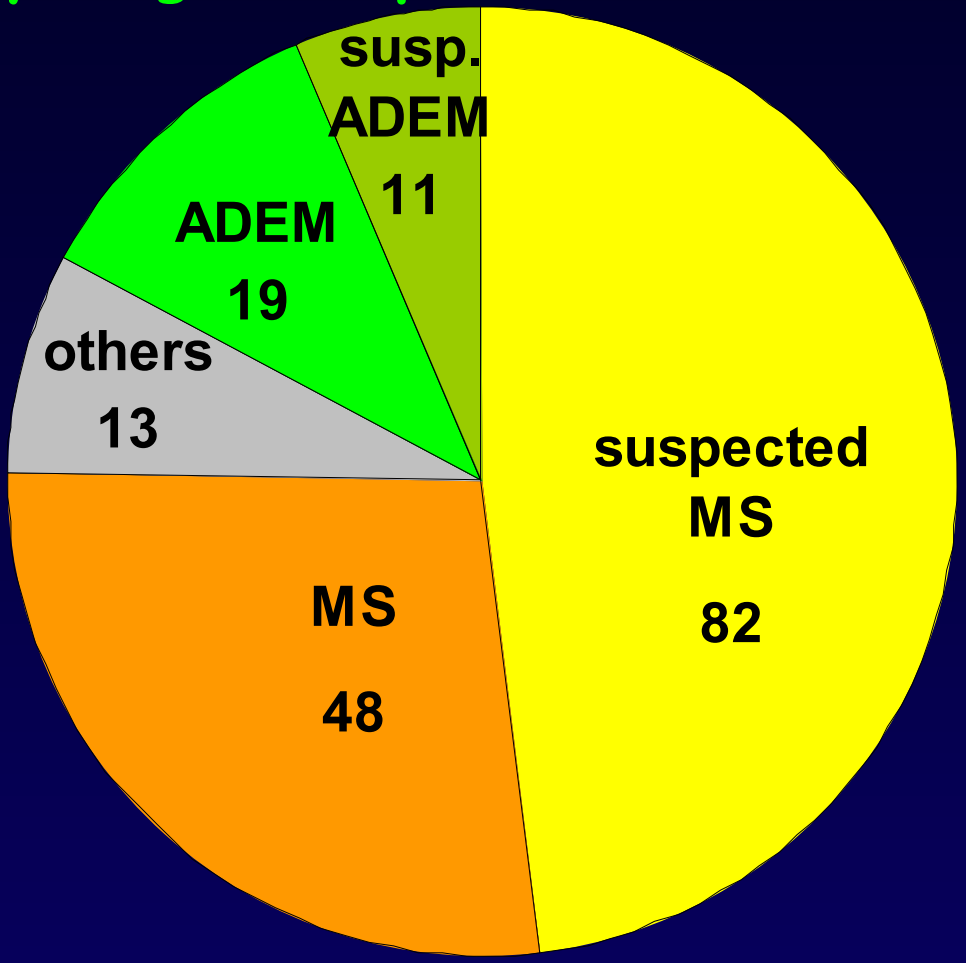
Diagnosis

and

Therapy

Incidence of Childhood MS

Newly diagnosed patients in Germany 1997-1999



MS	130
ADEM	30

Definition of childhood MS: 1st MS-attack before the age of 16

Diagnosis

„New" Diagnostic Criteria of McDonald *(Ann Neurol 2001;50:121)*

2 Attacks
+ 2 Lesions

or :

1 Attack
+ Dissemination in Space
+ Dissemination in Time (MRI):
New enhancing lesion > 3 months after 1st attack (2nd MRI)
or
New T2-lesion in MRI > 6 months after 1st attack (3rd MRI)

Diagnosis

Diagnosis of (childhood) MS

only if

other diseases

possibly causing

the symptoms

are excluded !

Childhood MS – Diagnoses to exclude (selection)

Leucodystrophies with known metabolic defect

Lysosomal diseases

Metachromatic Leucodystrophy

Globoidcell-Leucodystrophy (M. Krabbe)

Peroxisomal diseases

Adrenoleucodystrophy

Acylaspartase-Deficiency

M. Canavan

Leucodystrophies without known metabolic defect

M. Alexander

M. Aicardi-Goutieres

Orthochromatic/sudanophilic Leucodystrophy

Cystic Leucencephalopathy (van der Knaap)

Myelinopathia centralis diffusa (Hanefeld)

Leucodystrophies with primary hypomyelinisation

M. Pelizaeus-Merzbacher

Secondary Leucencephalopathies

Disturbances of Aminoacid Metabolism

Phenylketonuria

Disturbances of Organoacid Metabolism

Glutaraciduria Type 1

Mitochondrial Cytopathies

M. Leigh

Autoimmunological Diseases

Systemic Lupus erythematodes

Infectious Diseases

Pathway to Diagnosis

Laboratory Examinations

CSF

„Routine“:
- Cell count, Protein content, Cytology

Neurochemistry:
- Laktate
- Albumin-ratio, Immunoglobulin-ratio (IgG, IgA, IgM)
- Oligoclonal IgG
- specific Antibodies („MRZ-Reaction“: Measles, Rubella, Varicella zoster)

Infectiology:
- Cultures
- Antibody titers of neurotrophic germs
- PCR for neurotrophic germs

BLOOD

“Routine”:
- Differential blood count, Sedimentation rate, Chemogramm, Coagulation

Infectiology:
- Antibody titers of neurotrophic germs

Immunology:
- Auto-Antibodies, Complement Analysis, Immunoglobulins, ACE

Metabolism:
- Laktat, Pyruvat, VLCFA, Homocystein
- Vit. B_{12}, Folic Acid

URINE

“Routine”:
- Cell count, Protein content

Metabolism:
- Metabolic screening incl. Amino- and Organic Acids

Pathway to Diagnosis

Imaging

- **Magnetic resonance imaging (MRI)**

  of the **brain** and **spinal cord** (with gadolineum):

  - Lesions ?

  - Contrast enhancement ?

- **Magnetic resonance spectroscopy (MRS)**

  of the brain:

  - Pattern of metabolites?

