Viral CNS infections in neonates

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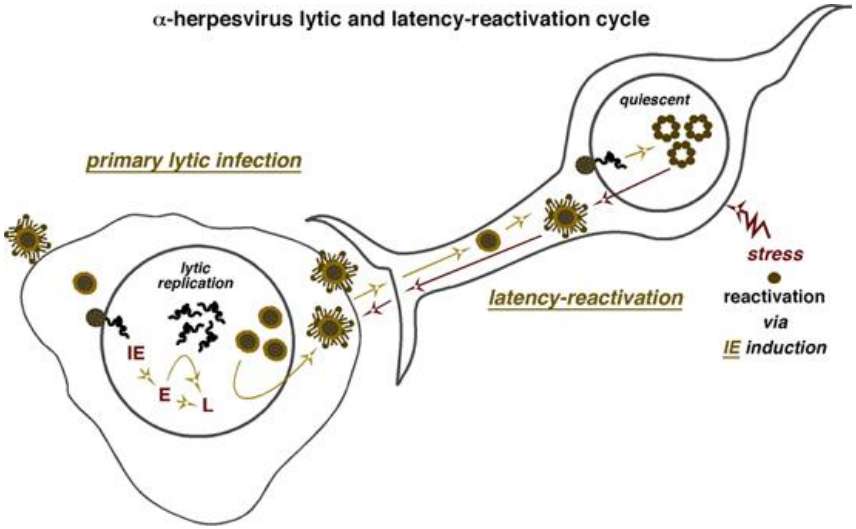
Overview

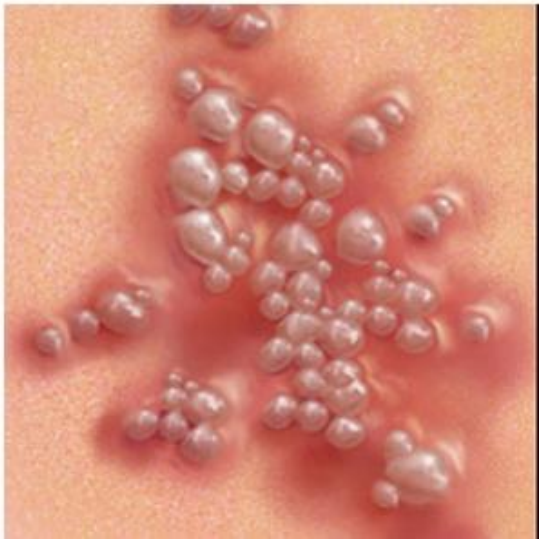
- Viral entry to the CNS
- Frequent patogens: Parechovirus, HSV, Enterovirus
- HSV encephalitis
- HSV encephalitis and receptor deficiencies
- Extended treatment after HSV encephalitis
- Enterovirus cases

Strategies used by neurotrophic viruses to cross the barrier system of the CNS

HSV primary viremia

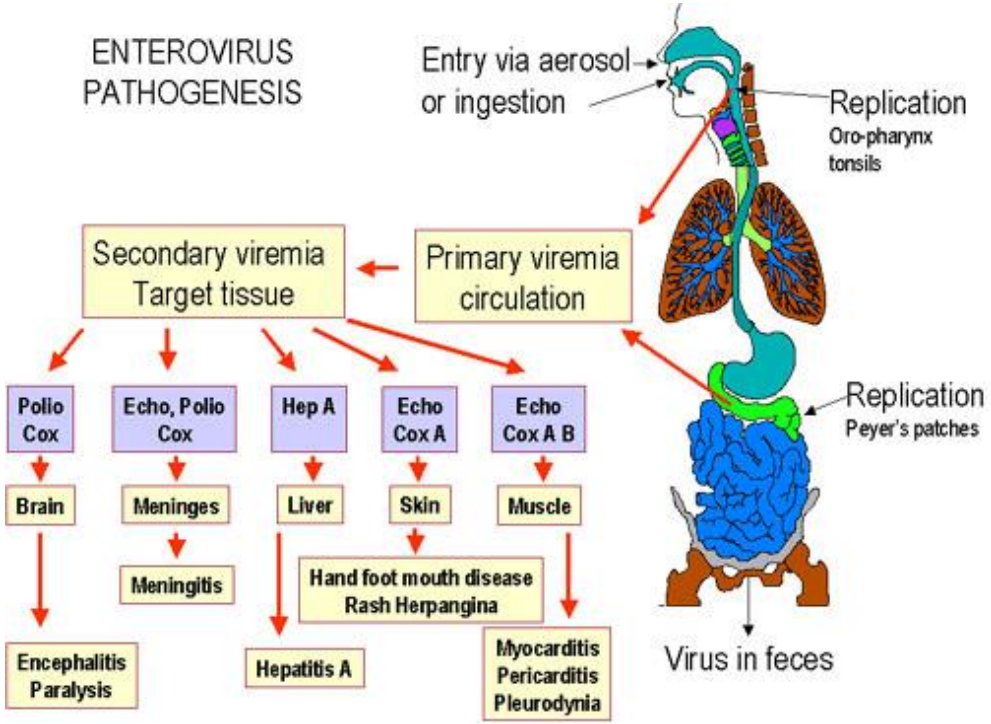
- HSV-1 replicates in oropharyngeal mucosa and the trigeminal ganglion becomes colonized
- HSV-2 replicates in genital, perigenital or anal sites with seeding to sacral ganglia





