Clinical and Epidemiological Aspects of Bornavirus Infection in Children and Adolescents

1st World Congress Virus and Infections

Emerging and Zoonotic Infections

Busan South Korea

August 1, 2010

Thomas Scholbach

Hospital for Children and Adolsescents, Chemnitz , Germany

t.scholbach@skc.de

Bornavirus

- Global occurance
  - Highly conserved genome (~ 98%)
    - independent of biological or geographical source independent of sampling year
- Intranasal infection
    - limbic system, cerebellum, mesencephalon, cortex
- can cause BD, an often-fatal immune-mediated neurologic disease

Schneider et al. J Virol 1994, 63-68

Kolodziejek et al. J Gen Virol (2005), 86, 385–398
de la Torre JID 2002;186 (Suppl 2)

Europe

802377 (R01083) 5-95

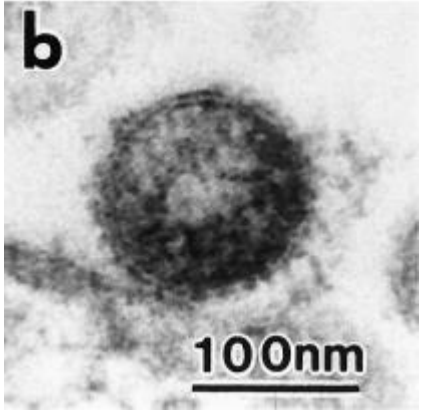
Thanks to

- Liv Bode, Patricia Reckwald
  - RKI Berlin
- Hanns Ludwig
  - FU Berlin
- Gerard Czech-Schmidt
  - Lab ILM Berlin
- Maren Vetterlein, Laura Tuca
  - Children‘s Hospital „St. Georg“ Leipzig

Agenda

1. Characterization
2. Human disease
3. Our investigation in children
4. Outlook

Characterization



- negative nonsegmented single-stranded RNA virus from order Mononegavirales
  - covered by an envelope with ~7-nm-long spikes
  - crescent-like inner structure with a nucleocapsid approximately 4 nm in width
  - replication and transcription in the nucleus
  - reproduce by budding at the cell surface
  - associated with incomplete small particles
- Naturally infecting solely neurons

- Acute and persisting infection of mammals, birds and humans

Kohno et al. JOURNAL OF VIROLOGY Jan. 1999, p. 760-766

BV-infection in mammals

- Encephalitis
- Movement disorders
- Memory and spatial orientation deficits
- Mood fluctuations
  - Aggressive – depressive behaviour
- Gastrointestinal symptoms
  - Refuse food
  - Do not reckognise food (olfactory nerve)

Neonatal BV infection in mice

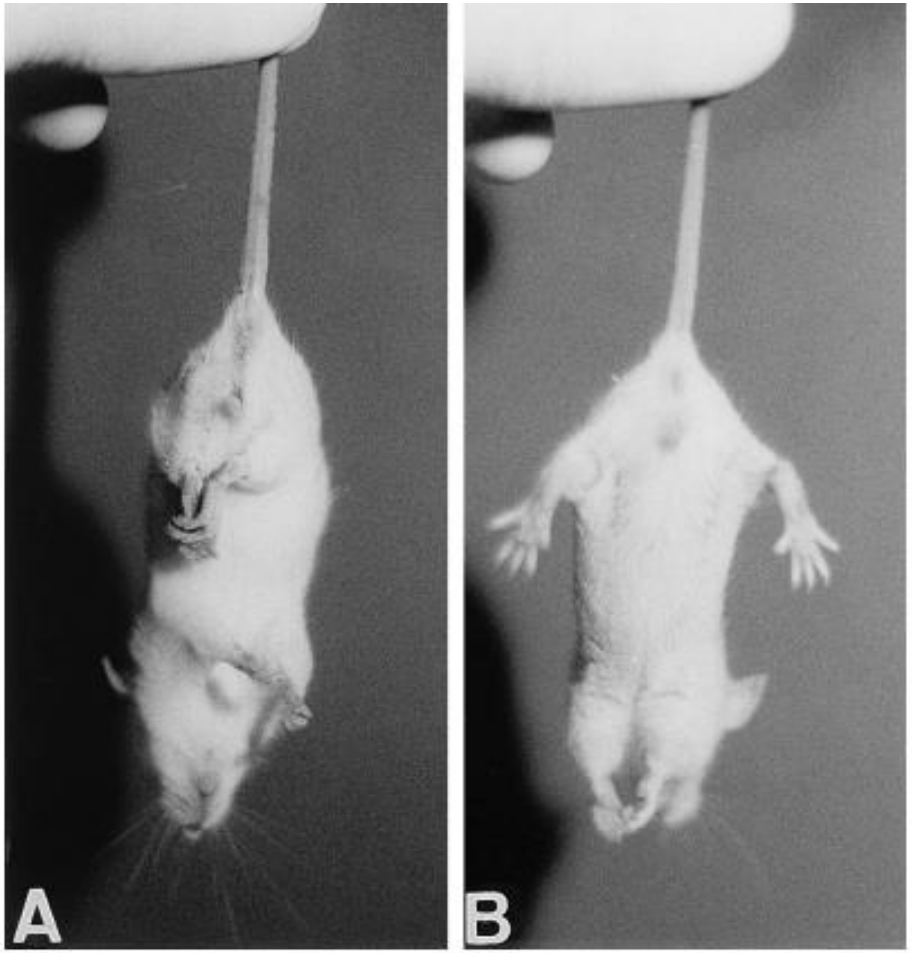


FIG. 1. (A) Characteristic nonphysiological position of the hind limbs of a BDV-infected MRL mouse with early signs of neurological disease. (B) Position of the hind limbs of a nonsymptomatic littermate.

Hallensleben et al. JOURNAL OF VIROLOGY,May 1998, p. 4379-4386

Age at time of infection matters

- Rats
  - Adult:
    - encephalitis, hyperactivity, aggressiveness, ataxia
    - Later: dementia, brain atrophy
  - Newborn
    - persistent infection of the neuronal tissue ; severe hippocampus damage; pronounced learning deficiencies
- Mice
  - Adult:
    - Nonsymptomatic
  - Newborn
    - Spastic paraplegia

Human BV infection

- Adults
  - Depression
  - Schizophrenia
- Other targets?
  - Children
  - Newborn
  - Pregnant women
  - Immunosuppressed
  - Aged ones
  - Fetuses
  - Transfused patients
  - Transplant recipients
- Other symptoms?
  - Similar to animals
  - Different ones

1.infection of **adolescent or adult** immunocompetent rats (an immune-mediated syndrome characterized by dramatic disturbances in movement and behavior

Nitzschke, 1963; Hirano et al., 1983; Narayan et al., 1983a,b; Ludwig et al., 1988; Solbrig et al.,1994, 1995, 1996a,b,c, 1998

2. infection of **neonatal** rats: a distinct syndrome characterized by cerebellar and hippocampal dysgenesis, hyperactivity, learning disturbances, transient cellular immune reaction

Hirano et al., 1983; Narayan et al., 1983b; Dittrich et al.,1989; Bautista et al., 1994, 1995; Hornig et al., 1999, Rubin et al., 1999, Hornig et al.,1999; Sauder and De la Torre, 1999

Longitudinal data for a full assessment of public health risk or pattern of spread in the human population is needed.

Neuropharmacological sequelae of persistent CNS viral infections: lessons from Borna Disease Virus

Marylou V. Solbrig , George F. Koob

Pharmacology, Biochemistry and Behavior 74 (2003) 777–787

Our aim

- to describe prevalence of BV in children
- to find clinical correlation to BV infection
- to treat in otherwise intractable severe cases

Material

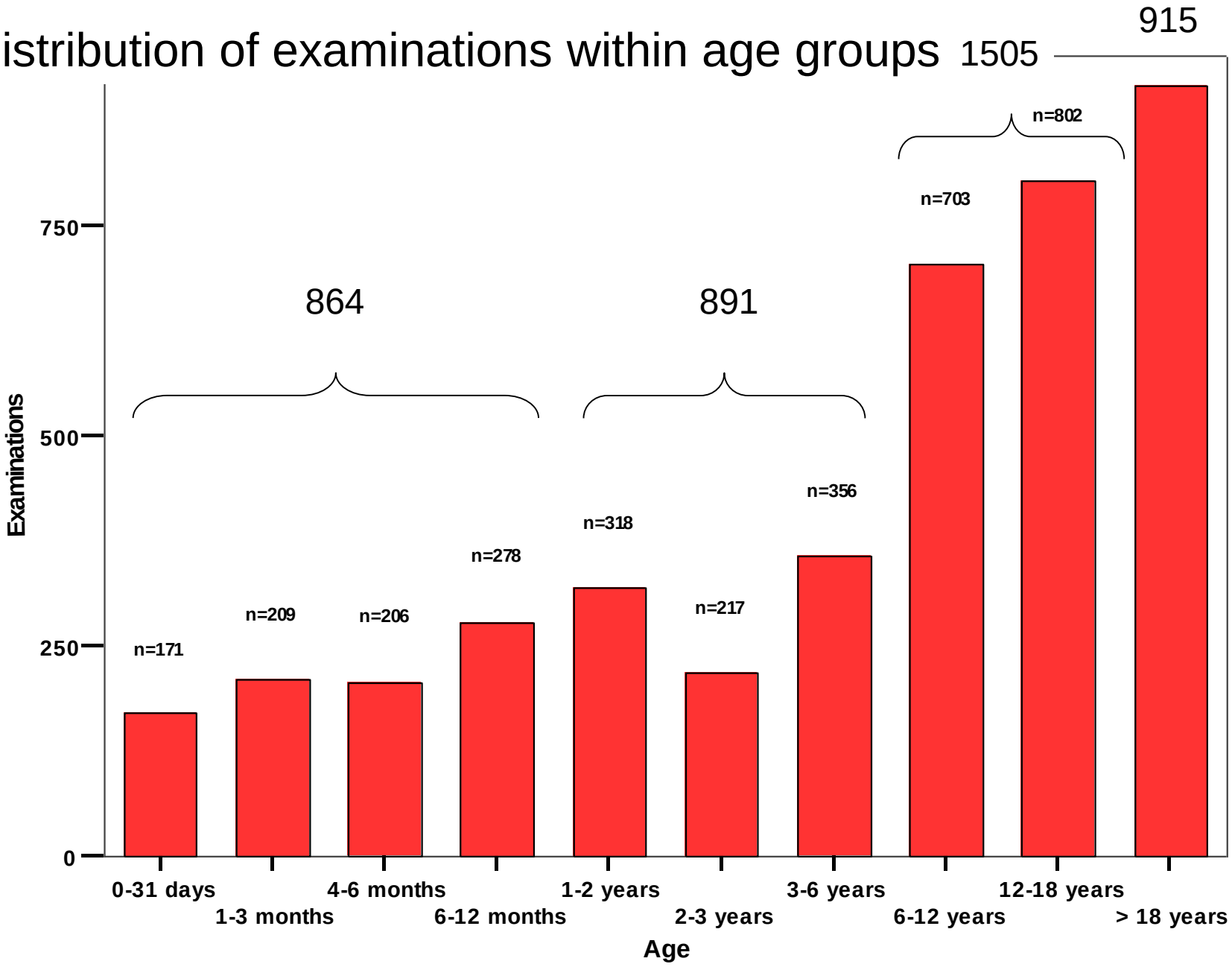
- 4175 examinations
- 2417 patients
  - (day 1 to 80 years – median 9 years)
- 171 newborn - examinations
- 118 newborns in follow up
- 1 – 54 examinations (mean 1,7)