Pathway to Diagnosis

Neurophysiological Examinations

- **Evoked Potentials (EP):**

  Visual tracts (visual EP)

  Acoustic tracts (acoustic EP)

  Sensory tracts (somatosensoric EP)

- **Transcranial magnetic stimulation (TMS):**

  Motor tracts

Pathway to Diagnosis

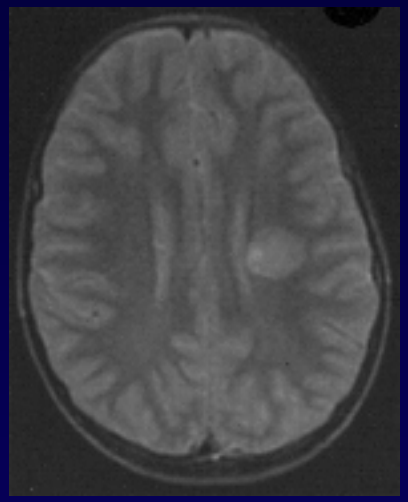
Case Report

David, born 1984

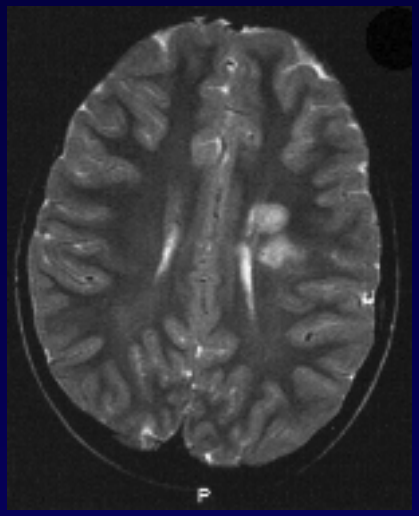
04/93 (8 yrs): Hemiparesis; *Diagnosis: Herpesencephalitis*

11/97 (13 yrs): Vertigo, Numbness; *Diagnosis: Circulatory Disturbances*

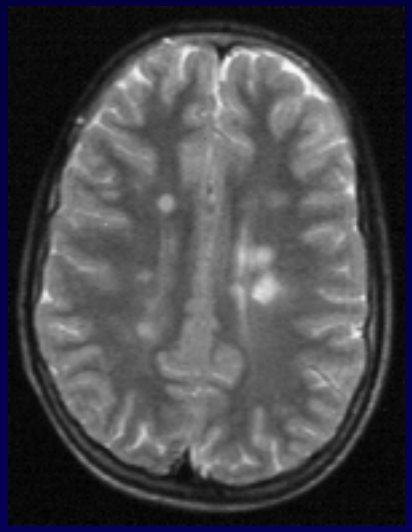
03/99 (15 yrs): Sensory Symptoms; *Diagnosis: MS*



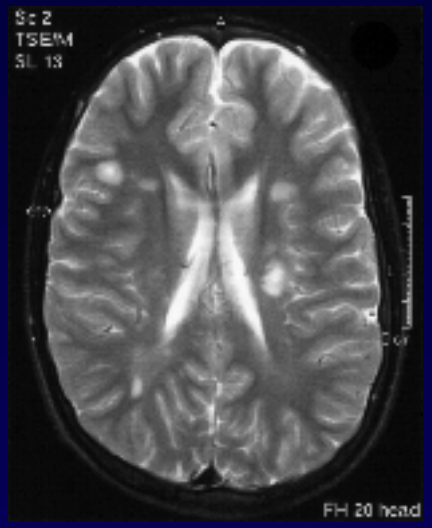
04/93: 1st attack



10/95: interval



11/97: 2nd attack



03/99: 3rd attack

Diagnosis 6 yrs after 1st attack

Diagnosis

Coping

J. B. (12 yrs): Actually I`m totally glad to know that I`m really sick. I thought I was nuts.

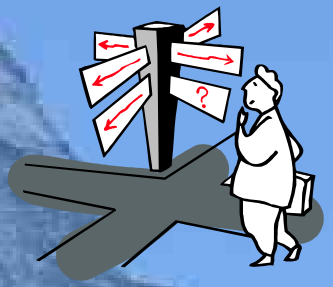
K. L. (15 yrs): I`m glad now that I have a real diagnosis, so that others believe me, that I`m not just imaging it.

Therapy

Aims:

CURE

CLINICAL STABILITY



LESS RELAPSES

REDUCTION OF NEW MRI-LESIONS

Therapy

„Fiction"

Some miracle drugs and non conventional methods

- Cobra venom
- Injection of fetal cells and tissue
- Pig brain implantation
- Hyperbar oxygen
- Intravenous yeast fungus
- Bee venom
- Fishoil
- (Mega-) Vitamins
- Trace elements
- Herbs
- Magnetic field therapy
- Ultrasound
- Acupuncture

Therapy

„Reality"

Relapse Treatment: Corticosteroids

Basic Treatment: Beta-Interferons
Glatirameracetate
Immunoglobulins
Azathioprine

Escalation Treatment: Mitoxantrone
Cyclophosphamid

Therapy

„Reality"

No approved treatment for childhood MS available

but:

- Childhood and adult onset MS are principally the same diseases
- Immunoglobulins and Corticosteroids are used for a wide range of immunological diseases in children and are generally well tolerated
- Beta-Interferons and Glatirameracetate are well tolerated in early onset MS (case reports or small numbers of patients)

Therapy

Why ?