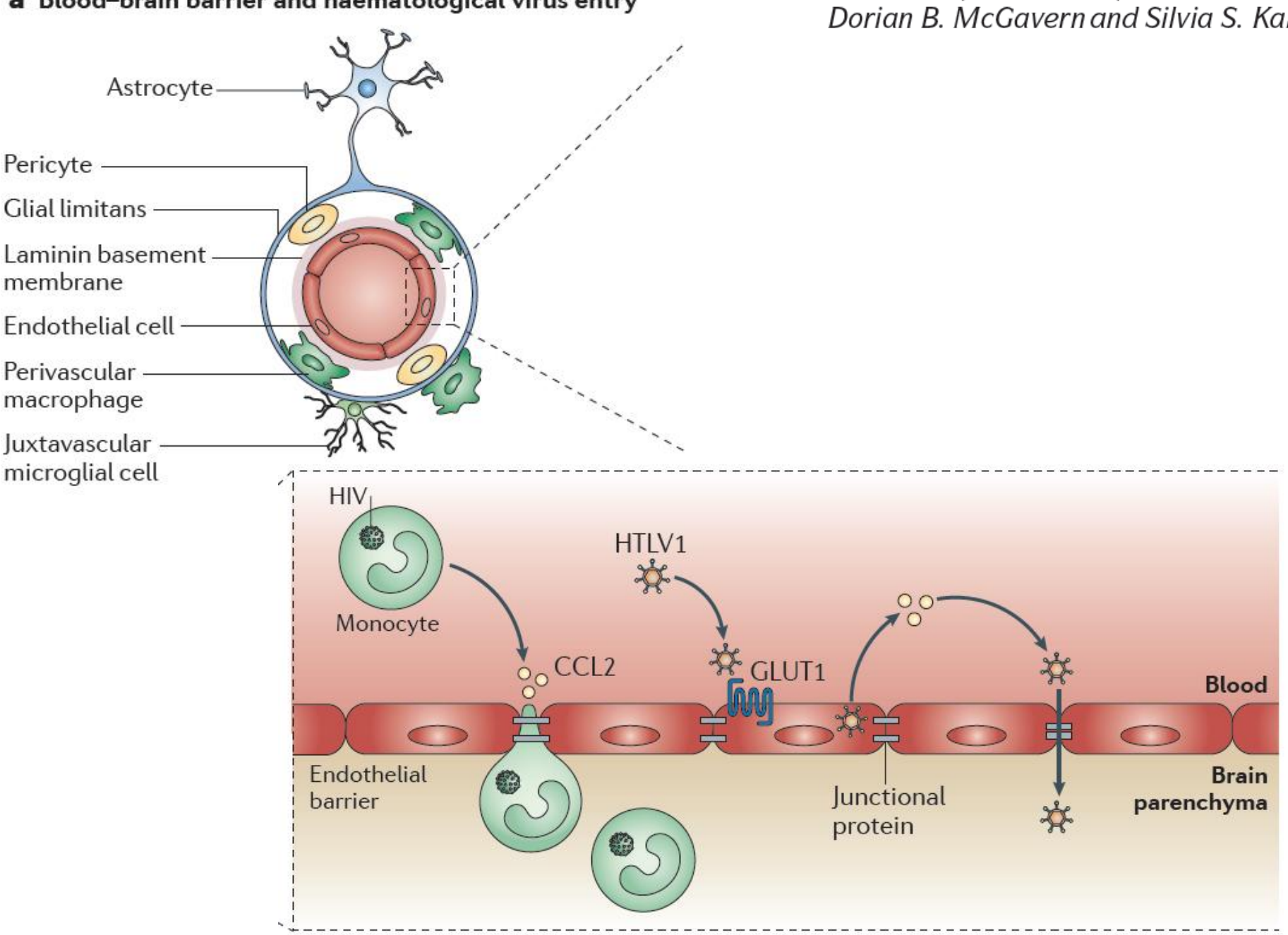
Enterovirus viremia

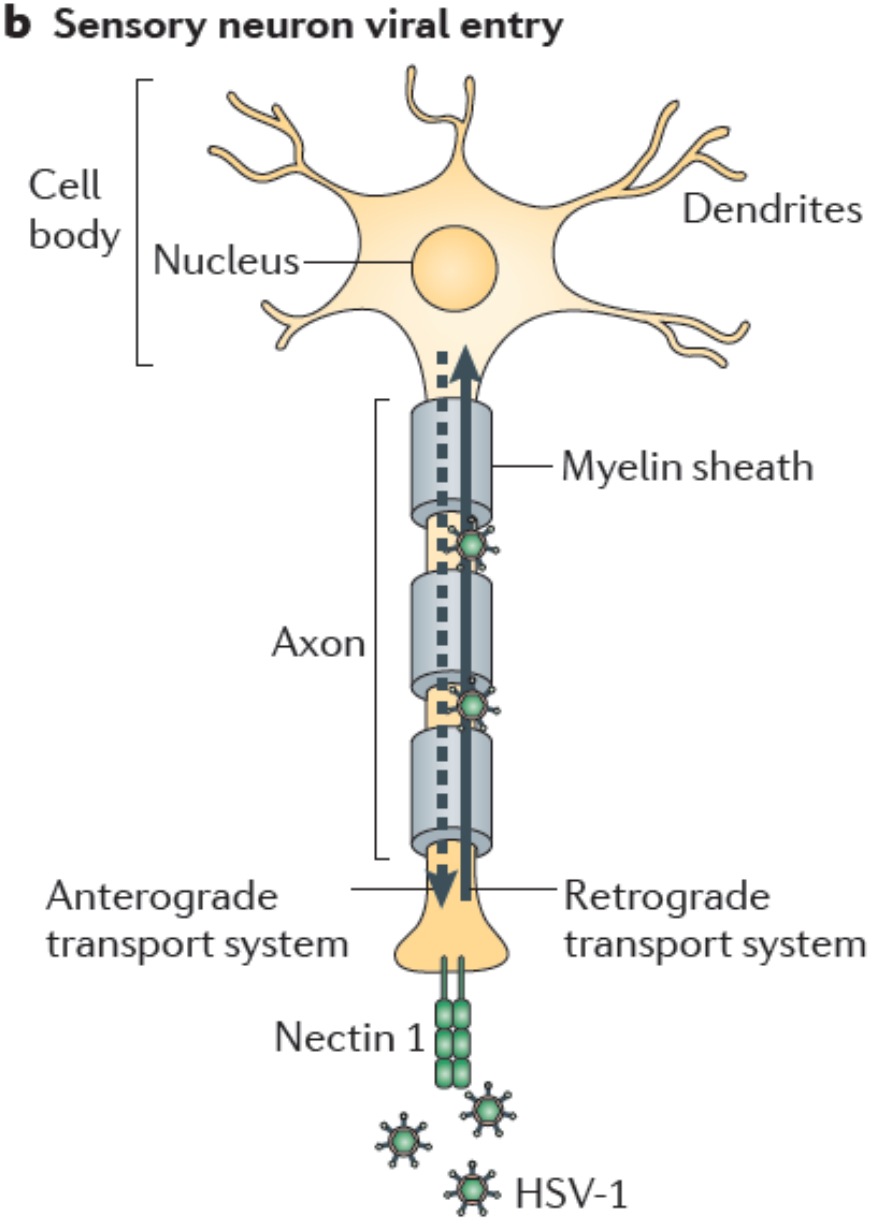
- Minor viremia either in oropharynx or in Peyers patches in lamina propria
- Major viremia from liver, lung, heart



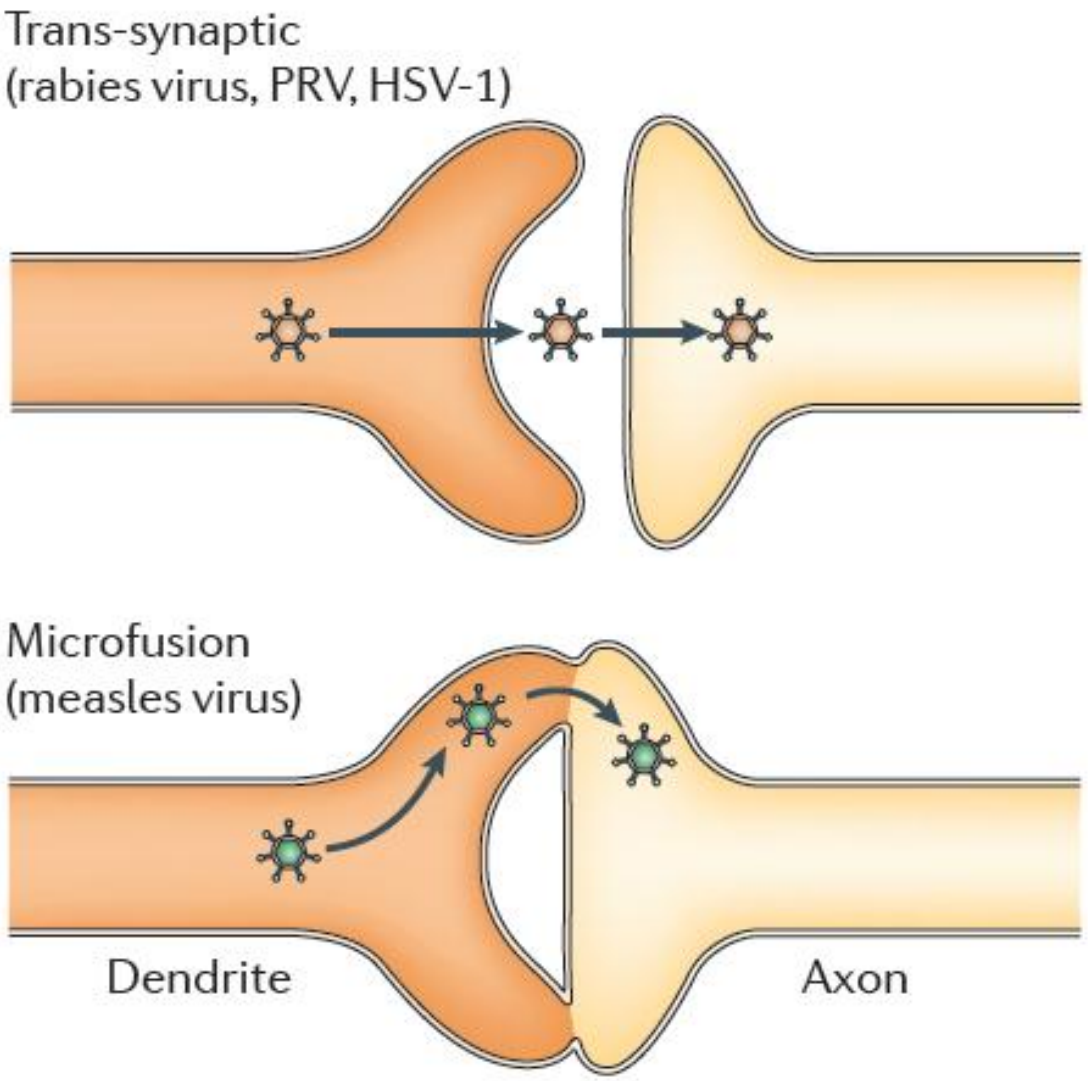
Different entrances to CNS

- **1) Crossing through vascular endothelium Neuro Muscular Junctions**
- JCV, Poliovirus, HTLV-1, EBV, WNV, Adenovirus
- **2) Trojan horse entry - infected leukocytes or macrophages**
- HIV, JCV, measlesvirus
- **3) Accessing peripheral nerves Avr. speed 3-10 mm/hour**
- Poliovirus poliovirus receptor PVR = CD155
- Coxsackievirus Adenovirus receptor CAR
- Rabiesvirus receptor NCAM
- HSV, VZV receptor PVRL1=Nectin1, PVRL2=Nectin2
- Influenzavirus H5N1 receptor ?
- **4) Occular infections**
- Adenovirus


a Blood–brain barrier and haematological virus entry
Astrocyte
Pericyte
Glial limitans
Laminin basement membrane
Endothelial cell
Perivascular macrophage
Juxtavascular microglial cell
HIV
Monocyte
HTLV1
CCL2
GLUT1
Blood
Endothelial barrier
Junctional protein
Brain parenchyma


b Sensory neuron viral entry
Cell body
Nucleus
Dendrites
Myelin sheath
Axon
Anterograde transport system
Retrograde transport system
Nectin 1
HSV-1