Methods

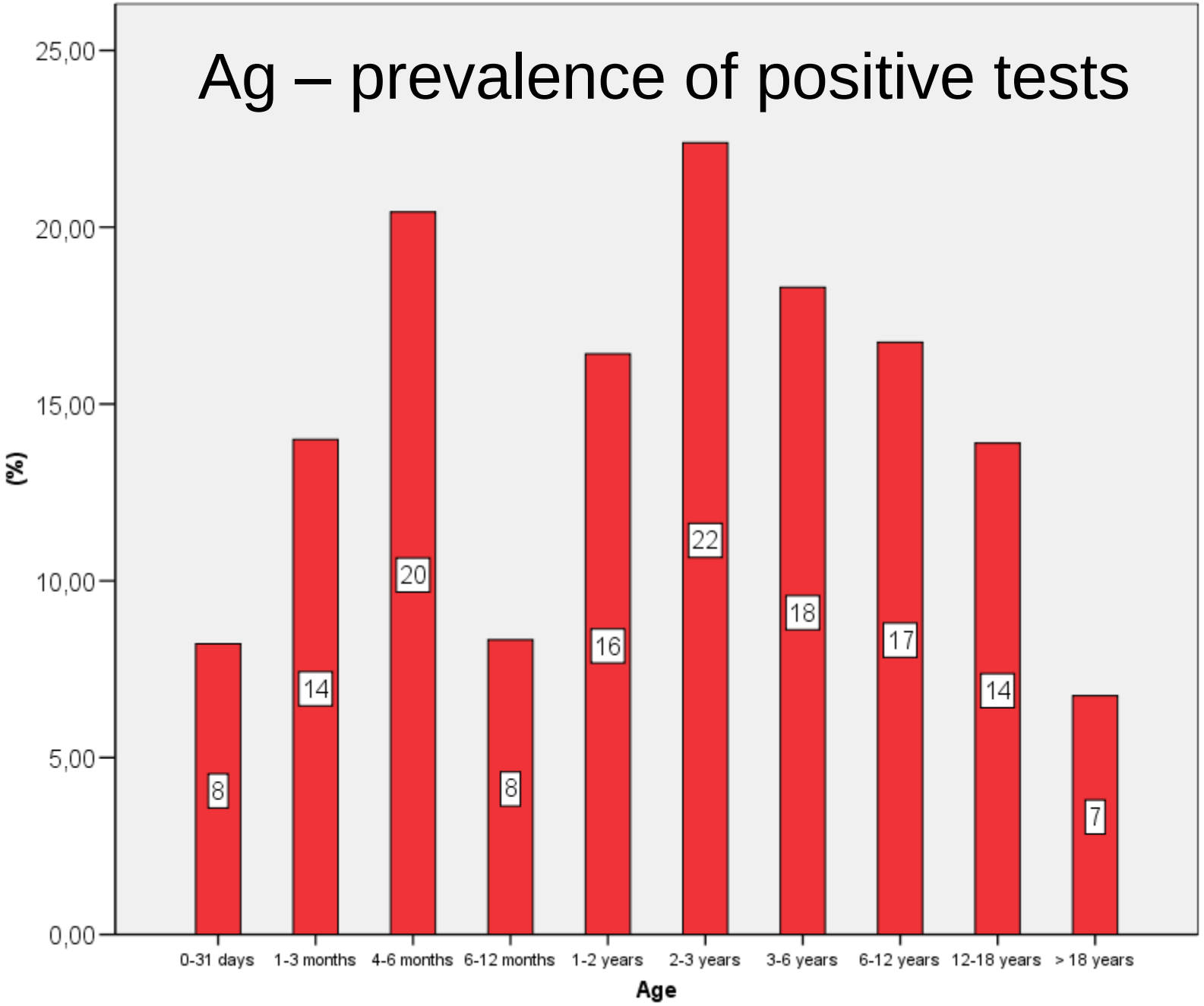
- symptom related clinical and laboratory investigations, thorough anamnesis
- BV-antigen, serum antibodies and circulating immune complexes : ELISA
- Statistics: Mann-Whitney-U-Test, Relative risk ratios

extinction value ELISA	
< 0.10	negative
0.10 - 0.12	questionable
0.12 - 0.15	weak positive
0.15 - 0.30	positive level 1
0.30 - 0.60	positive level 2
0.60 - 1.00	positive level 3
> 1.00	positive level 4

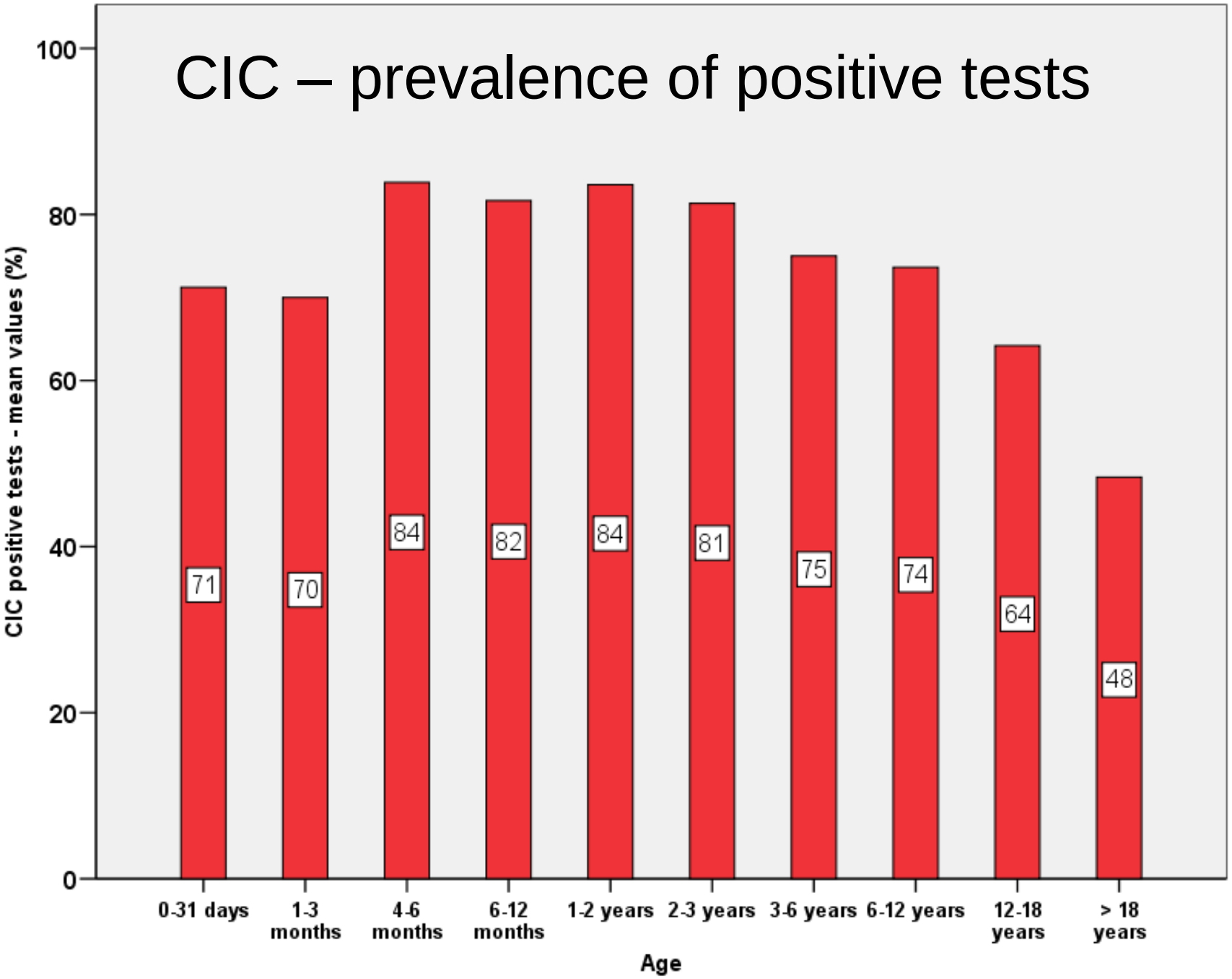
Distribution of examinations within age groups