Course of early onset MS: Age and Disability

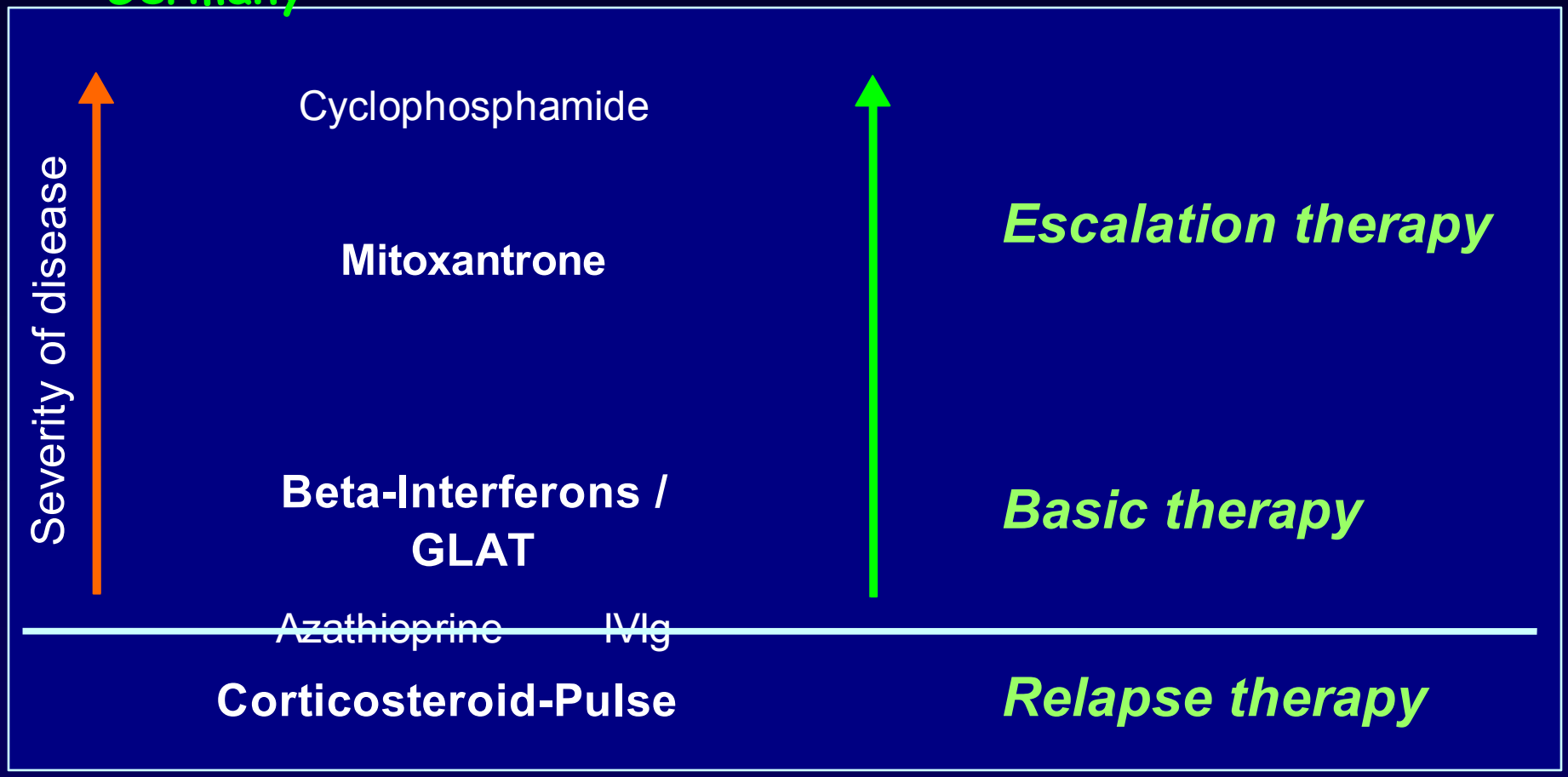
Simone et al, Neurology 2002;59:1922

Duration of disease in years MS	*EOMS*	*Adult onset*
EDSS 4 (moderate impairment)	**20**	**11**

Age when reaching MS	*EOMS*	*Adult onset*
EDSS 4 (moderate impairment)	**32** yrs	**41** yrs

Therapy

Treatment recommendations for adult onset MS in Germany



MS therapy consensus group

Therapy

Proposed treatment of attacks in childhood MS

- Methylprednisolone i.v.
- 20 mg/kg/d
- 3 to 5 days
- no tapering

Therapeutic Protocol Pediatric Neurology Göttingen

Therapy

Possible basic therapy of childhood MS

	Beta-Interferons			Glatiramer -acetate	Immuno-globulins
Substance	IFN-beta 1 a	IFN-beta 1 a	IFN-beta 1 b	Glutamine Lysine Alanine Tyrosine	IgG (+ IgM)
Trademark	Rebif®	Avonex ®	Betaferon ®	Copaxone ®	diverse
Application	s.c.	i.m.	s.c.	s.c.	i.v.
Dosage	22-44 µg 3x/wk	6 MIU 1x/wk	8 MIU 3x/wk	20 mg 1x/d	0,15-2 g/kg 1x/month

Therapy

Glatirameracetate (Copaxone®) in early onset MS

- 7 patients with MS onset between 9 and 16 years
- Initiation of treatment before the age of 18
- Daily injections of 20 mg Glatirameracetate
- Patients were followed for 24 months
- RESULTS:
  - Treatment was safe and well tolerated
  - 2 / 7 patients remained relapse-free
  - 3 / 7 patients showed stable EDSS

Kornek et al, Neuropediatrics 2003;34:120

Therapy

Beta-Interferon 1a (Rebif®) in early onset MS

- 26 patients with MS onset between 9 and 16 years
- Initiation of treatment before the age of 18
- Injections of 22 to 44 µg of Beta-Interferon 1a (Rebif®) 3 x / week
- Patients were followed for 6 months to 4 years
- RESULTS:
  - Treatment was safe and generally well tolerated
  - Yearly relapse rate dropped from 1.6 to 0.4
  - All patients showed stable EDSS