c Reterograde spread



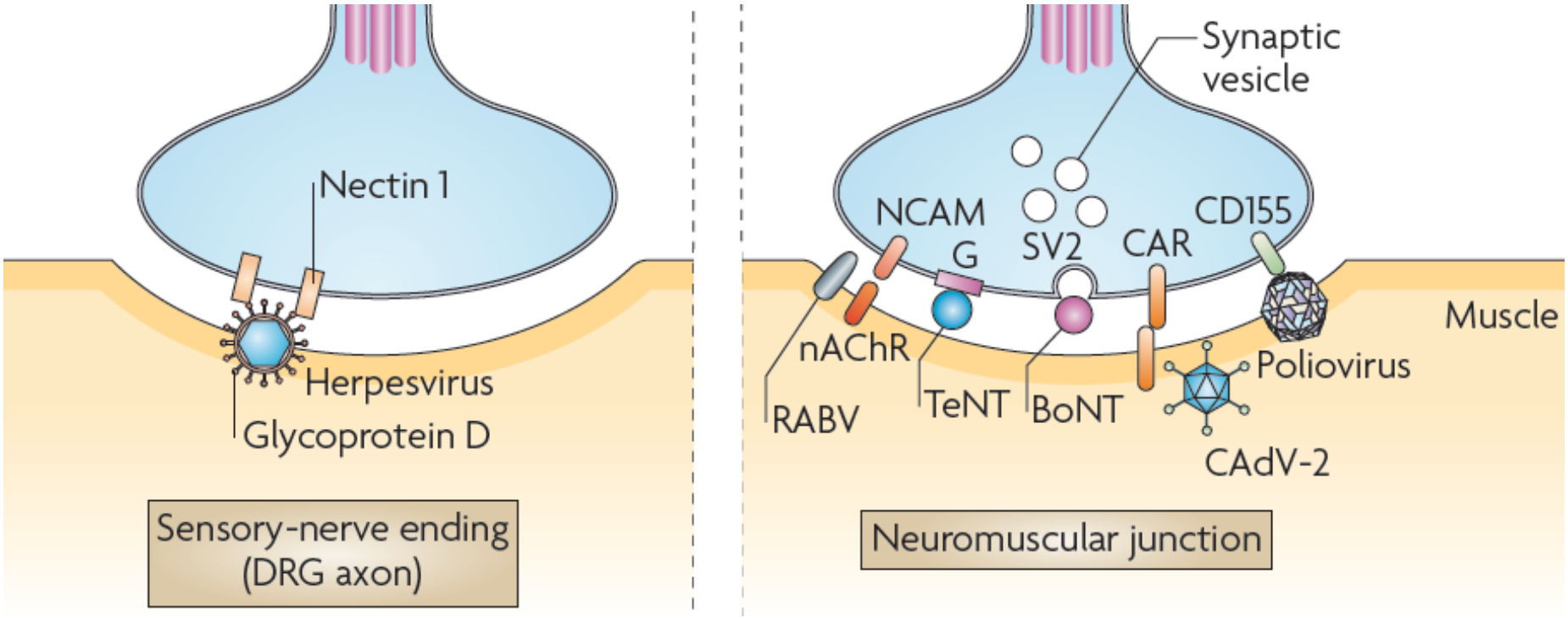
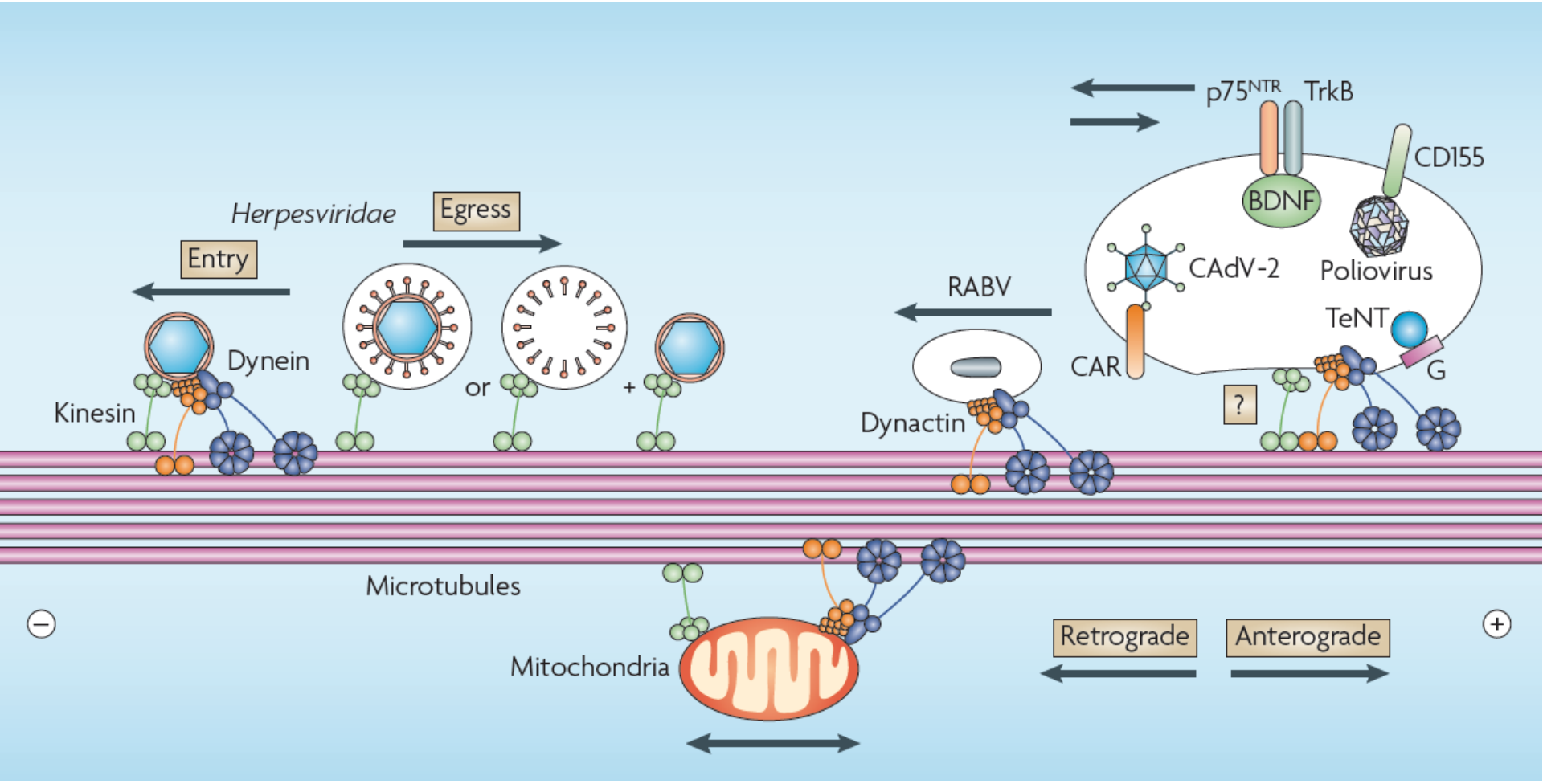
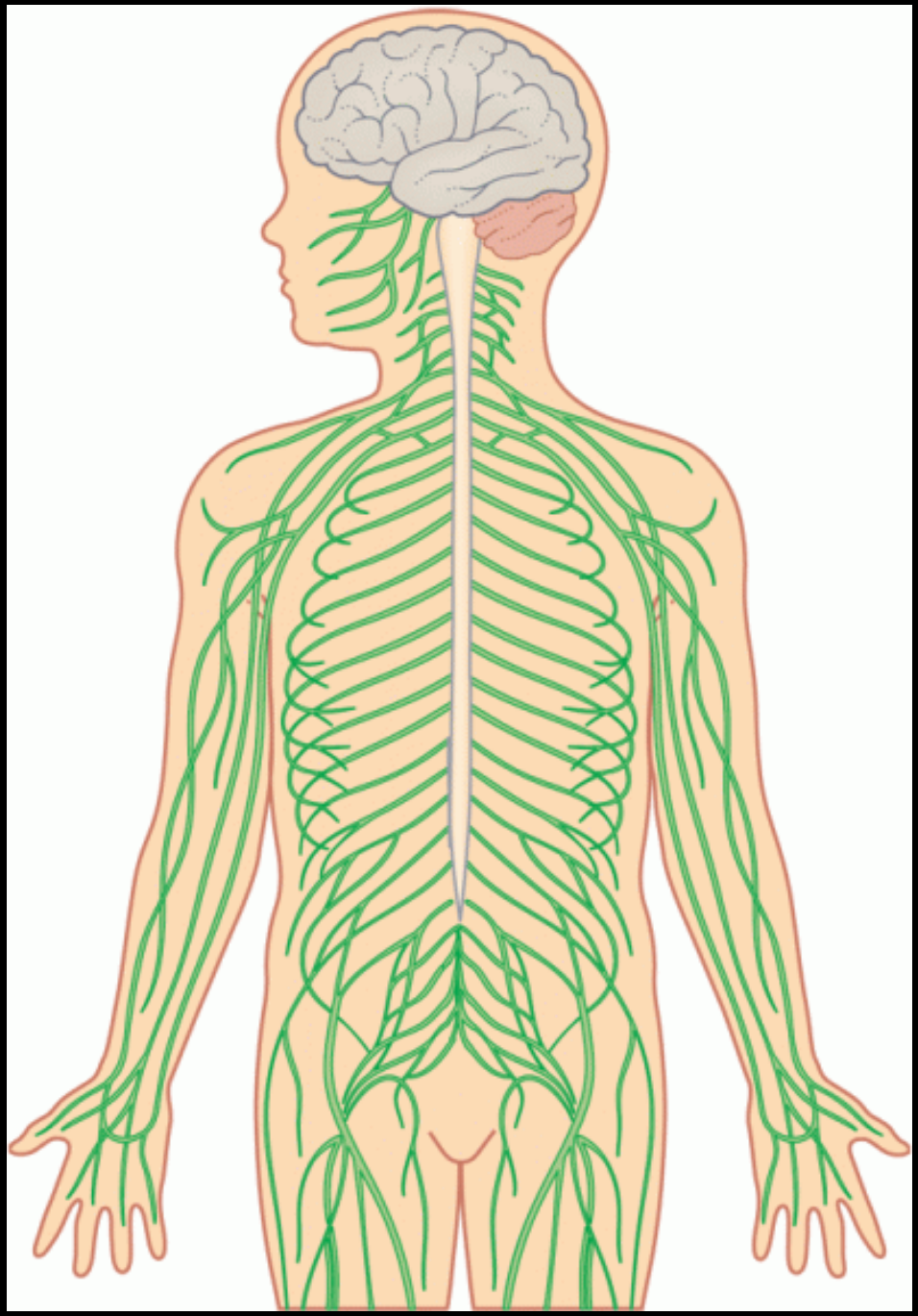


Figure 1 | **Neuronal architecture and axonal transport.**

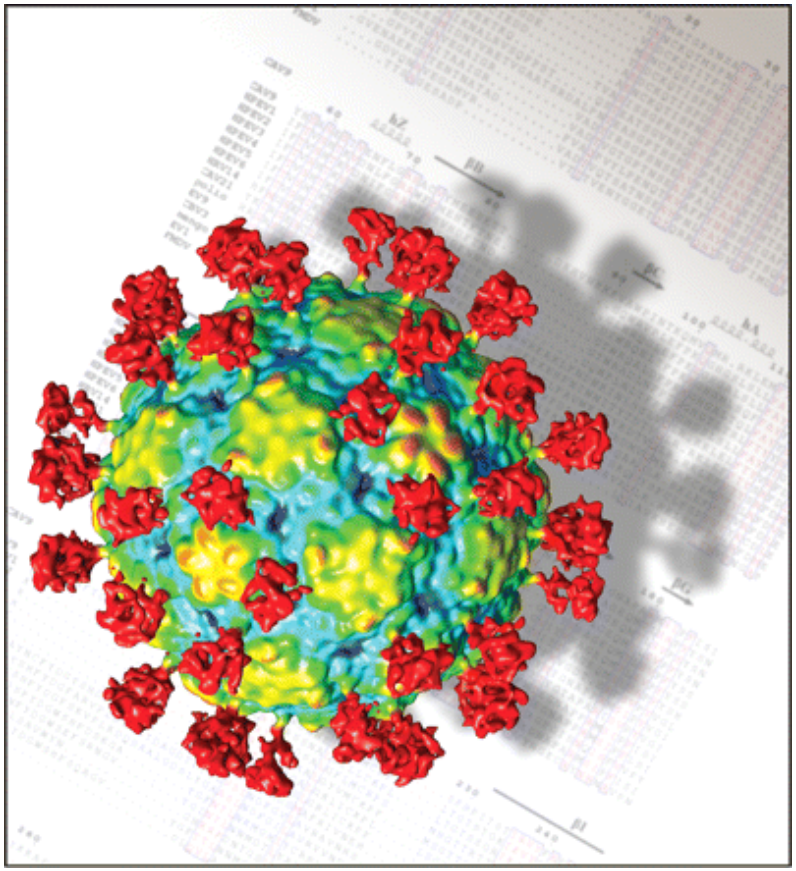

p75NTR
TrkB
CD155
BDNF
Poliovirus
CAdV-2
RABV
TeNT
CAR
G
?
Herpesviridae
Egress
Entry
Dynein
Kinesin
or
+
Dynactin
Microtubules
Mitochondria
Retrograde
Anterograde