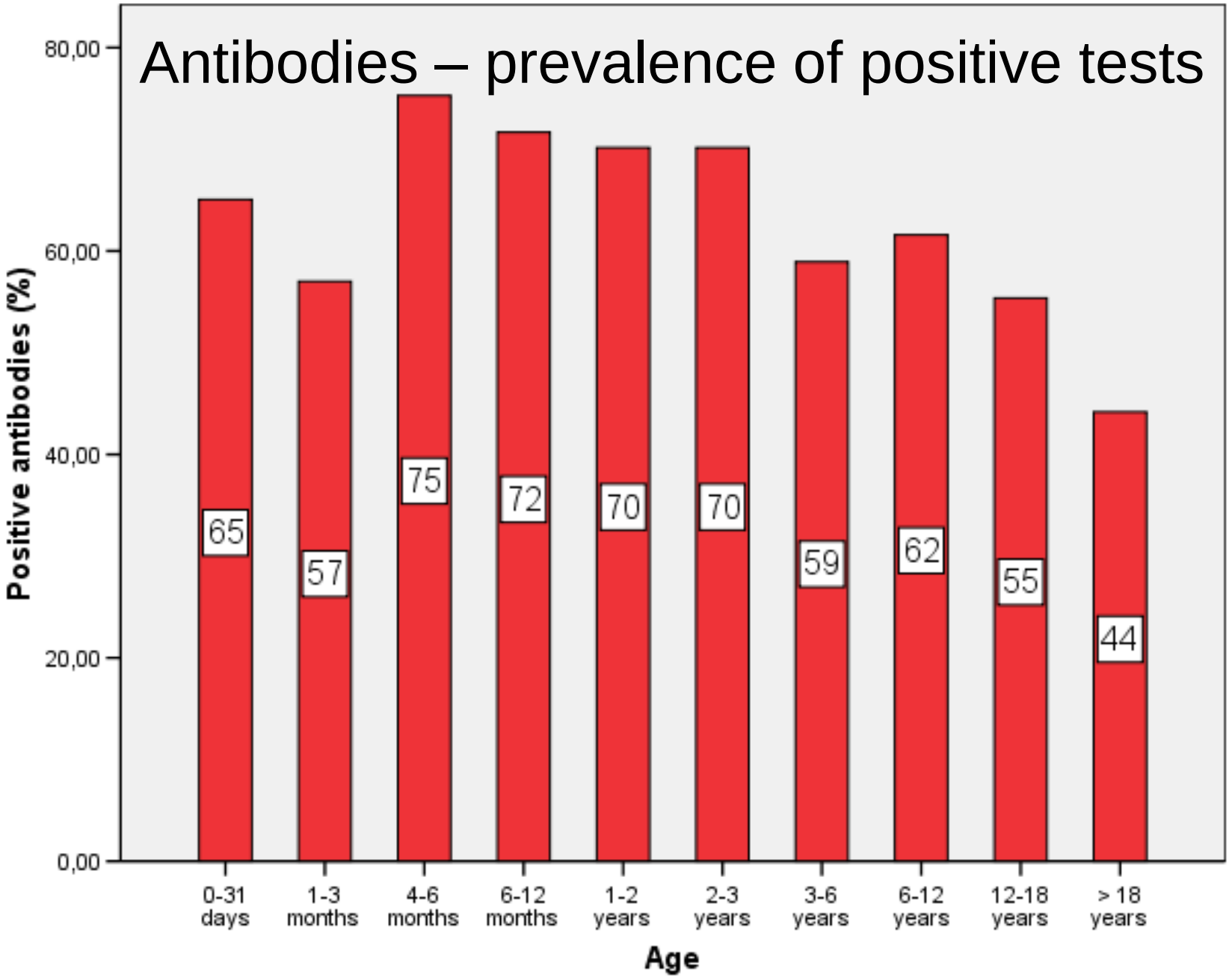
Ag – prevalence of positive tests



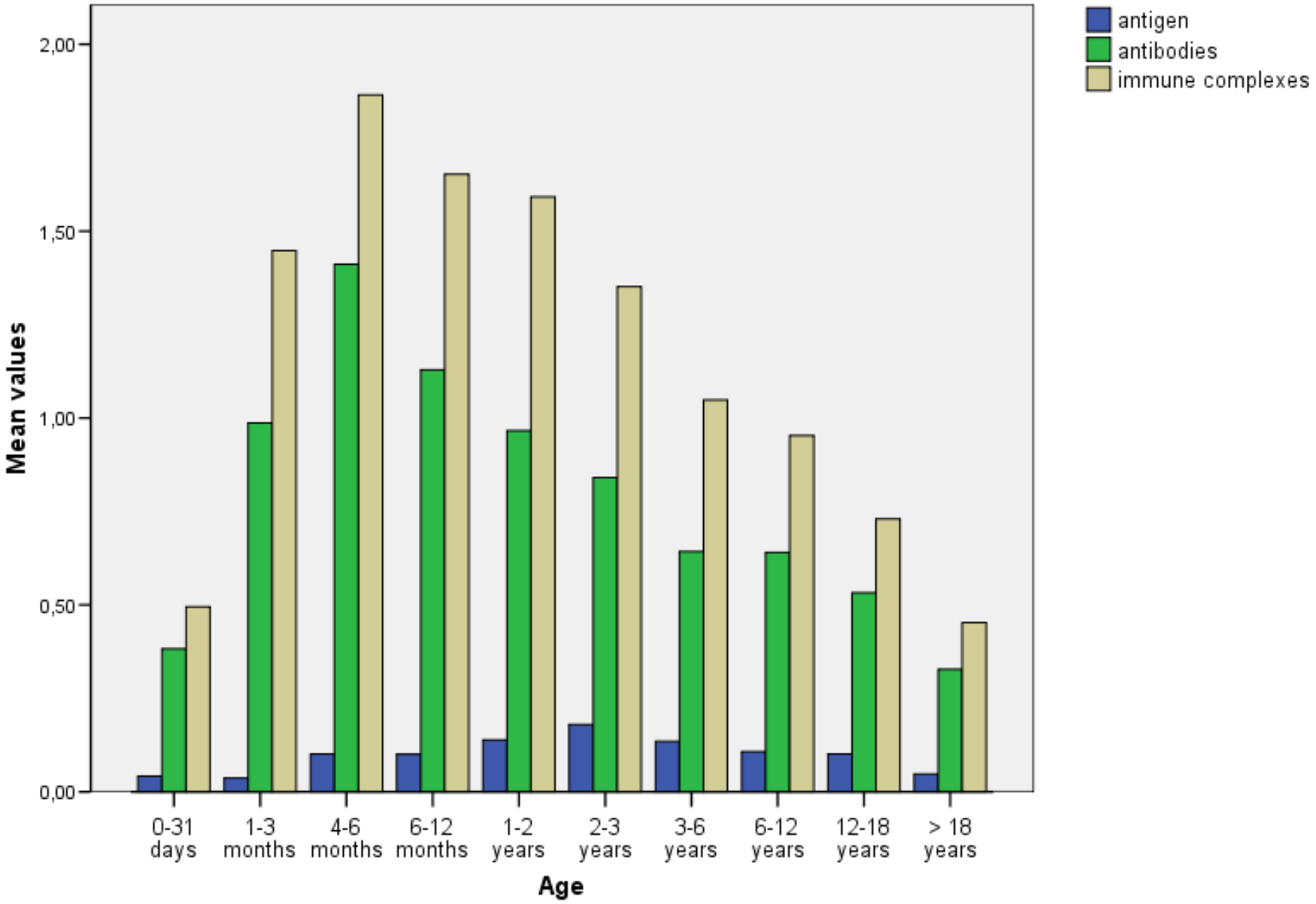
CIC – prevalence of positive tests



Antibodies – prevalence of positive tests



Course of activity markers (range 0-4)



118 mother (M) –newborn (NB)-pairs positive BV markers at the day of birth:

- 3 of 114 mothers were antigen positive at labor (level 1, 2 and 3 respectively),
- two of their children (of mothers with level 2 or 3) had BVAG at level 2.
- The level of antigenemia in mothers at labor were thus less than in the general population (2,6% vs. 7%).
- The mother with level 1 BVAG had nevertheless a child with level 1 CIC whereas the other mothers had children with level 4 (mother BVAG 3) and 2 (mother BVAG 2).
- Among the mothers without antigenemia 24 newborns were CIC positive (level 1-3, mean 1,46).

	M	NB
Ag	3	2
Ab	19	24
CIC	20	27

Infection of mothers and their newborns

Investigations at birth and 4 weeks later

- 39 mother-newborn pairs
- Condition: positive maternal markers
- Risk: Positive neonatal markers

Positive marker	OR (RelRisk Ratios) at birth	OR (RelRisk Ratios) later than 4 weeks after birth
Antibodies	4,6 (2,3) 95% CI OR: 1,1-18,8	2,2 (1,2) 95% CI OR: 0,8-6,4
Immune complexes	3,2 (1,5) 95% CI OR: 0,8-12,9	0,4 (0,9) 95% CI OR: 0,1 -1,4
Antigen	0,05 95% CI OR: 0,01-0,2	0,9 95% CI OR: 0,9-1,0