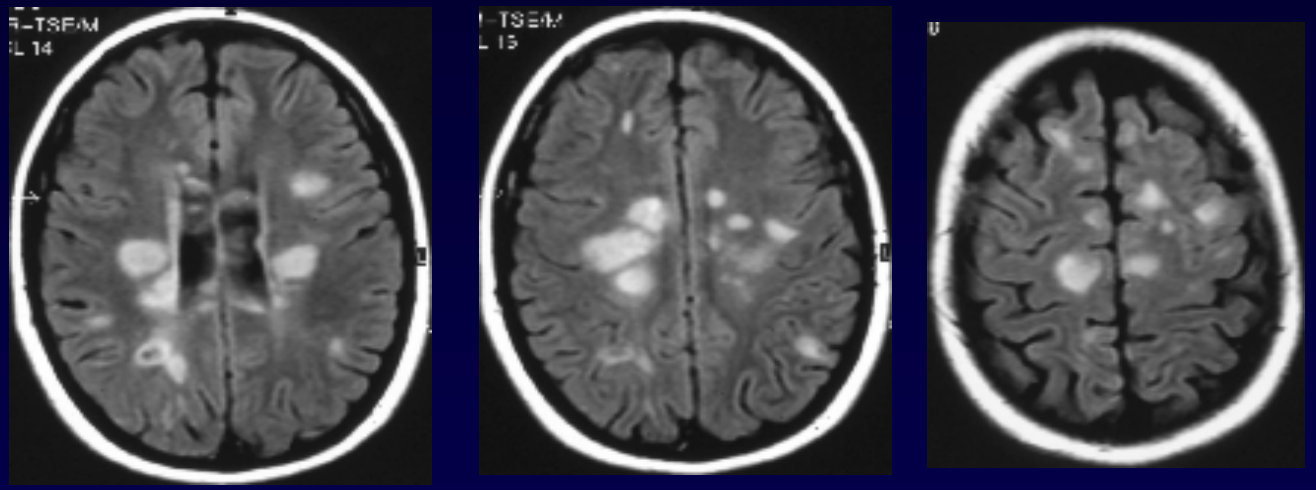
Case Report

Natalie, born 1984

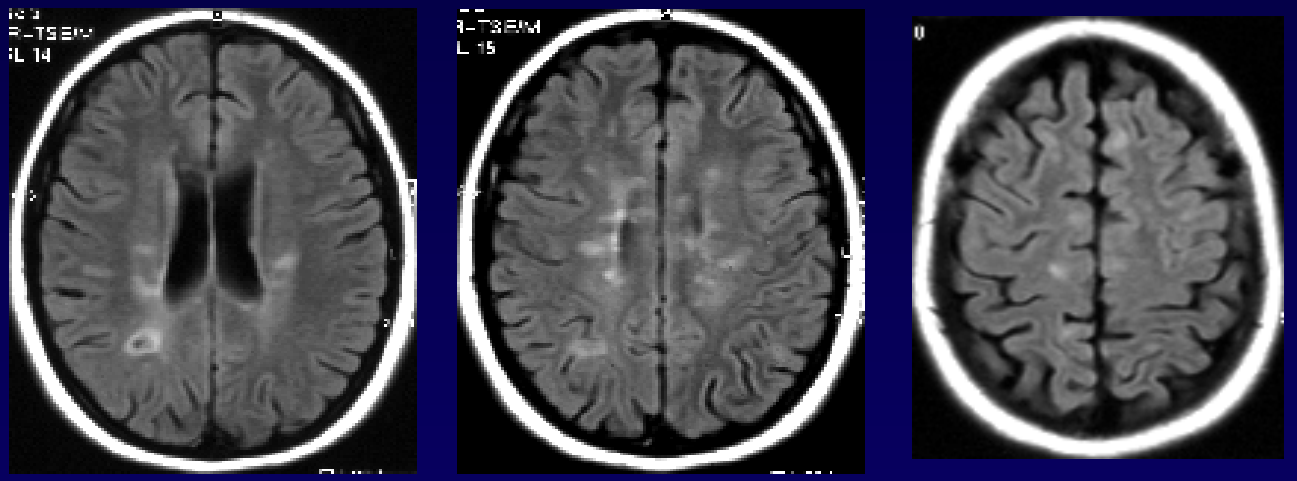
06/98 (13 yrs): **1st attack**: sensory loss right leg

09/99 - 03/00: **6 attacks** with sensory, motor and visual symptoms

03/00:
1 ¾ years of
clinical disease and
7 attacks



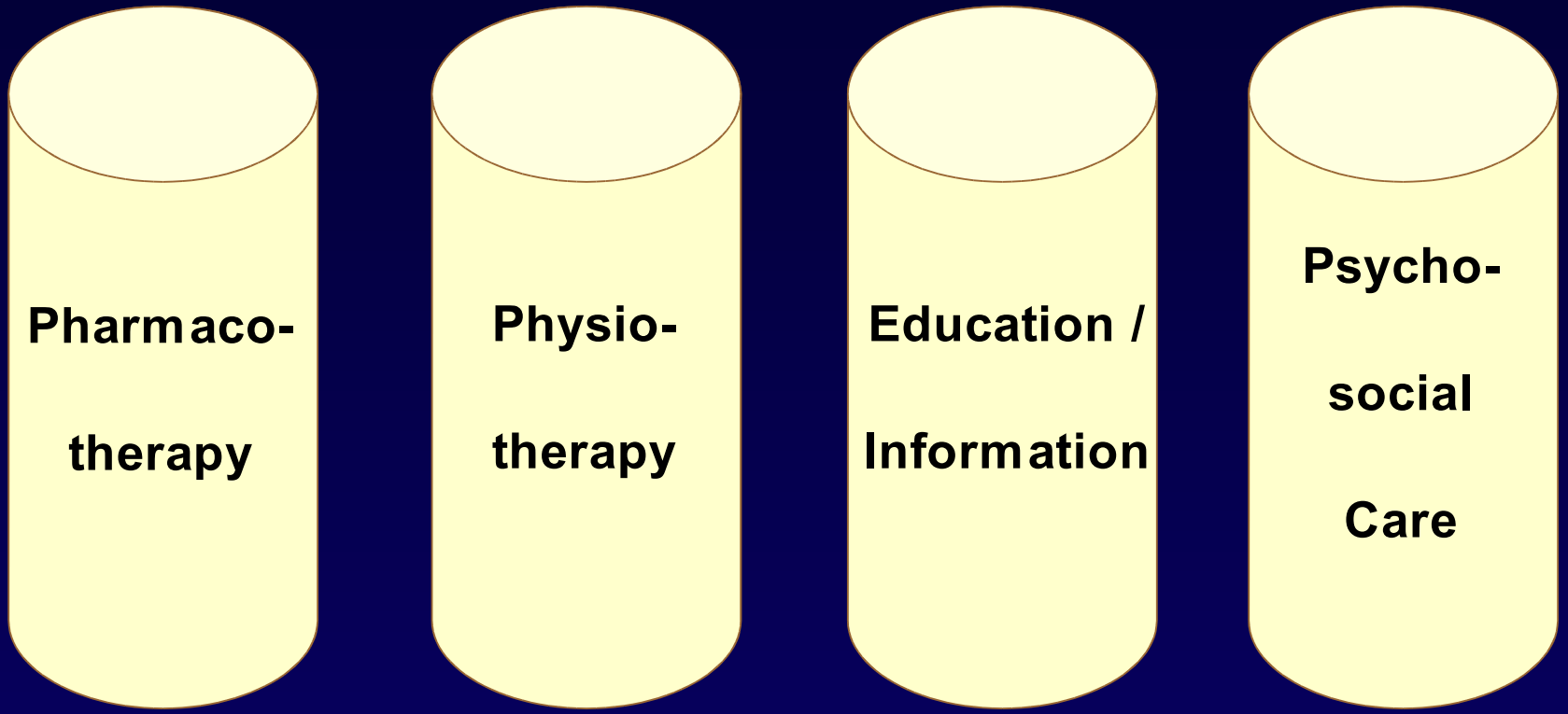
09/00:
After 6 months of
Beta-Interferon 1a
(Rebif®)