Parechovirus in neonates

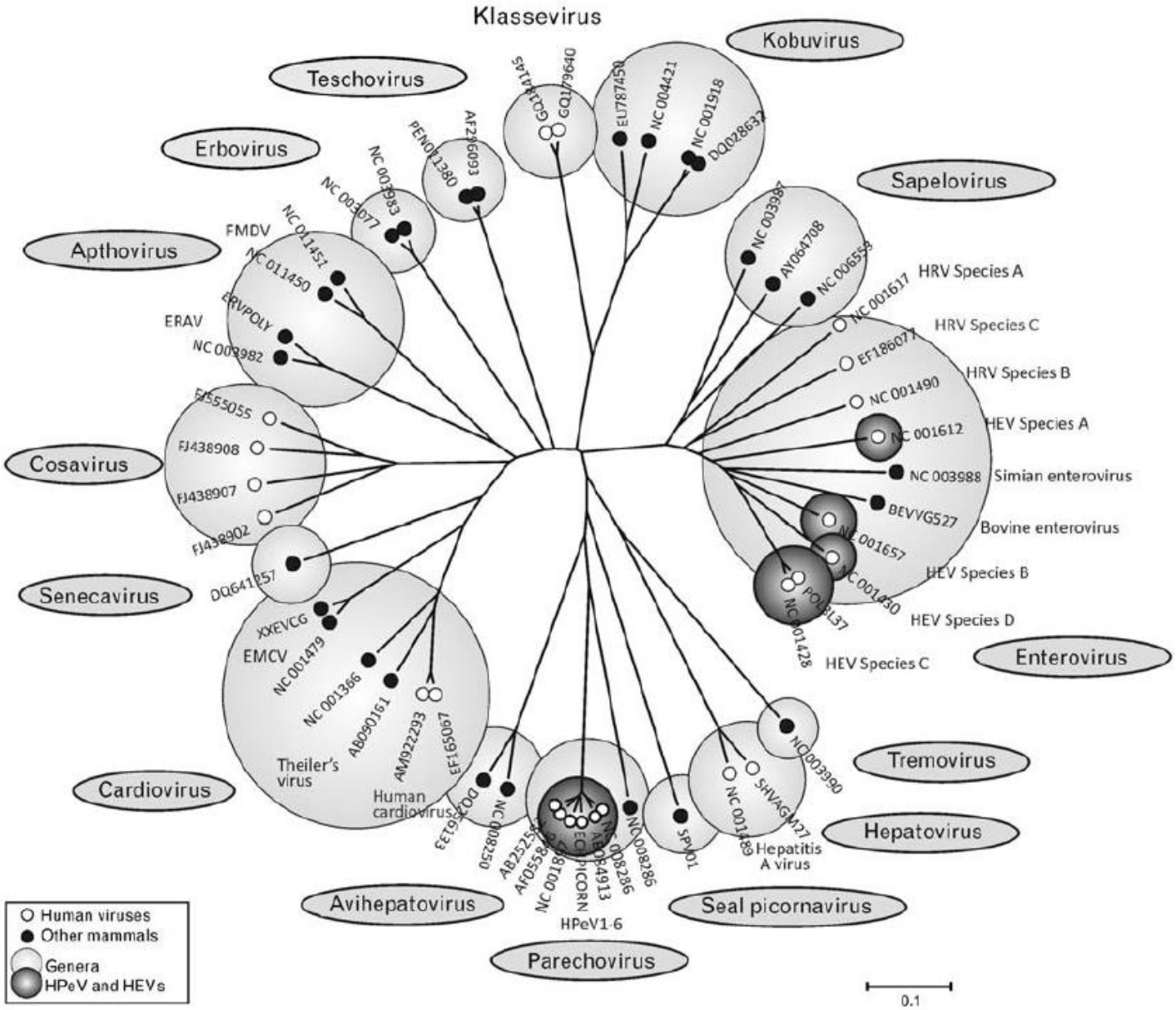
Parechoviruses in children: understanding a new infection

Heli Harvala[a], Katja C. Wolthers[b] and Peter Simmonds[c]



Current Opinion in Infectious Diseases 2010, 23:224–230

Picornavirus family



Human Parechoviruses as an Important Viral Cause of Sepsislike Illness and Meningitis in Young Children

Katja C. Wolthers,[1] Kimberley S. M. Benschop,[1] Janke Schinkel,[1] Richard Molenkamp,[1] Rosemarijn M. Bergevoet,[1] Ingrid J. B. Spijkerman,[3] H. Carlijn Kraakman,[4] and Dasja Pajkrt[2]

[1]Department of Medical Microbiology, Laboratory of Clinical Virology, and, [2]Department of Pediatric Infectious Diseases, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, and Departments of [3]Medical Microbiology and [4]Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Table 1. Characteristics of children tested for human parechovirus (HPeV) and/or enterovirus (EV) infection.

Characteristic	Total population (n = 761)	HPeV-positive patients (n = 33[a])	EV-positive patients (n = 108)
Age, median months (IQR)	0.9 (0.3–5.0)	1.2 (0.6–2.6)	0.9 (0.4–1.8)
Sex, no. (%)			
Female	294 (39)	10 (30)	41 (38)
Male	467 (61)	23 (70)	67 (62)

NOTE. IQR, interquartile range.

[a] Of 716 children tested for HPeV.

Table 2. Human parechovirus (HPeV) and enterovirus (EV) prevalence in CSF.

	Proportion (%) of virus-positive patients			
Virus	2004	2005	2006	Total
HPeV	16/196 (8.2)	1/239 (0.4)	16/281 (5.7)	33/716 (4.6)
EV	31/216 (14.4)	37/262 (14.1)	40/283 (14.1)	108/761 (14.2)

Table 3. Clinical characteristics of 29 patients with human parechovirus in CSF.

Variable	Finding
Age, months	
Mean	3.7
Median (range)	1.2 (0.2–58)
Duration of hospital stay, days	
Mean	7.2
Median (range)	5.0 (1.0–39)
Antibiotic treatment	23/28 (82)
Duration of antibiotic treatment, days	
Mean	5.7
Median (range)	7.0 (3.0–10)
Fever	28/29 (97)
Irritability	24/28 (86)
Sepsislike illness	15/28 (54)
Suspected sepsislike illness	6/28 (21)
Meningitis	3/26 (12)
Seizures	2/28 (7)
Encephalitis	1/26 (4)
Paralysis	1/27 (4)
CSF	
Cell count, mean no. of cells/mm^3 (range)	4.6 (3.1–22)
Normal glucose level	19/25 (76)
Elevated protein level	13/21 (62)
Rash	5/29 (17)
Gastrointestinal tract symptoms	11/28 (39)
Respiratory tract symptoms	10/28 (36)

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Conclusion. EV-specific PCRs do not detect HPeVs. The addition of an HPeV-specific PCR has led to a 31% increase in detection of a viral cause of neonatal sepsis or central nervous system symptoms in children aged <5 years. HPeV can be considered to be the second cause of viral sepsis and meningitis in young children, and rapid identification of HPeV by PCR could contribute to shorter duration of both antibiotic use and hospital stay.

Specific Association of Human Parechovirus Type 3 with Sepsis and Fever in Young Infants, as Identified by Direct Typing of Cerebrospinal Fluid Samples

H. Harvala,[1] I. Robertson,[2] T. Chieochansin,[1,3] E. C. McWilliam Leitch,[2] K. Templeton,[1] and P. Simmonds[2]

[1]Specialist Virology Centre, Royal Infirmary of Edinburgh, and [2]Centre for Infectious Diseases, University of Edinburgh, Summerhall, Edinburgh, United Kingdom; [3]Biomedical Science Centre of Excellence in Clinical Virology, Chulalongkorn University and Hospital, Bangkok, Thailand

Methods. A total of 1575 cerebrospinal fluid (CSF) samples obtained during 2006–2008 were screened for HPeV by means of nested polymerase chain reaction. All samples for which results were positive were typed by sequencing of viral protein (VP) 3/VP1. Screening for HEV was performed in parallel, as was detection of HPeV in respiratory and fecal surveillance samples, to identify virus types circulating in the general population.

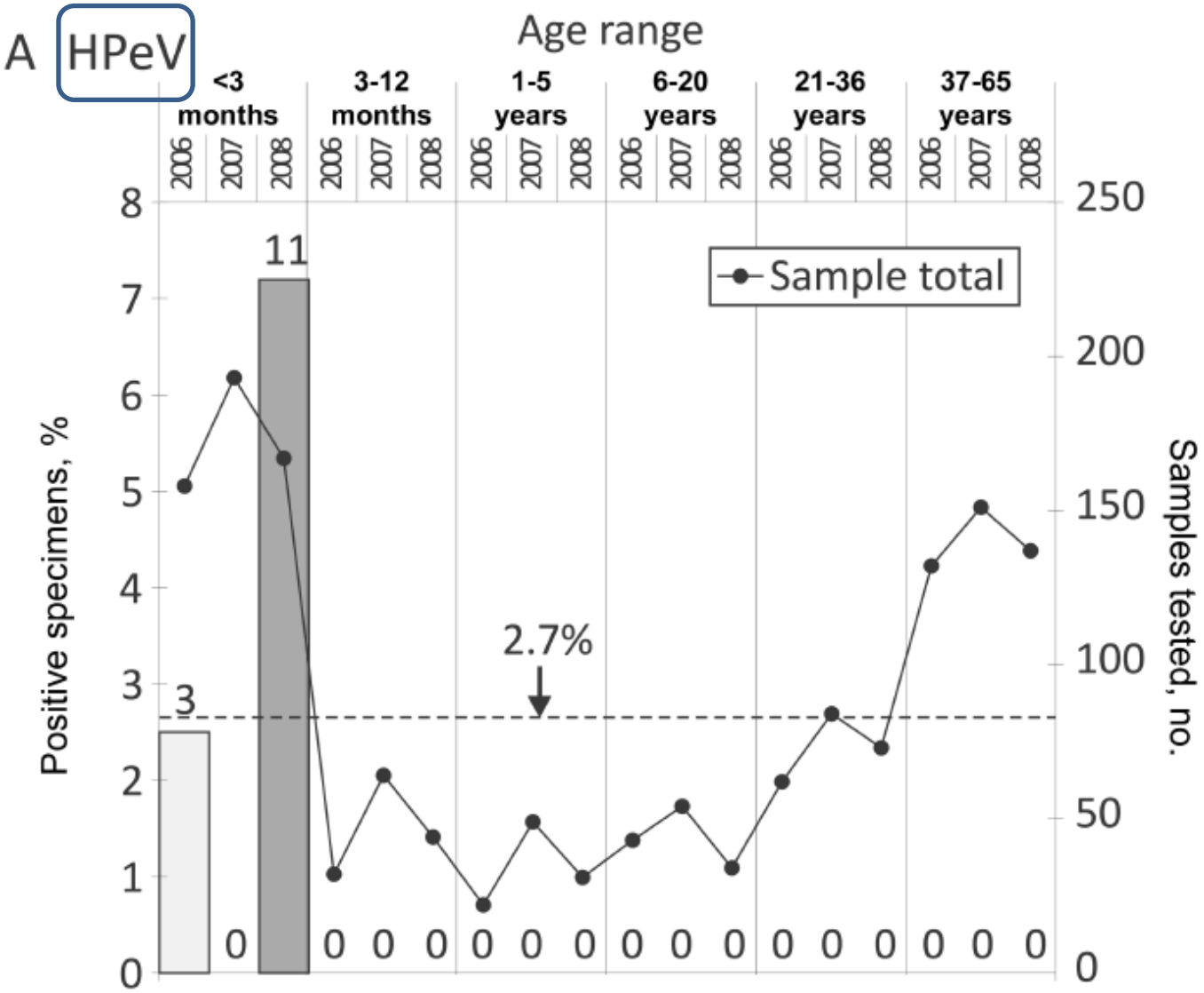
Table 1. Patient demographic and clinical characteristics and parechovirus typing results.