Patients (N = 580) from 2178 in total

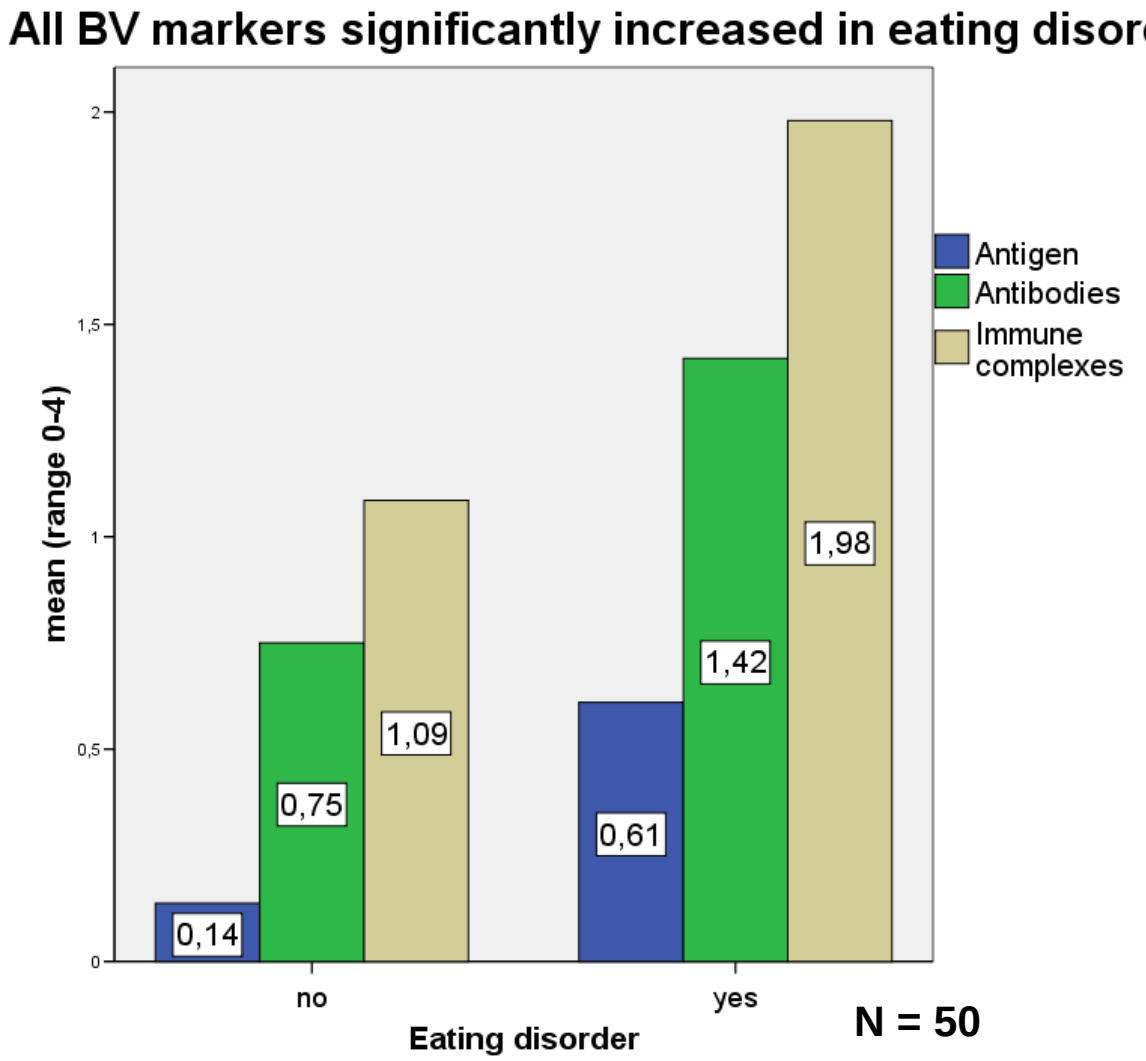
Abdominal pain	**210**
Failure to thrive	**165**
Loss of appetite	**139**
Headache	**135**
Depression	**88**
Manifest eating disorder	**50**
Epileptic seizures	**47**
Migraine	**44**
statomotoric retardation	**35**
Crohn disease	**29**
Ataxia	**17**
Ulcerative colitis	**13**
Anorexia	**10**

Relative risks for BV markers to detect disease

2178 patients investigated, semiquantitative evaluation 1-4

Disease / Symptom (n)	Relative risks for detection of BV level >=1 **95% CI [..]**				Relative risks for detection of BV level >=2 **95% CI [..]**		
	Ag	**Ab**	**CIC**		**Ag**	**Ab**	**CIC**
Crohn Disease (29)	2,86 1,1– 7,6	1,83 0,9-3,8	1,10 0,5-2,3		1,27 0,2-9,5	3,21 1,5-6,7	1,19 0,5-2,6
Colitis ulcerosa (13)	4,09 1,1-15,0	2,05 0,7-6,3	1,76 0,5-5,7		0,97 0,97-0,98	5,28 1,8-15,8	1,63 0,7-5,8
Ataxia (17)	5,75 2,0-16,5	1,44 0,6-3,8	1,88 0,7-5,3		4,83 1,1-21,7	1,38 0,4-4,2	0,94 0,3-2,7
Developmental Delay (35)	4,14 1,8-9,3	2,19 1,1-4,4	3,16 1,4-7,3		6,33 2,4-16,9	1,80 0,8-3,8	3,90 2,0-7,8
Eating disorder (50)	6,95 3,7-12,9	3,38 1,8-6,3	2,25 1,2-4,3		8,94 4,1-19,4	4,31 2,5-7,6	3,80 2,1-6,8
Failure to thrive (165)	2,53 1,6-4,0	1,72 1,3-2,4	2,12 1,5-3,0		3,21 1,7-6,2	2,01 1,4-2,9	2,46 1,8-3,4
Epileptic seizures (47)	2,41 1,1-5,5	1,75 1,0-3,1	1,86 1,0-3,5		2,48 0,8-8,2	1,9 1,0-3,6	2,01 1,1-3,6

Comparison of BV marker levels between healthy and diseased individuals



Ataxia

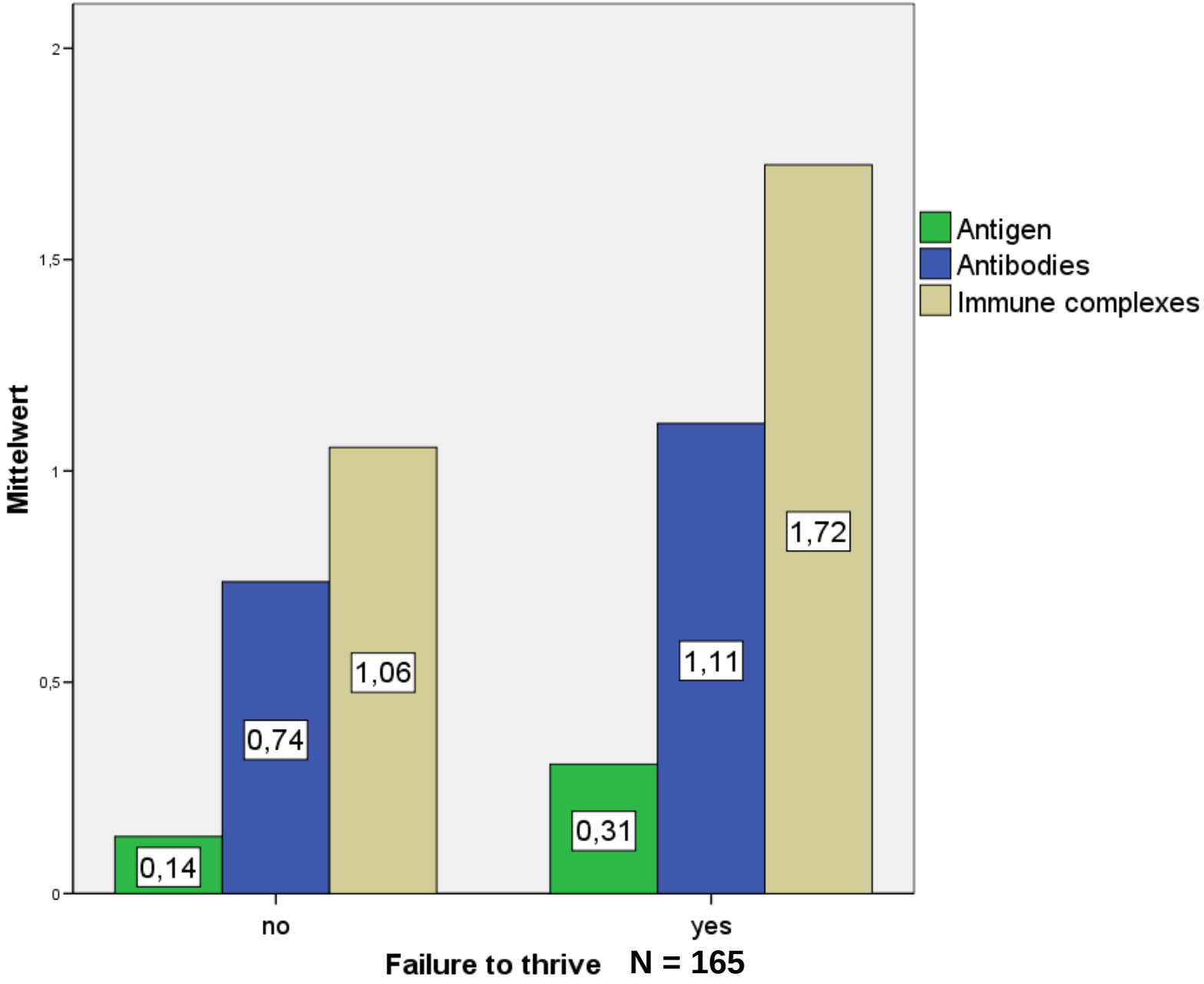
- Purkinje cell loss in neonatally infected rats
- While BDV infection of rats on postantal day 1 results in dramatic cerebellar hypoplasia associated with the loss of PCs and granule cells, the cerebella of rats infected on day 15 are not hypoplastic

(Rubin et al. 1999. Viral teratogenesis: brain developmental damage associated with maturation state at time of infection. Brain Res. Dev. Brain Res.112:237–244.)