09/03: Relapse-free since 3 yrs under immunomodulation

Therapy

Pillars of childhood MS treatment



Conclusions

Diagnosis

- Early diagnosis after 1st attack possible
- Comprehensive examinations to exclude differential diagnoses

Therapy

- Absence of approved treatment for childhood MS
- Proposal:

Attack: High dose Methylprednisolone

B*asic:* **Beta-Interferons / Glatirameracetate**

Immunoglobulins

- Comprehensive therapeutic concept incl. psychosocial care

„Whatever the future of drug therapy in multiple sclerosis may be,

it will always be necessary

to treat the patient as well as the disease."

D. McAlpine

MS in Childhood

D. Pohl

I. Hennemuth

A. Ohlenbusch

K. Rostásy

F. Hanefeld

MS in Childhood : Therapy

Monitoring

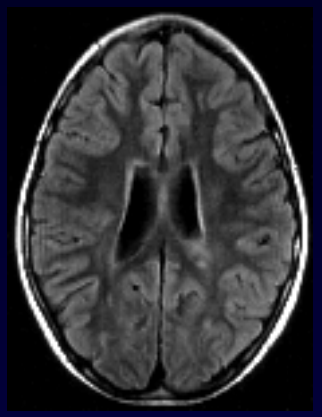
„Göttingen protocoll“

- Clinical neurological examination
- Neuroophthalmologic examination
- Craniospinal MRT
- Evoked Potentials and transcranial magnetic stimulation
- Ultrasound of the bladder
- Laboratory examinations