Year of collection, specimen	Age, months	Sex	Month	Diagnosis	Subject location	Virus type
2006						
CSF-721/06	<3	F	Apr	Sepsis	GCW	HPeV3
CSF-874/06	<3	M	July	Sepsis	GCW	HPeV3
CSF-1112/06	<3	F	Nov	Fever	GCW	HPeV3
2008						
CSF-2147/08	<3	F	Apr	Sepsis	GCW	HPeV3
CSF-2162/08	<3	M	Apr	Neonatal sepsis	PHDU	HPeV3
CSF-2169/08	<3	M	Apr	Neonatal fever	GCW	HPeV3
CSF-2273/08	<3	M	June	Sepsis	GCW	HPeV3
CSF-2288/08	<3	M	June	Neonatal sepsis	PITU	HPeV3
CSF-2307/08	<3	F	June	Sepsis	GCW	HPeV3
CSF-2327/08	<3	M	June	Sepsis	GCW	HPeV3
CSF-2369/08	<3	M	July	Fever	GCW	HPeV3
CSF-2387/08	<3	M	July	Sepsis	GCW	HPeV3
CSF-2389/08	<3	F	July	Sepsis	GCW	HPeV3
CSF-2426/08	<3	F	Aug	Neonatal sepsis	PITU	HPeV3

N=14

NOTE. CSF, cerebrospinal fluid; F, female; GCW, general children ward; HPeV3, human parechovirus type 3; M, male; NNU, neonatal unit; PHDU, pediatric high-dependency unit; PITU, pediatric intensive care unit.

Age distributions of human parechovirus (HPeV)–infected *(A)* and human enterovirus (HEV)–infected *(B)* study subjects,



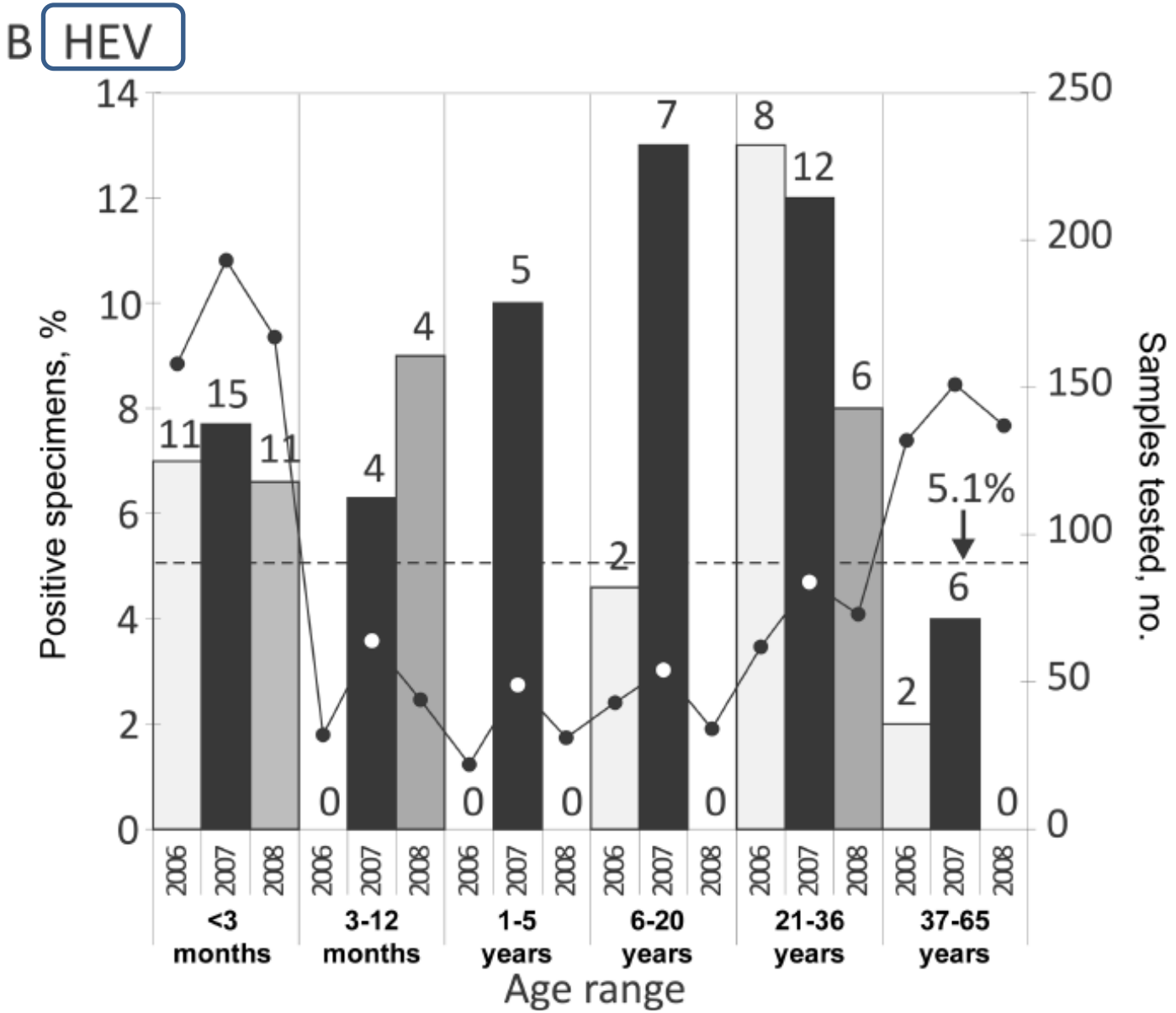


Figure 2. Age distributions of human parechovirus (HPeV)–infected *(A)* and human enterovirus (HEV)–infected *(B)* study subjects, subdivided by referral year (2006, 2007, and 2008). The numbers above the bars denote total numbers of subjects with positive specimens. Dotted lines denote mean frequencies of detection of HPeV and HEV for the whole study group.

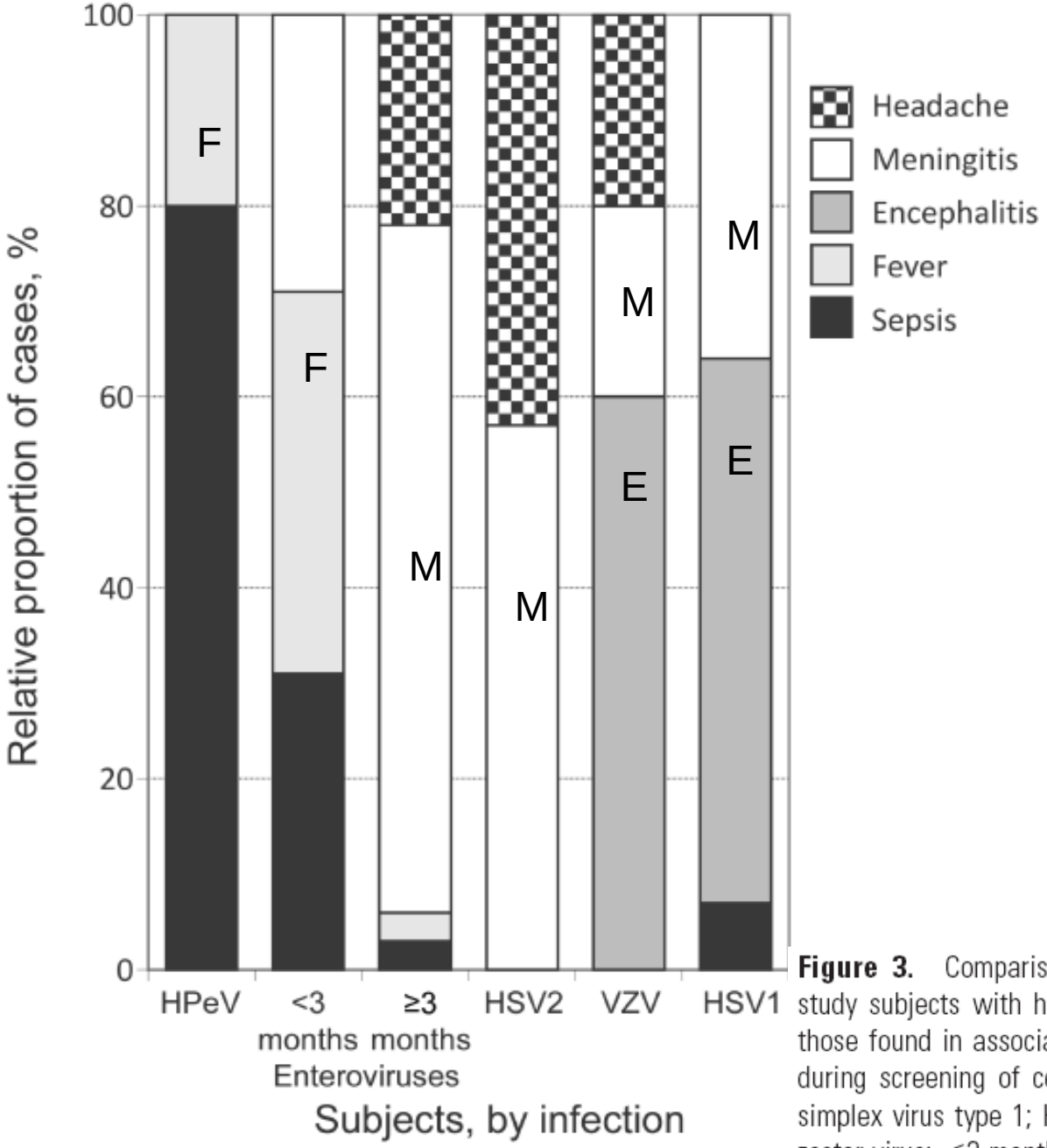


Figure 3. Comparison of recorded symptoms of and/or diagnoses for study subjects with human parechovirus (HPeV)–positive samples with those found in association with infection due to other viruses detected during screening of cerebrospinal fluid (CSF) specimens. HSV1, herpes simplex virus type 1; HSV2, herpes simplex virus type 2; VZV, varicella-zoster virus; <3 months, subjects aged <3 months; ≥3 months of age, subjects ≥3 months of age.