Relevance of failure to thrive

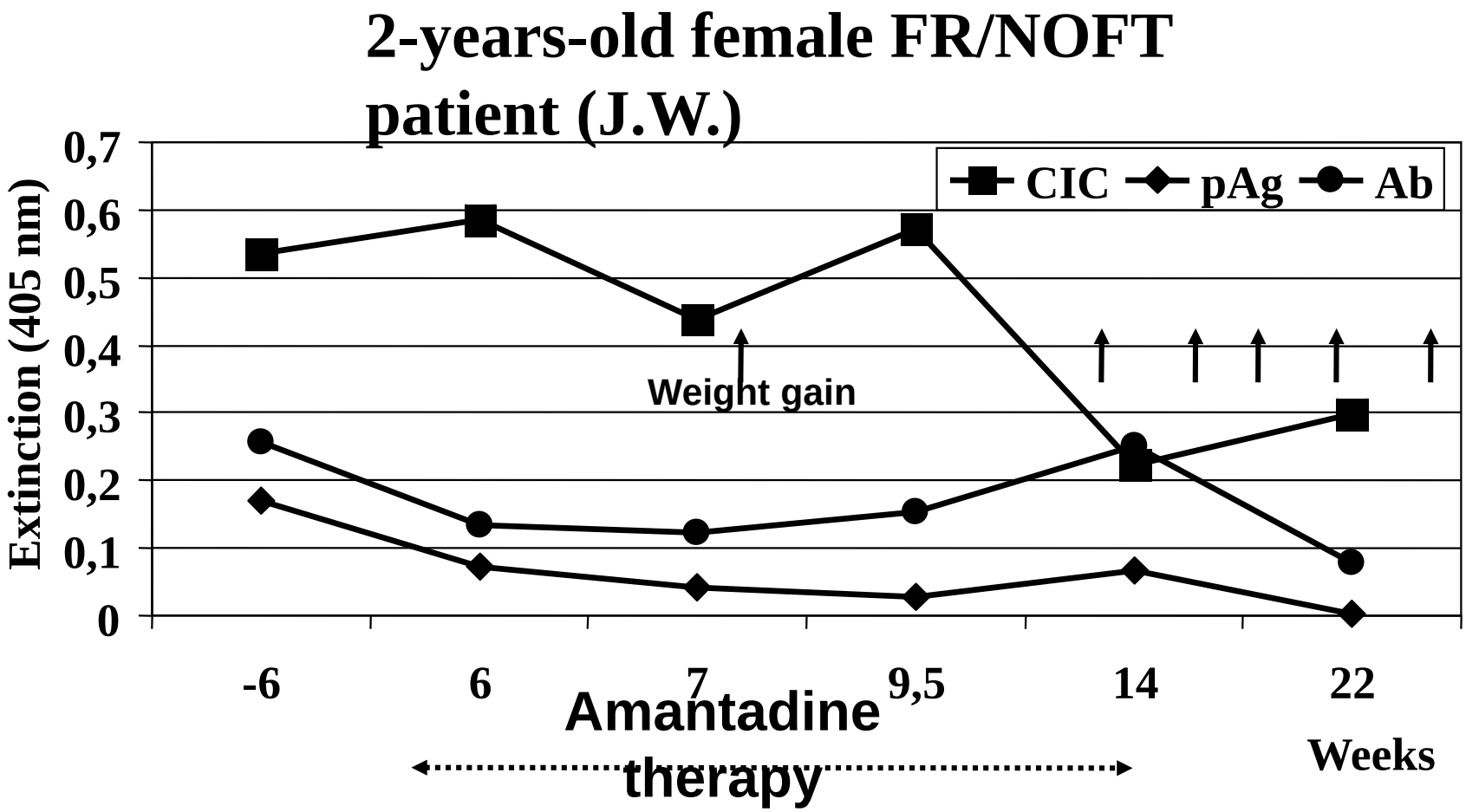
- Medical:
  - Signif. lower mental development index (Chatoor et al *Pediatrics* 2004;113;e440-e447)
- Psychological
  - „Failure to thrive as a manifestation of child neglect“ (Block (2005) Pediatrics **116**(5): 1234-7)
  - „The study failed to show that specialist health visitor intervention conferred additional benefits for the child“ (Raynor (1999). Arch Dis Child **80**(6): 500-6)
  - „social and maternal characteristics had little influence on infants' weight gain, apart from a strong, but transient effect of postnatal depression“ (Wright (2006). Arch Dis Child **91**(4): 312-7.
- Economic:
  - significant longer stay in hospital ($p < 0{,}001$, N :2380 vs. 44)
  - „Insecurely attached children with early histories of NOFT were rehospitalized nearly twice as often as securely attached children“ (Brinich *Journal of Child Psychology and Psychiatry* 1989, Vol. 18, No. 2, Pages 142-152)

Highly significant higher BV markers in failure to thrive-group

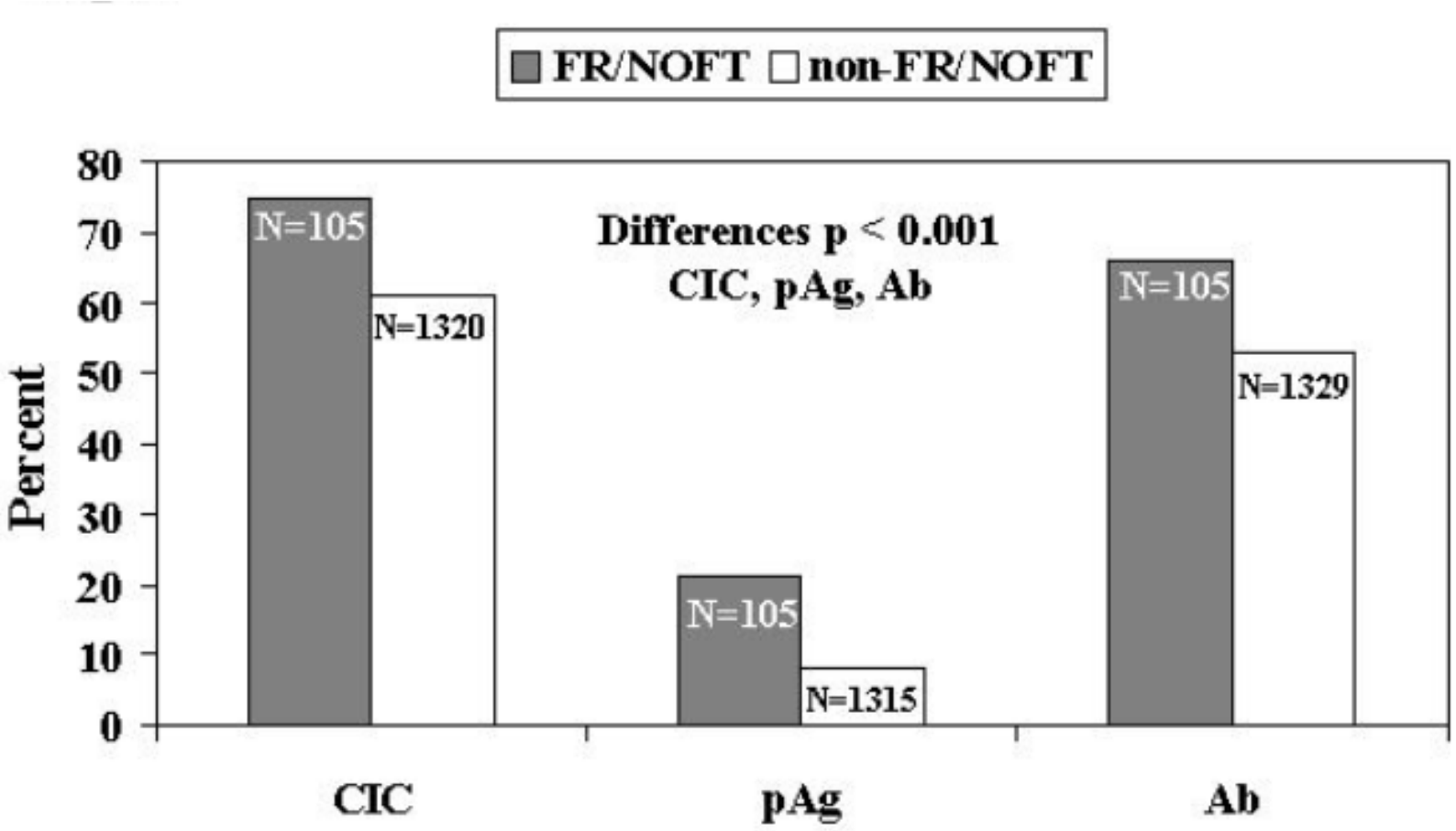


Effect of amantadine therapy

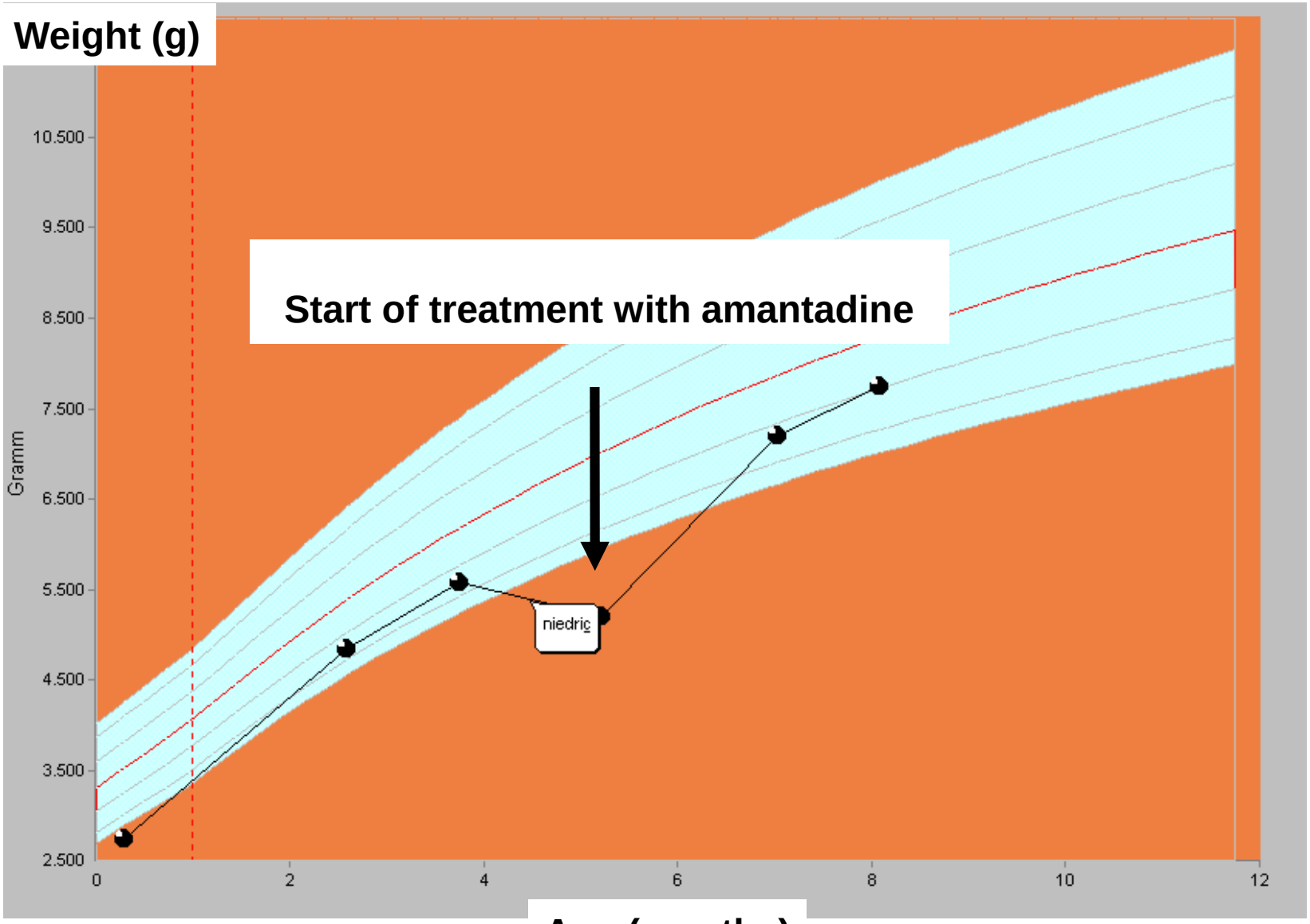
- 10 of 11 children with food denial responded with weight gain and /or improvement of their food acceptance