Course

MRI: Subclinical Activity

Pat. GA

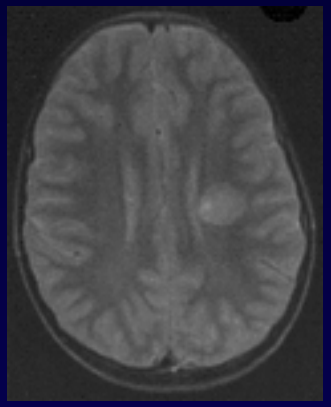


1999

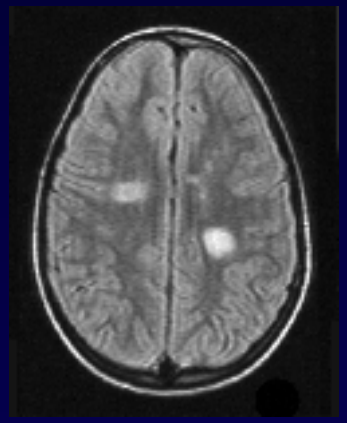
Pat. DG

Pat. LB

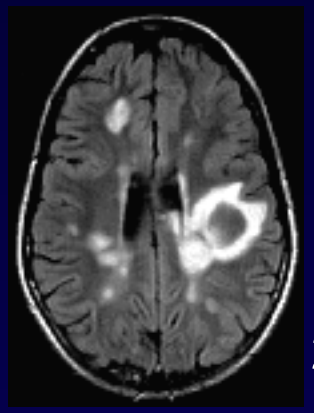
1st attack



1993

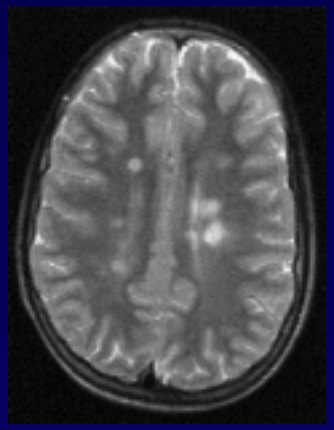


1997

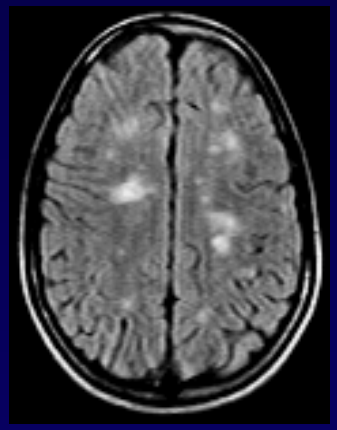


2001

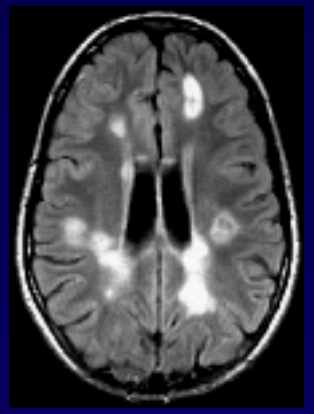
2nd attack



1997



2002



2002

Therapy

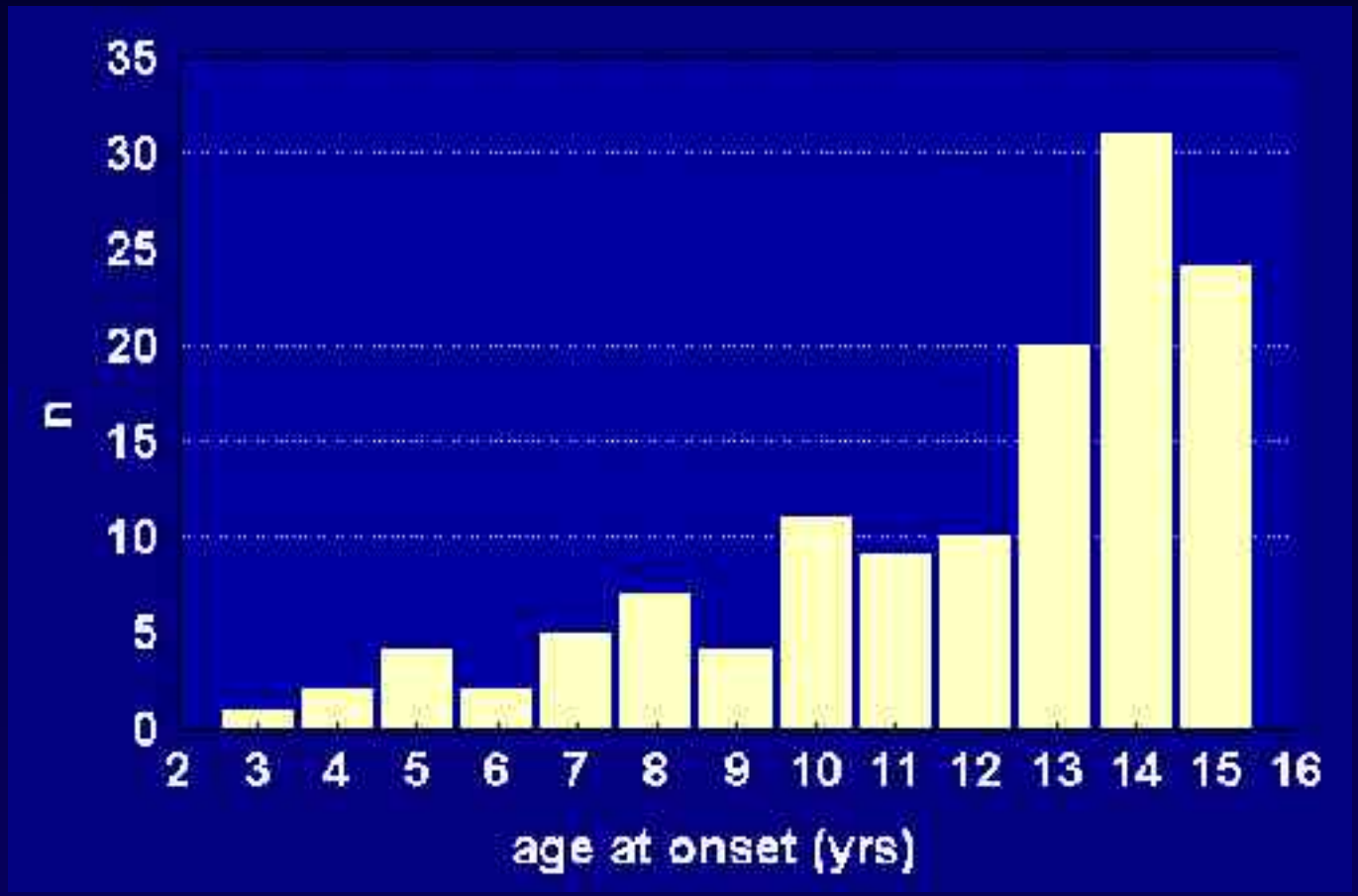
Beta-Interferon 1a (Rebif®) in early onset MS

Side effects

local reactions	5 / 25
initial flu-like symptoms	12 / 25
mild transient liver enzyme elevations	4 / 25
acute polyserositis	1 / 25