Comparison of Human Parechovirus and Enterovirus Detection Frequencies in Cerebrospinal Fluid Samples Collected Over a 5-Year Period in Edinburgh: HPeV Type 3 Identified as the Most Common Picornavirus Type

Heli Harvala,[1,2]* Nigel McLeish,[2] Jasmina Kondracka,[2] Chloe L. McIntyre,[2] E. Carol McWilliam Leitch,[2] Kate Templeton,[1] and Peter Simmonds[2]

[1]*Specialist Virology Centre, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom*
[2]*Centre for Infectious Diseases, University of Edinburgh, Edinburgh, United Kingdom*

METHODS

Clinical Samples

A total of 4,168 CSF samples referred to the Specialist Virology Centre in Edinburgh during the 5-year period (July 2005–June 2010) were included in this study.

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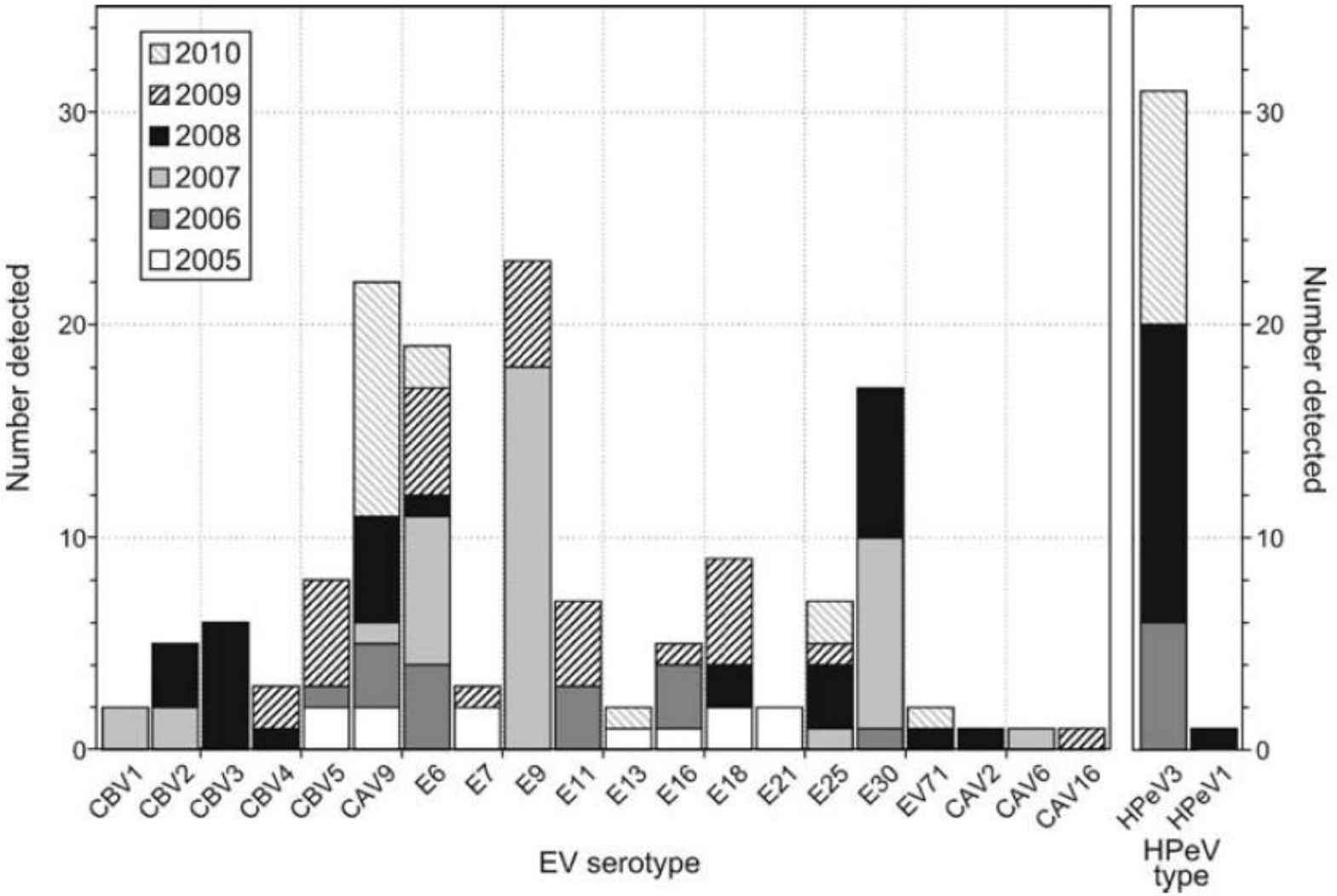
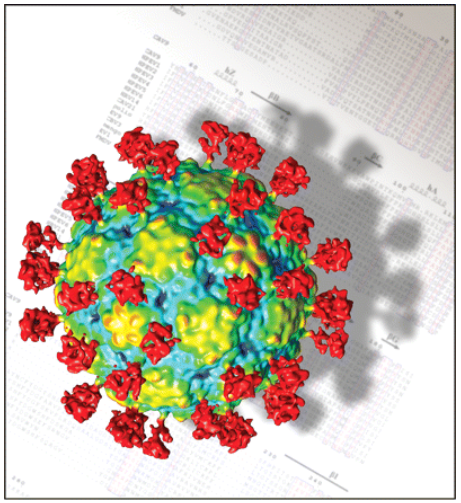


Fig. 5. The number of individual serotypes and HPeV types detected over the 5-year period of the study.

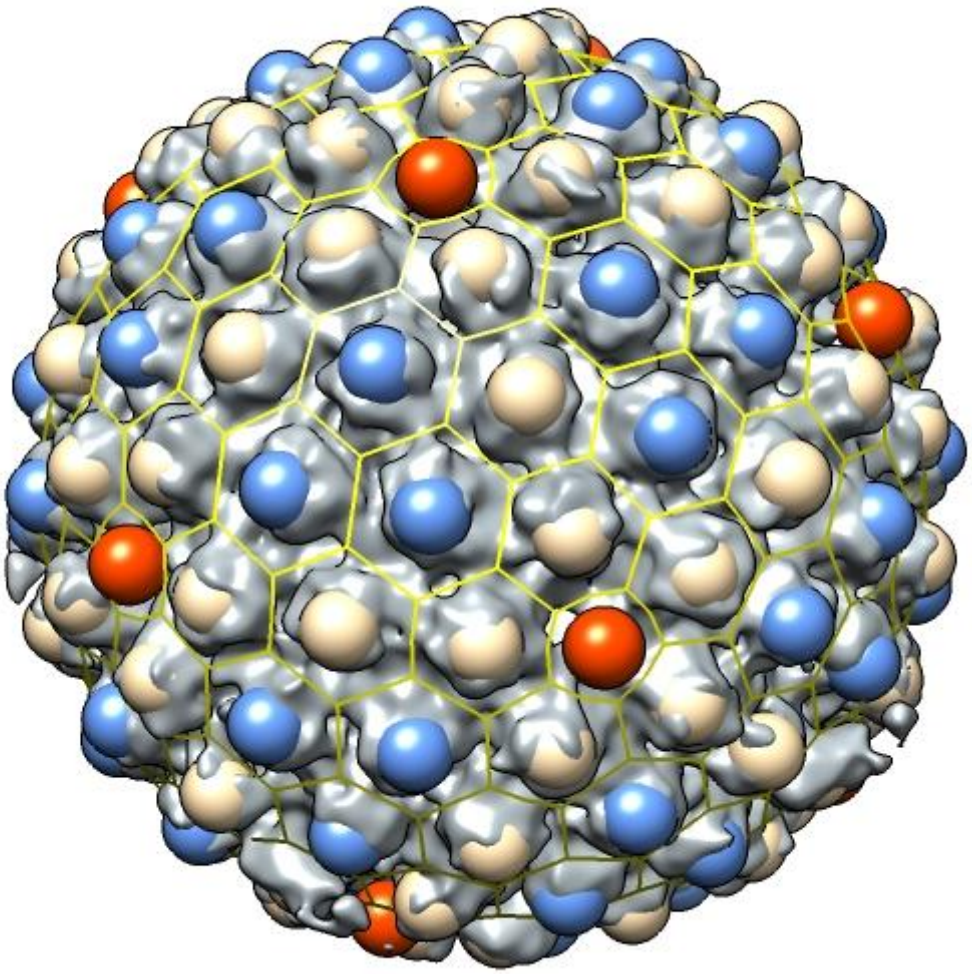
Parechovirus HPeV3



- Important patogen in neonates
- Sepsis like symptoms
- Fever, irritability
- CSF can be normal <5
- Incubation period 2-14 days
- Standard Enterovirus EV PCR will not detect HPeV3 in CSF!
- HPeV3 is probably under-diagnosed

Herpes simplex virus type 1 and 2

Herpes simplex virus



Neonatal herpes simplex virus infection

- Intrapartum infection 85%
- Post partum infection 10%
- Intrauterine infection 5%

HSV status in pregnant women in Sweden

- HSV-1 IgG pos 60-70%
- HSV-2 IgG pos 15-30%
- Approx. 25% of the pregnant have no HSV IgG – meaning a risk for primary HSV infection