2-years-old female FR/NOFT patient (J.W.)
CIC
pAg
Ab
Extinction (405 nm)
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Weight gain
-6
6
7
9,5
14
22
Weeks
Amantadine therapy

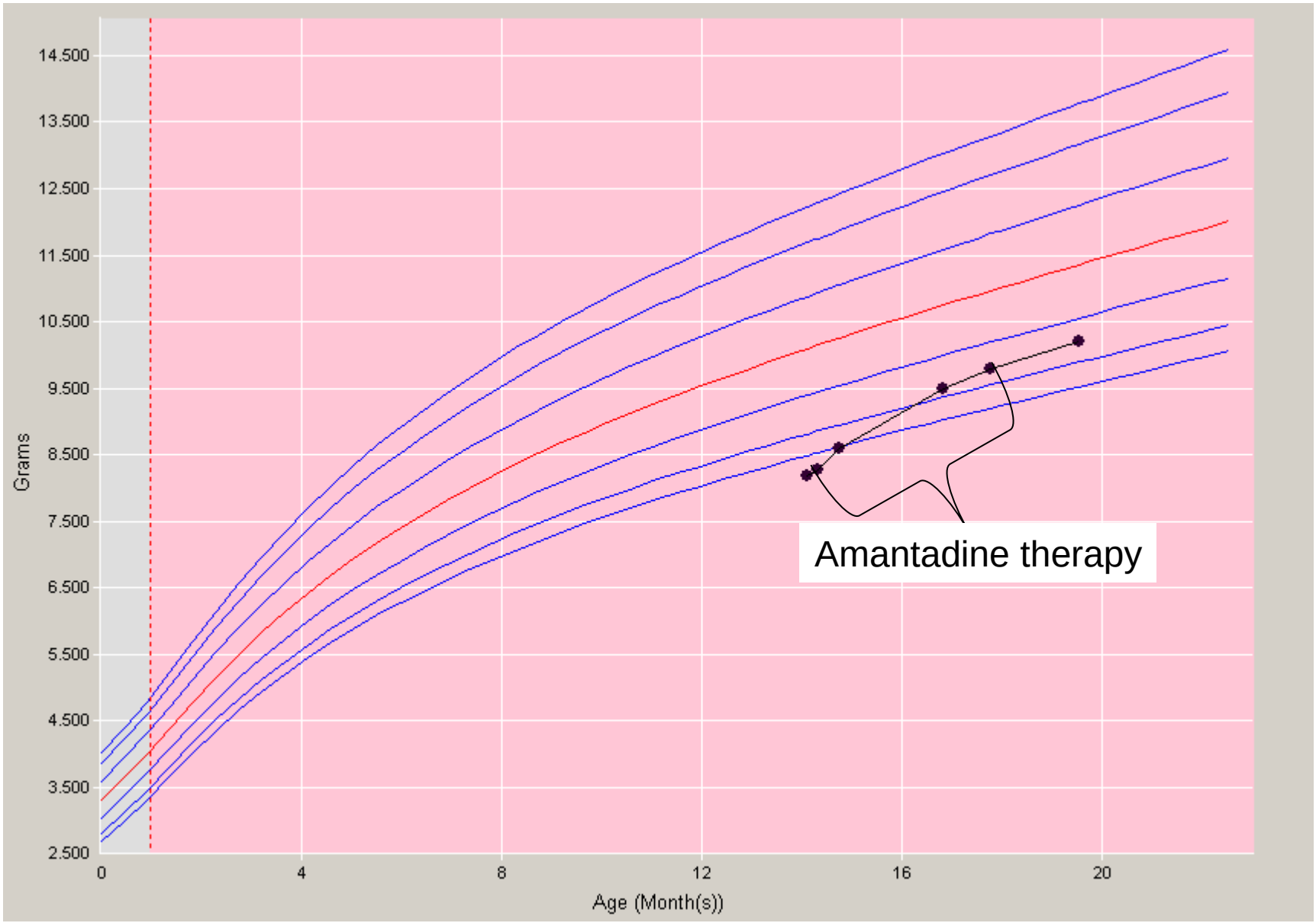
Non-organic failure to thrive (NOFT) and food rejection (FR)



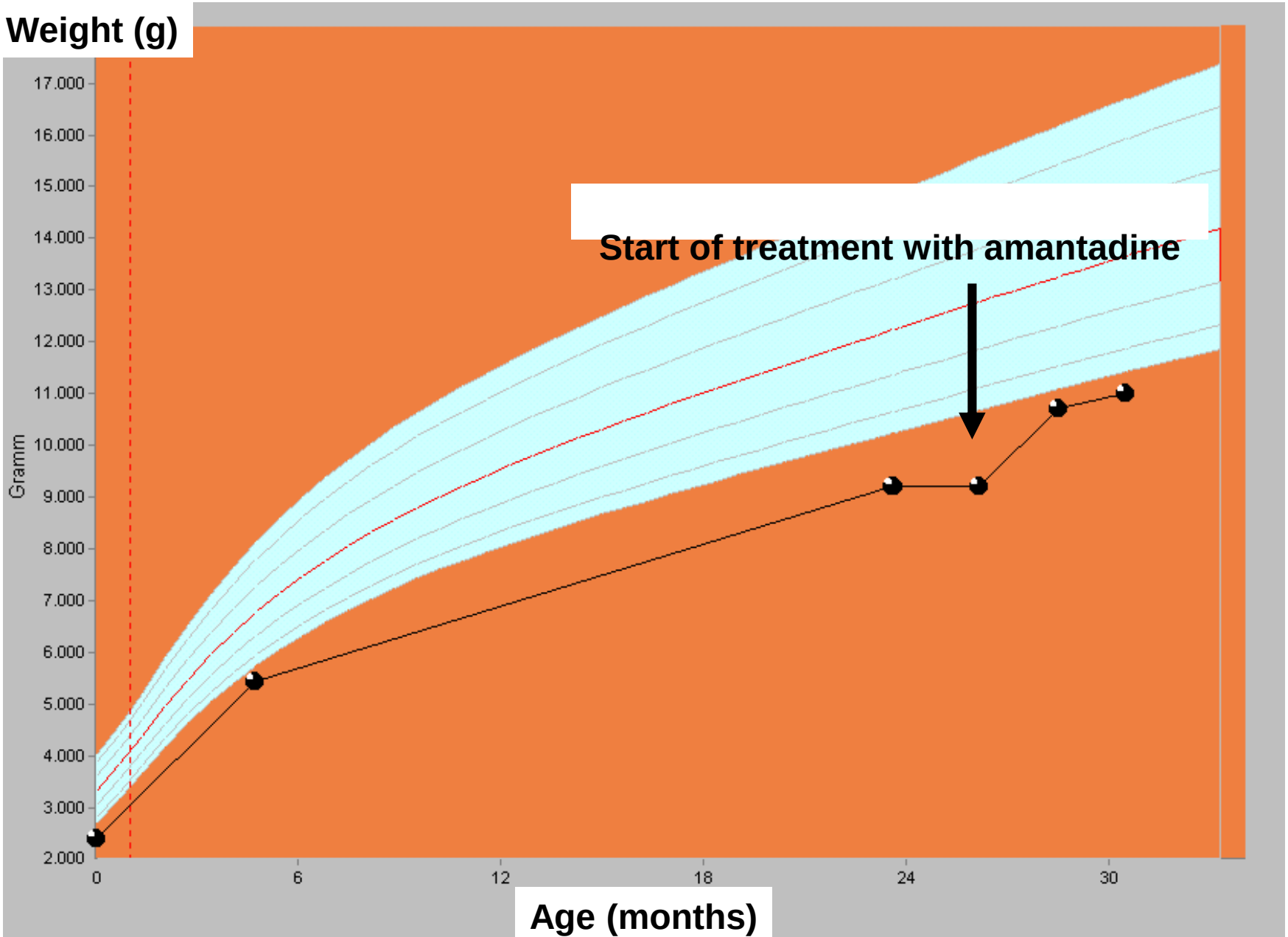
Effect of amantadine in a child with failure to thrive (K. G-L)