I ESPED-Survey

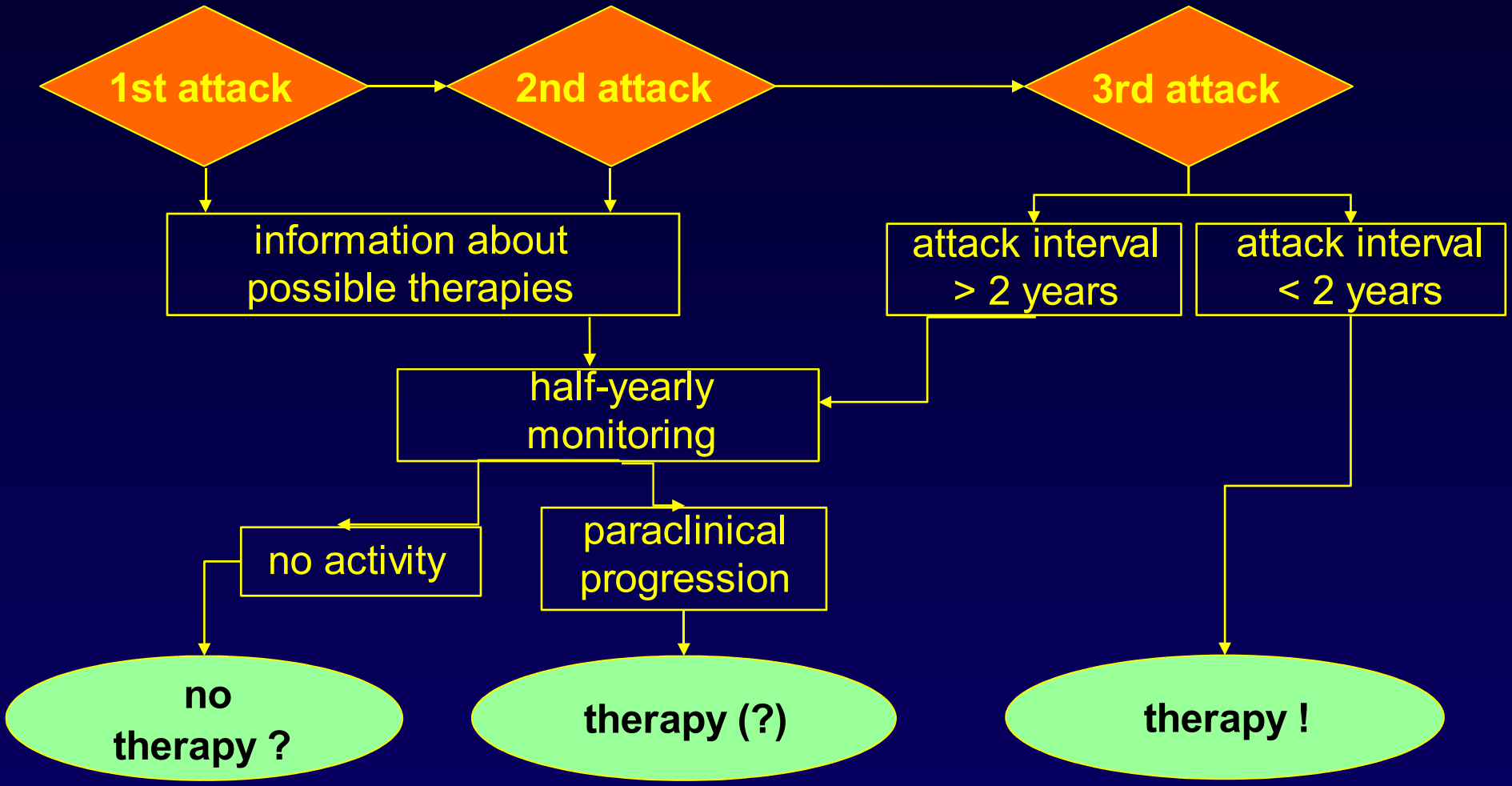
Age at MS-Onset



age	%	n
< 6 yrs	5%	7
<10 yrs	19%	25
>12 yrs	58%	75

Therapy

Indication for long term therapy in childhood MS, *"Göttingen protocol"*



Case Report 1

Alexandra S., born 1986

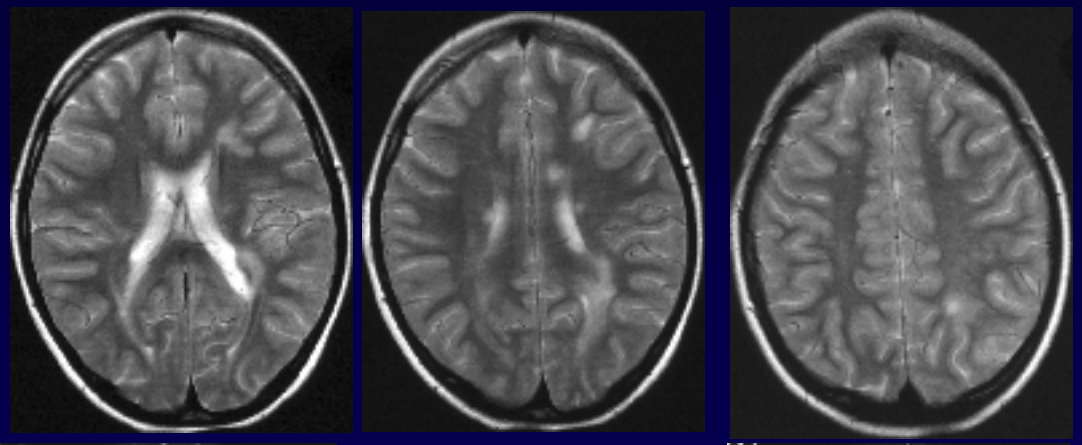
08/94 (8 yrs): **1**st **attack**: headache, nausea, gait ataxia, strabismus, paraesthesiae

01/95 (8 yrs): **2**nd **attack**: vertigo, nystagmus, diplopia

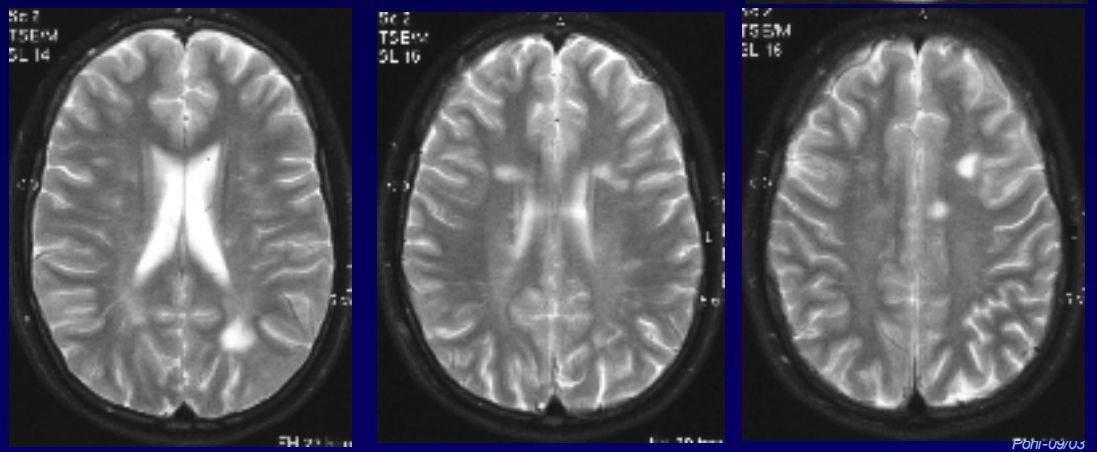
01/99 (12 yrs): **3**rd **attack**: optic neuritis, nystagmus, diplopia

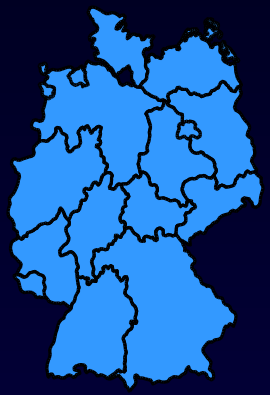
08/01 (15 yrs): **neurological sequelae:** discrete unilateral nystagmus