Risk for HSV transmission

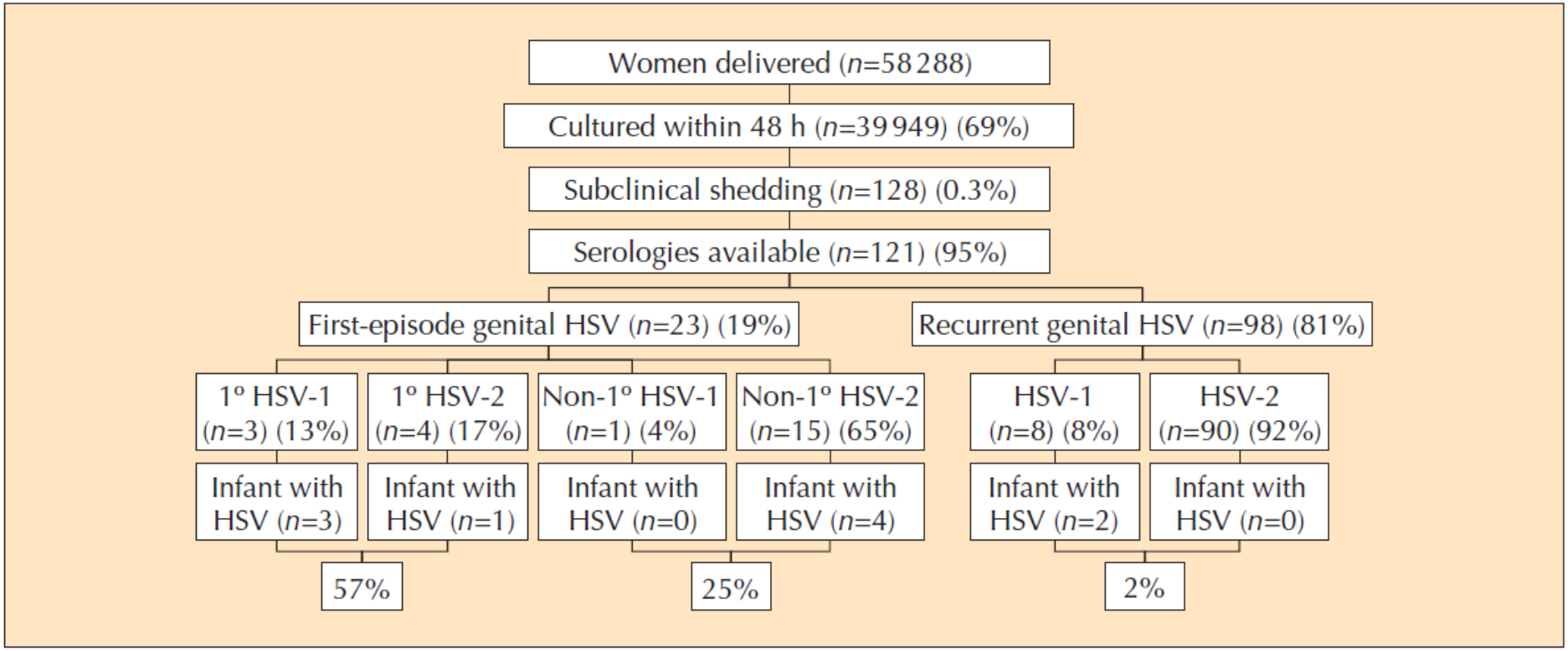


Figure 1:
Frequency of neonatal herpes infection among women with first-episode and recurrent herpes simplex virus (HSV) infection.[25] Adapted with permission from: JAMA *2003;**289:**203–209.*

Type of HSV infection

- Skin, eye, mouth (SEM)
- CNS disease with or without SEM
- Disseminated infection including multiple organs liver, lung etc.
- Without treatment SEM can progres to CNS and/or disseminated disease!

Incubation period for neonatal HSV infection

- Reported as 2-26 days
- Shorter for Skin-Eye-Mouth median 6-7 days
- Longer for CNS median 13-14 days

Clinical manifestation of HSV encephalitis

- Seizures, lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle and pyramidal tract signs
- With or without disseminated disease
- CSF pleocytosis (50–100 white blood cells/mm3 predominantly mononuclear)
- Disseminated disease: worse prognosis

Discrimination of primary vs. recurrent infection in pregnant

- HSV-1 DNA PCR pos in swab
- HSV-1 IgG neg = primary infection
- HSV-1 IgG pos = recurrent infection
- HSV-2 DNA PCR pos in swab
- HSV-2 IgG neg = primary infection
- HSV-2 IgG pos = recurrent infection
- Not all laboratories have specific HSV-1/HSV-2 assays or HSV-IgM specific assays

Samples for HSV DNA PCR

- Skin swabs from any vesicles or lesions
- Conjunctiva
- Mouth, throat, respiratory tract
- EDTA-plasma
- Urine
- CSF can be negative in 1. sample – repeat LBP if there is still a suspecion

Treatment of herpes simplex CNS-infection

- Aciclovir 500mg/m^2 i.v. x 3 for 3 weeks or aciclovir 20 mg/kg i.v. x 3 daily for 3w
- Lower dosis for premature

Preemptive treatment

- Infant born vaginally or after prolonged rupture of membranes to a woman with clinically apparent first episode at delivery (vesicles but HSV-antibody negative)
- Take samples from mouth, nasopharynx, conjunctiva => herpes-PCR
- Start prophylactic treatment with aciclovir 20 mg/kg x 3 daily

Observation – treatment only if infant HSV PCR pos

- Mother with recurrent infection (HSV IgG +)
- Take samples from infant (mouth, nasopharynx and conjunctiva) to HSV DNA PCR
- Inform parents to look for vesicles
- Repeat testing after 5 and 10 days in case of massive exposure
- Start treatment if positive results only

Prognosis for HSV encephalitis

- Better for HSV-1 than for HSV-2
- Higher morbidity for HSV-2
- More sequlae after HSV-2

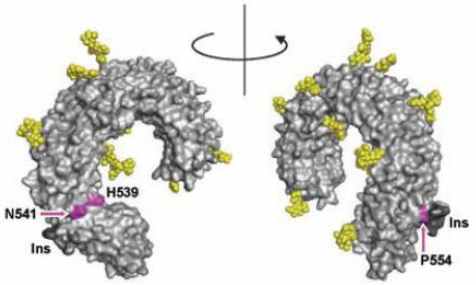
HSV encephalitis a rare disease – bad luck or bad genes ?

Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency

Armanda Casrouge,[1*] Shen-Ying Zhang,[1,2*] Céline Eidenschenk,[1*] Emmanuelle Jouanguy,[1,2*] Anne Puel,[1] Kun Yang,[1,2] Alexandre Alcais,[1] Capucine Picard,[1,3] Nora Mahfoufi,[1] Nathalie Nicolas,[1] Lazaro Lorenzo,[1] Sabine Plancoulaine,[1] Brigitte Sénéchal,[4] Frédéric Geissmann,[4] Koichi Tabeta,[5]† Kasper Hoebe,[5] Xin Du,[5] Richard L. Miller,[6] Bénédicte Héron,[7] Cyril Mignot,[7] Thierry Billette de Villemeur,[7] Pierre Lebon,[8] Olivier Dulac,[9] Flore Rozenberg,[8] Bruce Beutler,[5] Marc Tardieu,[10] Laurent Abel,[1] Jean-Laurent Casanova[1,2,11]‡

Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is the most common form of sporadic viral encephalitis in western countries. Its pathogenesis remains unclear, as it affects otherwise healthy patients and only a small minority of HSV-1–infected individuals. Here, we elucidate a genetic etiology for HSE in two children with autosomal recessive deficiency in the intracellular protein UNC-93B, resulting in impaired cellular interferon-α/β and -λ antiviral responses. HSE can result from a single-gene immunodeficiency that does not compromise immunity to most pathogens, unlike most known primary immunodeficiencies. Other severe infectious diseases may also reflect monogenic disorders of immunity.

TLR3 Deficiency in Patients with Herpes Simplex Encephalitis



Shen-Ying Zhang,[1,2,3] Emmanuelle Jouanguy,[1,2,3] Sophie Ugolini,[4] Asma Smahi,[5] Gaëlle Elain,[6] Pedro Romero,[7] David Segal,[8] Vanessa Sancho-Shimizu,[1,2] Lazaro Lorenzo,[1,2] Anne Puel,[1,2] Capucine Picard,[1,2,9] Ariane Chapgier,[1,2] Sabine Plancoulaine,[1,2] Matthias Titeux,[10] Céline Cognet,[4] Horst von Bernuth,[1,2] Cheng-Lung Ku,[1,2] Armanda Casrouge,[1,2] Xin-Xin Zhang,[3] Luis Barreiro,[11] Joshua Leonard,[8] Claire Hamilton,[1,2] Pierre Lebon,[12] Bénédicte Héron,[13] Louis Vallée,[14] Lluis Quintana-Murci,[11] Alain Hovnanian,[10] Flore Rozenberg,[12] Eric Vivier,[4] Frédéric Geissmann,[6] Marc Tardieu,[15] Laurent Abel,[1,2] Jean-Laurent Casanova[1,2,3,16]*

Some Toll and Toll-like receptors (TLRs) provide immunity to experimental infections in animal models, but their contribution to host defense in natural ecosystems is unknown. We report a dominant-negative *TLR3* allele in otherwise healthy children with herpes simplex virus 1 (HSV-1) encephalitis. TLR3 is expressed in the central nervous system (CNS), where it is required to control HSV-1, which spreads from the epithelium to the CNS via cranial nerves. TLR3 is also expressed in epithelial and dendritic cells, which apparently use TLR3-independent pathways to prevent further dissemination of HSV-1 and to provide resistance to other pathogens in TLR3-deficient patients. Human TLR3 appears to be redundant in host defense to most microbes but is vital for natural immunity to HSV-1 in the CNS, which suggests that neurotropic viruses have contributed to the evolutionary maintenance of TLR3.

Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity

Yiqi Guo,[1,2,3] Magali Audry,[1] Michael Ciancanelli,[1] Laia Alsina,[4,5,6] Joana Azevedo,[7,8] Melina Herman,[1,2,3] Esperanza Anguiano,[4,5] Vanessa Sancho-Shimizu,[2,3] Lazaro Lorenzo,[2,3] Elodie Pauwels,[1,2,3] Paul Bastard Philippe,[1] Rebeca Pérez de Diego,[2,3] Annabelle Cardon,[2,3] Guillaume Vogt,[1] Capucine Picard,[2] Zafitsara Zo Andrianirina,[9] Flore Rozenberg,[10] Pierre Lebon,[10] Sabine Plancoulaine,[1,2,3] Marc Tardieu,[11] Valérie Doireau,[9] Emmanuelle Jouanguy,[1,2,3] Damien Chaussabel,[4,5,12] Frederic Geissmann,[7,8] Laurent Abel,[1,2,3] Jean-Laurent Casanova,[1,2,3,13] and Shen-Ying Zhang[1,2,3]

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JEM

NEMO is a key component of NF-κB– and IRF-3–dependent TLR3-mediated immunity to herpes simplex virus

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Clinical implications: Mutations in the NF-κB essential modulator (NEMO) affect the activation of both NF-κB and IRF-3 in response to TLR3 stimulation and may therefore increase susceptibility to HSE.