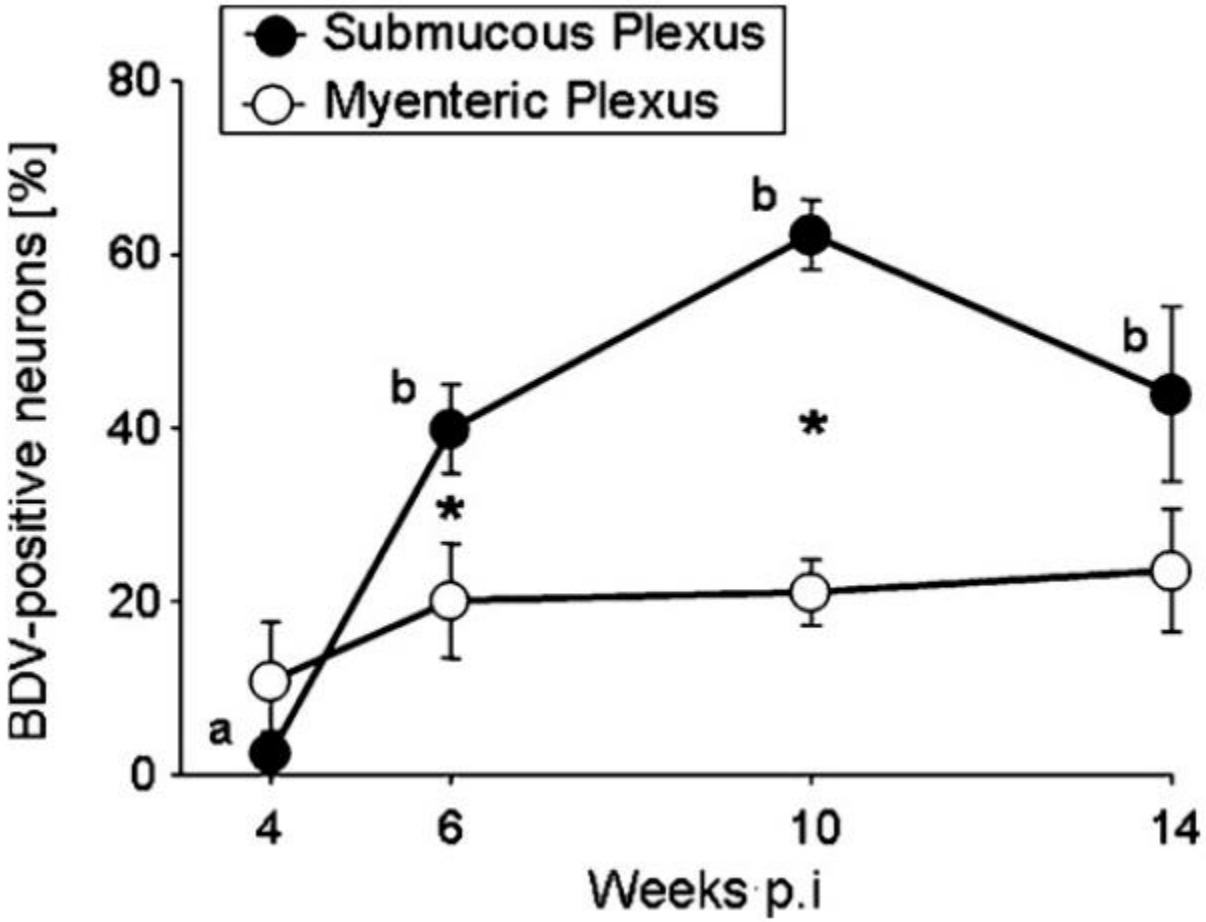
B. A.


14.500
13.500
12.500
11.500
10.500
9.500
8.500
7.500
6.500
5.500
4.500
3.500
2.500
Grams
0
4
8
12
16
20
Age (Month(s))
Amantadine therapy

Effect of amantadine in a child with severe failure to thrive (W.J.)

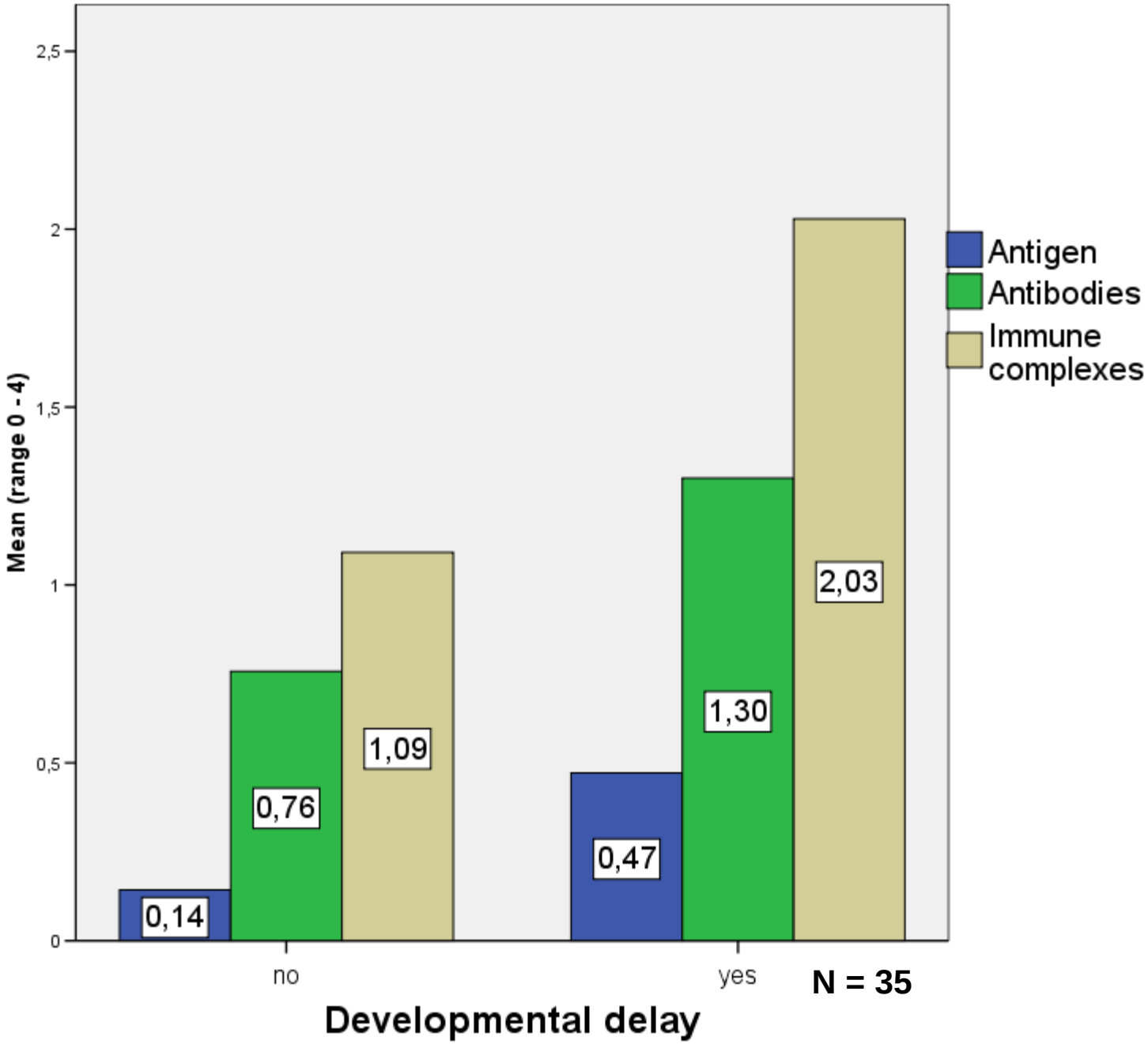


Analysis of 10062 myenteric and 4209
submucous neurones from 24 myenteric and 24 submucous plexus
preparations of 12 intracerebrally infected Lewis rats

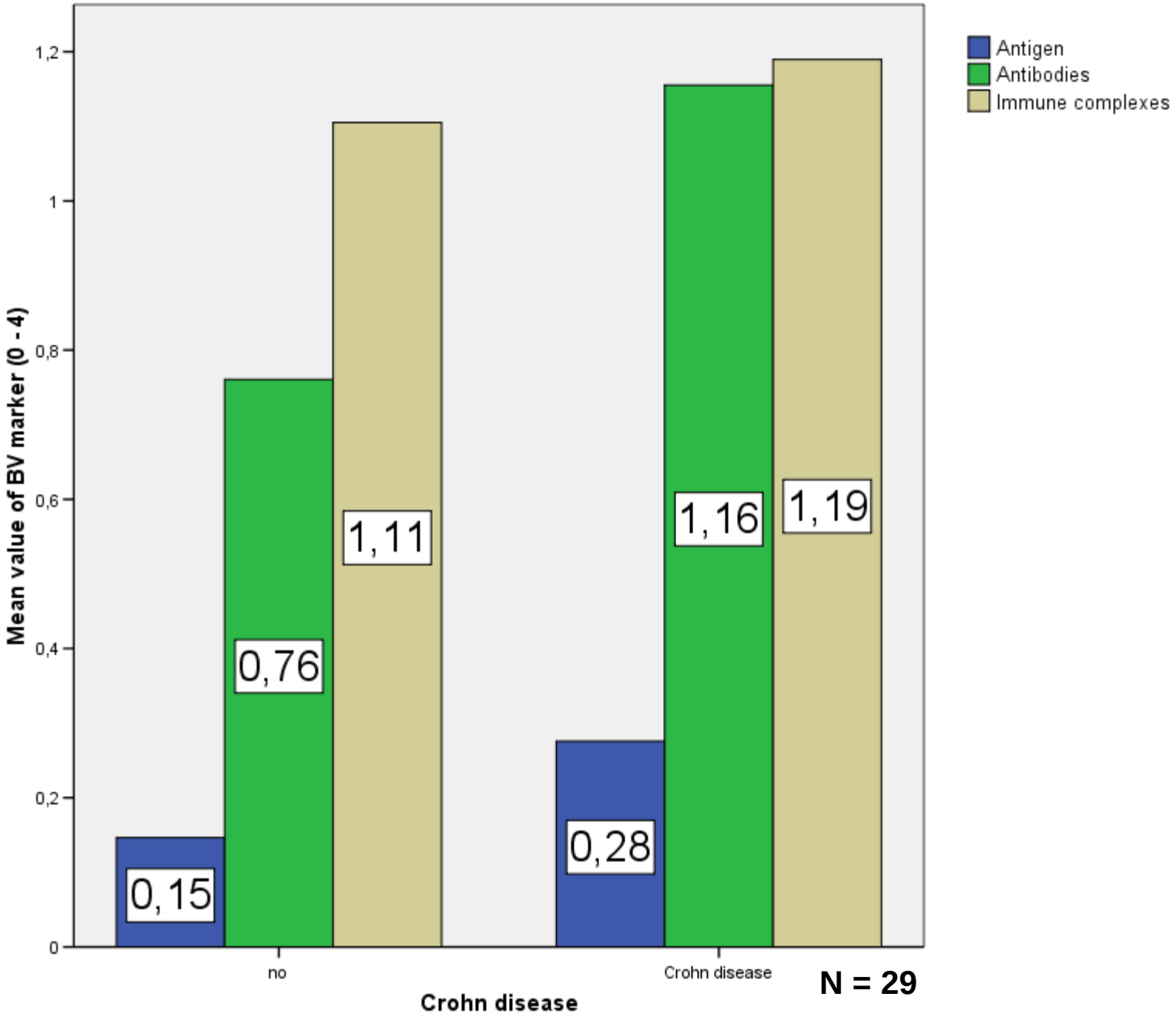


H. Pfannkuche et al. / Veterinary Microbiology 127 (2008) 275–285

All BV markers significantly increased in group of delayed children



Significant higher BV-antigen and -antibodies in Crohn disease



Significant Symptoms pointing to BV infection
M-W-U-test : $p < 0,05$ - * ; $p < 0,01$ - **