04/95:
lesions after
8 months of clinical disease and
2 attacks



08/01:
lesions after
6 ½ years of clinical disease and
3 attacks





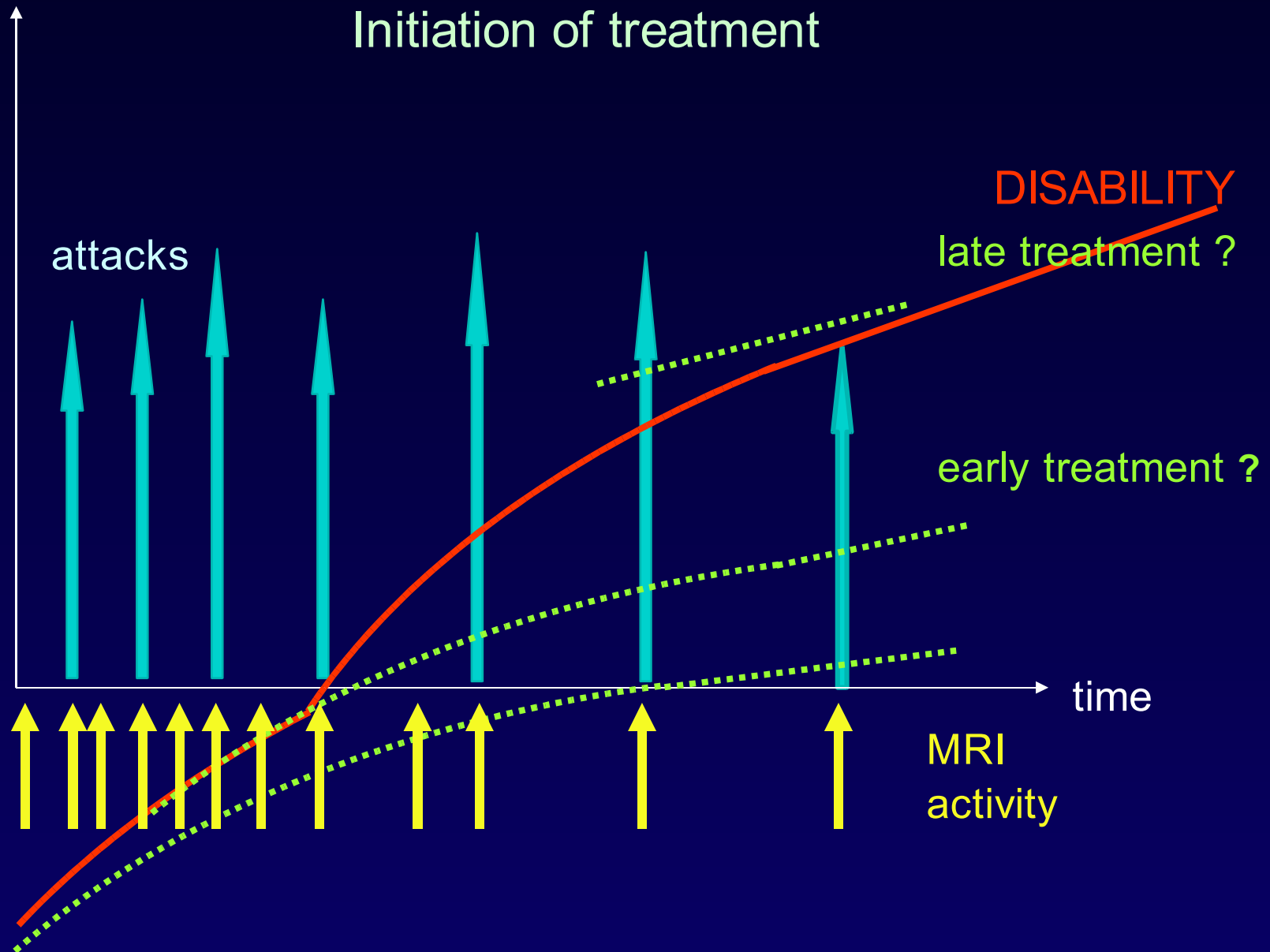
Epidemiology

Germany 1997-1999

Adult onset MS	Early onset MS
~ 120.000 patients	~ 200 patients (< 16 Jahre)
prevalence ~ 1,5 / 1.000	prevalence ~ 1,5 / 100.000
~ 4.000 new cases / year	> 40 new cases / year
incidence ~ 5 / 100.000	incidence ~ 0,5 / 100.000 children

ESPED-registry 1997-1999

Base Therapy



MS in Childhood

Therapy

„Outlook“

- Immunomodulatory Therapies
  - ⇨ Oral Drugs ?
- *Chlamydia pneumoniae*
  - ⇨ Antibiotic Therapy ?
- „Axonal Hypothesis“
  - ⇨ Neuroprotective Strategies ?

Diagnosis

Diagnosis of MS possible after:

1 Attack

and

Dissemination

in

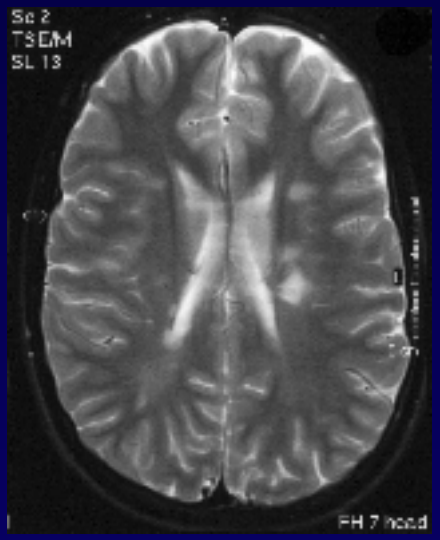
Time

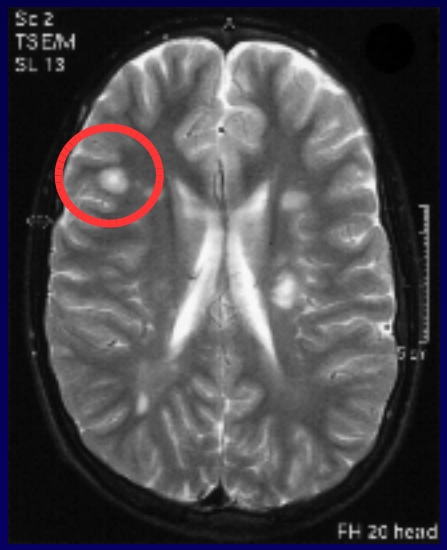
and

Space

in

MRI





Definition of childhood MS

Early Onset Multiple Sclerosis (EOMS):

1st MS-attack before the age of 16

Pathway to Diagnosis

Clinical History

- **Familiy:**

  Relatives with:

  (-) Autoimmune disease ?

  (+) MS, optic neuritis ?

- **Patient:**

  (-) Joint pain? Fever attacks? Aphtous lesions?

  (+) History of acute and reversible neurological symptoms?

Pathway to Diagnosis

Physical Examination

- Vision ?
- Sensititivity ?
- Coordination ?
- Strength ?
- Reflexes ?
- Spacticity ?

Pathway to Diagnosis

Clinical History of the Family and the Patient !

Physical Examination !