Symptom	Ab	Ag	CIC
Crohn	*	*	
Colitis ulcerosa	*	*	
Depression			*
Abdominal pain	**		
Failure to thrive	**	**	**

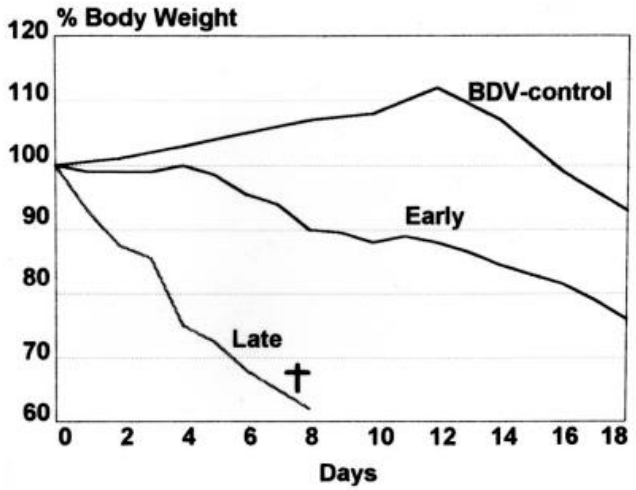


FIG. 4. Growth curves of BDV-infected, CY-treated rats receiving adoptive transfer of P205 T cells late (Late) or early (Early) after immunosuppression and of untreated, BDV-infected control animals (BDV-control). Day zero was the day of cell transfer (Early and Late) or BDV infection (BDV-control). †, death.

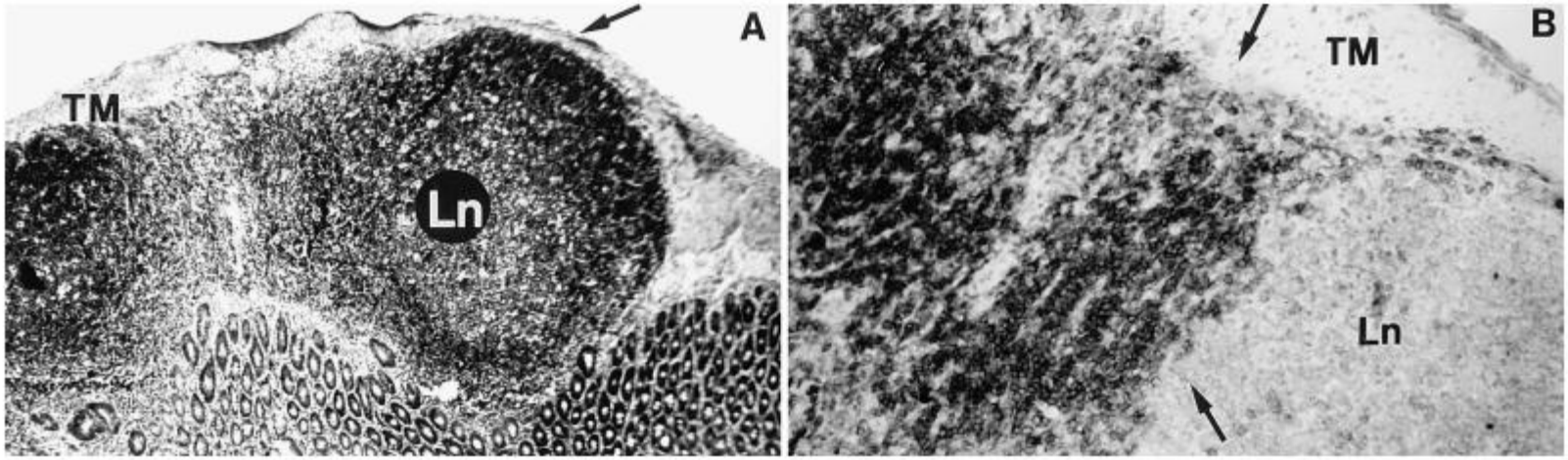


FIG. 3. Severe lymphocellular proliferation in Peyer's patches and diffuse proliferation within the intestinal wall in a BDV-infected immunosuppressed rat subjected to adoptive transfer of $CD4^+$ T-cell line P205 at day 10 after CY treatment. (A) Lymphocytic infiltration extends from the epithelial layer (lamina epithelialis) into the muscular layer (tunica muscularis), which is markedly reduced in size (arrow). Staining was done with hematoxylin and eosin. Magnification, ×50. (B) Immunohistochemical analysis of a corresponding slide with MAb OX-38 showing that most of the diffusely infiltrating cells outside the nodule are CD4 positive (arrows). TM, tunica muscularis; Ln, solitary lymph nodule. Immunohistochemical staining was done by the ABC method. Magnification, ×80.

Pflanz et al. JOURNAL OF VIROLOGY, Feb. 1995, p. 896-903

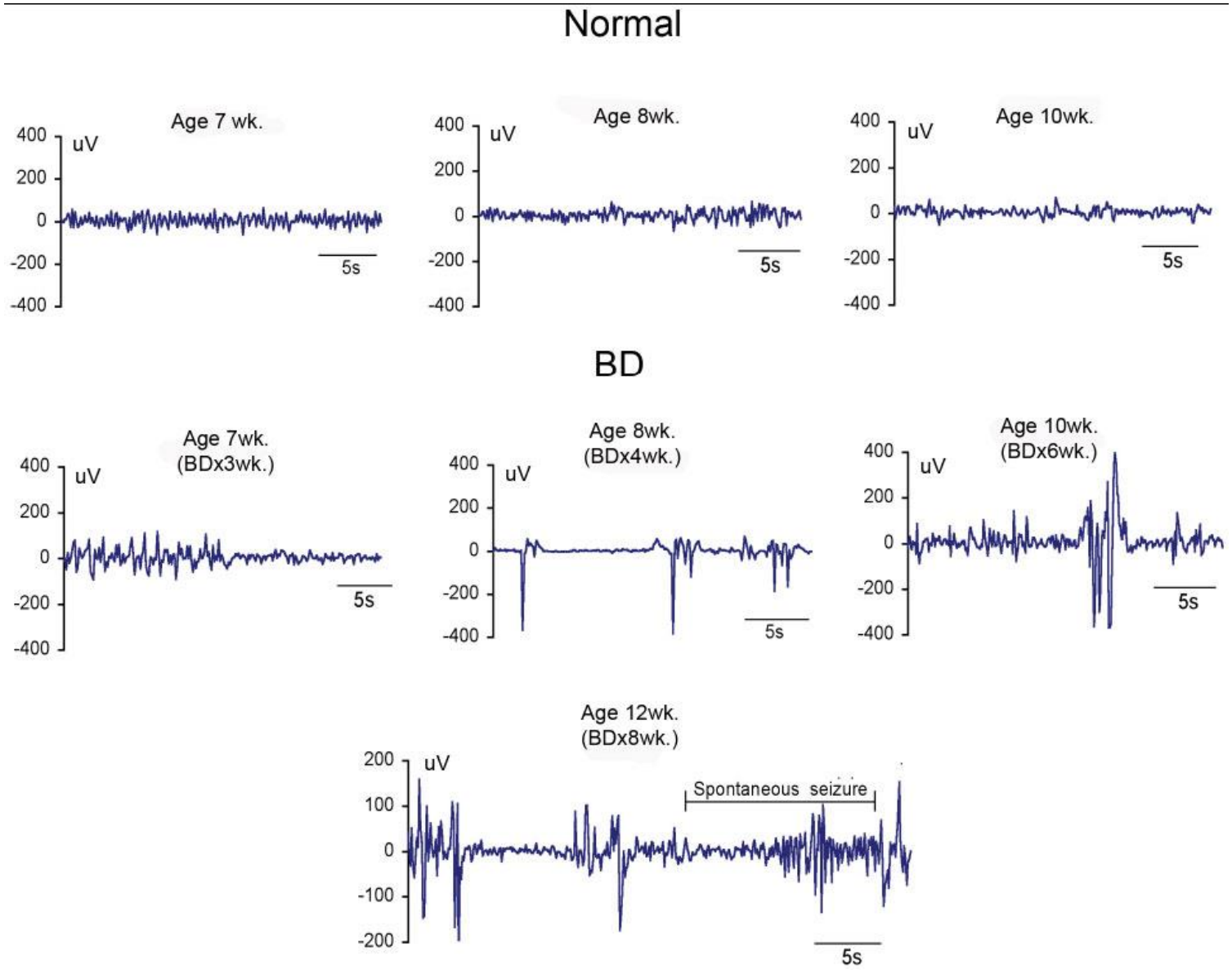
Significant Symptoms pointing to BV infection
M-W-U-test : $p < 0,05$ - * ; $p < 0,01$ - **

Symptom	Ab	Ag	CIC
Ataxia		**	
Migraine			**
Headache			*
Epileptic seizures	**		*

„Borna disease virus in the rat caused epileptic responses“ Marylou V. Solbrig et al. Brain (2006), 129, 642–654

Epileptic patterns in BV infected periadolescent rats

Marylou V. Solbrig et al. Brain (2006), 129, 642–654



Conclusion

- Prevalence of BV in children
  - Virus contact within the first year of life
  - Mostly no symptoms
  - Maximum prevalence 1 – 2 years of age

- Clinical correlation to BV infection
  - Food denial
  - Failure to thrive
  - Crohn disease
  - Ulcerative colitis
  - Epilepsy
  - Migraine etc.

- Treatment in otherwise intractable severe cases
  - Amantadine in severe cases of food denial and failure to thrive successful

Perspective

- Contemplate BV genesis of symptoms
- Functional disorders
  - Cerebral -Intestinal
  - Mental
  - Psychological
- Broader studies focused on distinctive symptoms
- Treatment of severe cases