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Biochimie 89 (2007) 878–883

Human primary immunodeficiencies of type I interferons

Emmanuelle Jouanguy [a,b,c], Shen-Ying Zhang [a,b,c], Ariane Chapgier [a,b], Vanessa Sancho-Shimizu [a,b], Anne Puel [a,b], Capucine Picard [a,b,d], Stéphanie Boisson-Dupuis [a,b], Laurent Abel [a,b], Jean-Laurent Casanova [a,b,c,*]

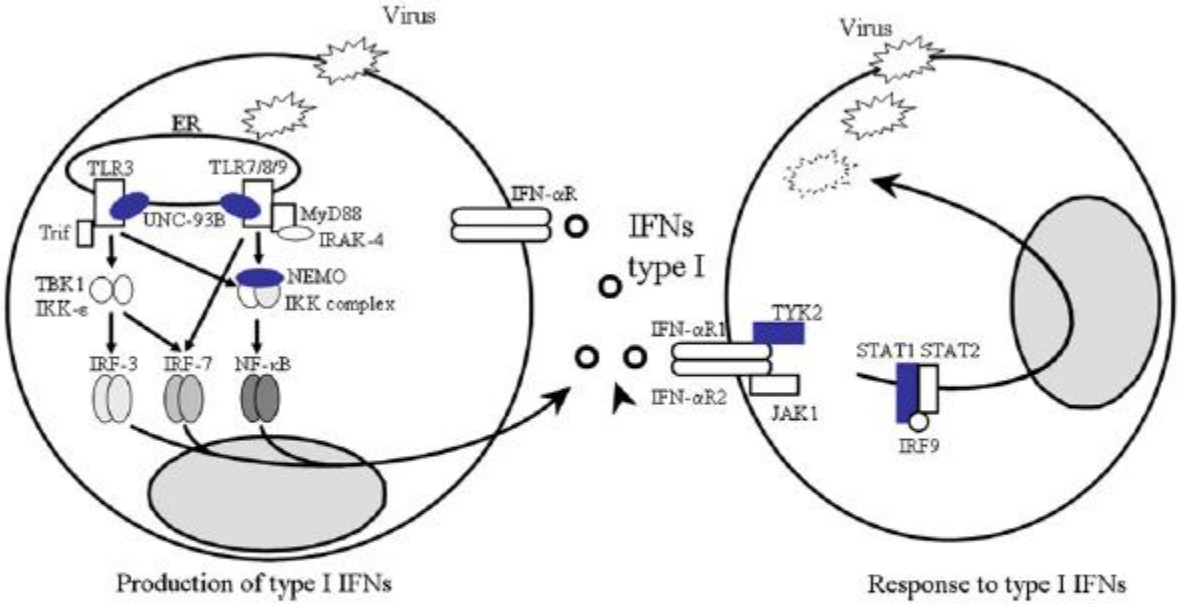
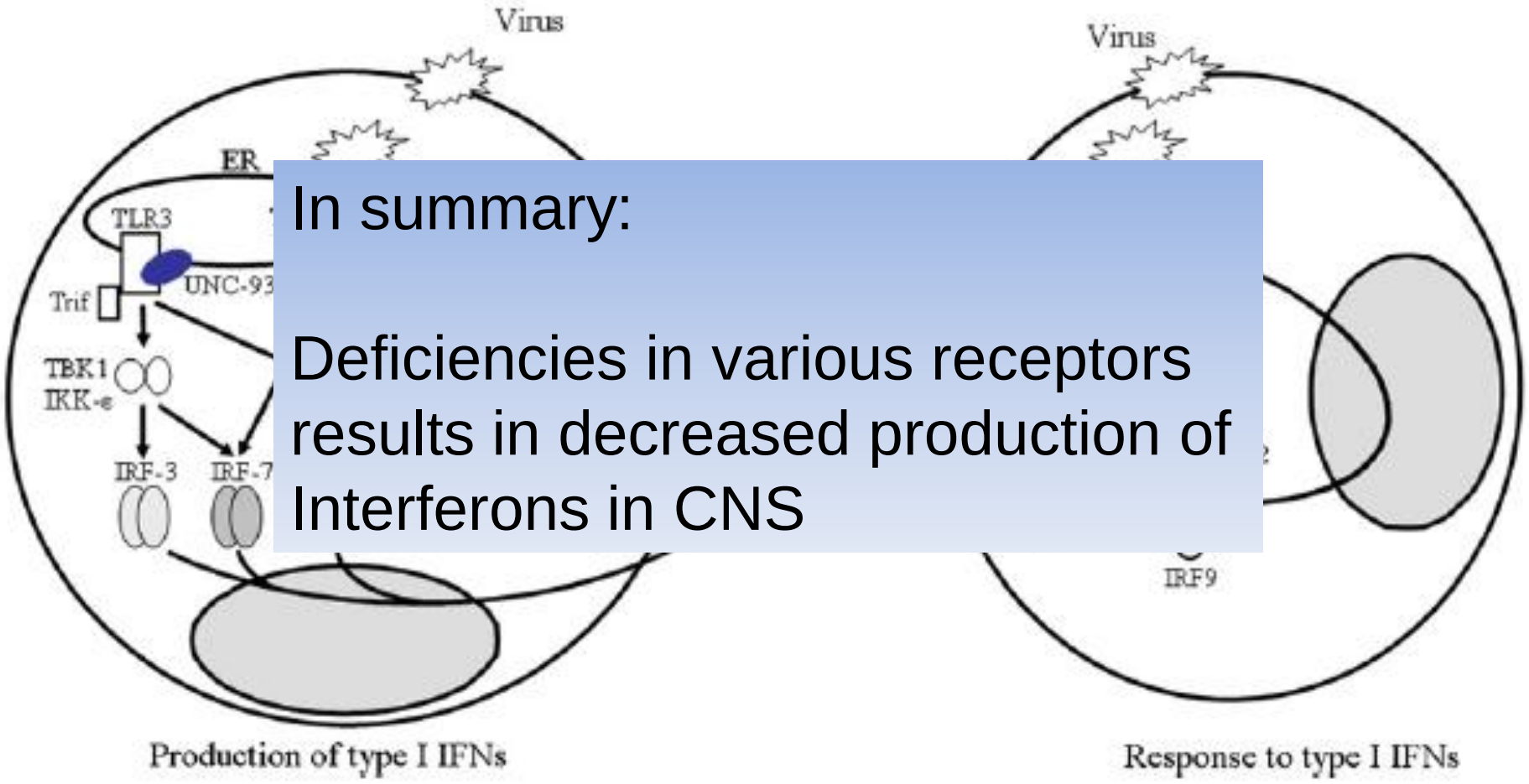


Fig. 1. Impairment of viral immunity in patients with UNC-93B, TYK2 and STAT1 deficiency. Proteins disabled by recessive mutations predisposing the patient to viral infections are shown in blue. Production is shown on the left and the response on the right of the figure. Viral infections of cells induce type I IFN production by an UNC-93B-dependent pathway. The recognition of dsRNA by TLR3 in the endosomal compartment leads to TRIF recruitment to the receptor, inducing type I IFN production principally via the TBK1/IKK-ε/IRF-3 pathway, but also by the pathway involving IRF-7. Stimulation with TLR7/8/9 leads to the recruitment of a complex of MyD88, IRAK-4 and IRF-7. NEMO belongs to the IKK complex. This complex is activated by TLR3, but also by TLR7/8/9. UNC-93B may interact with TLRs at the membrane, stabilising or inducing the signalling cascade. Type I IFNs induce the transcription of genes with antiviral activities via a TYK2-STAT1 pathway, in an autocrine and paracrine (not illustrated) manner, leading to the control of viral infection.

Biochimie 89 (2007) 878–883



In summary:

Deficiencies in various receptors results in decreased production of Interferons in CNS

TLR3 deficiency renders astrocytes permissive to herpes simplex virus infection and facilitates establishment of CNS infection in mice

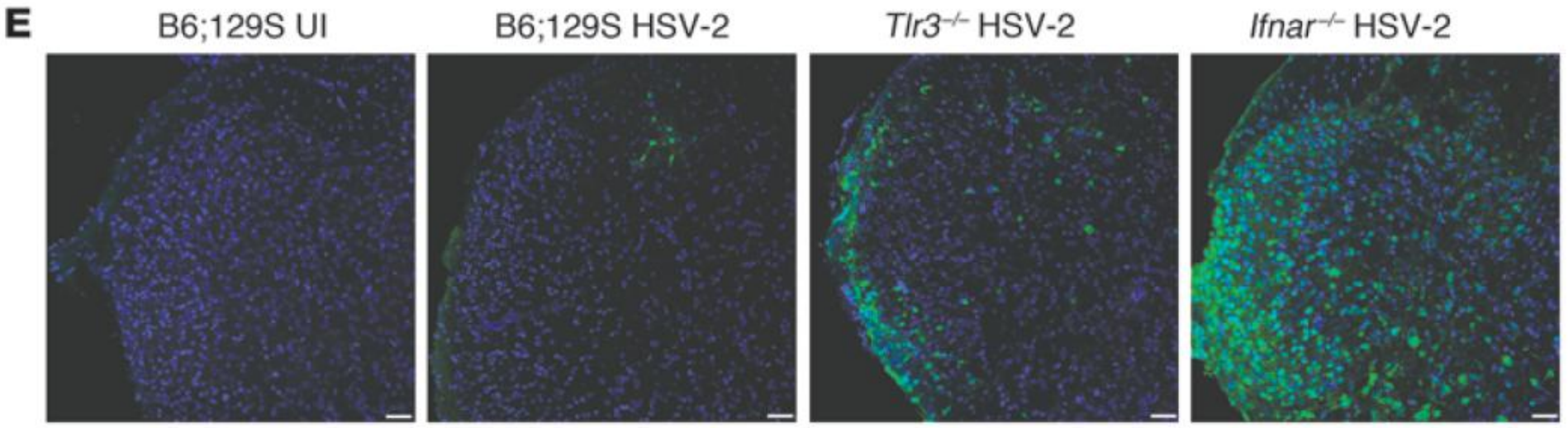
Line S. Reinert,[1] Louis Harder,[1] Christian K. Holm,[1] Marie B. Iversen,[1] Kristy A. Horan,[1] Frederik Dagnæs-Hansen,[1] Benedicte P. Ulhøi,[2] Thomas H. Holm,[3] Trine H. Mogensen,[4] Trevor Owens,[3] Jens R. Nyengaard,[5] Allan R. Thomsen,[6] and Søren R. Paludan[1]

Here, we show that in mice TLR3 provides early control of HSV-2 infection immediately after entry into the CNS by mediating type I IFN responses in astrocytes.

Thus, TLR3 acts in astrocytes to sense HSV-2 infection immediately after entry into the CNS, possibly preventing HSV from spreading beyond the neurons mediating entry into the CNS.

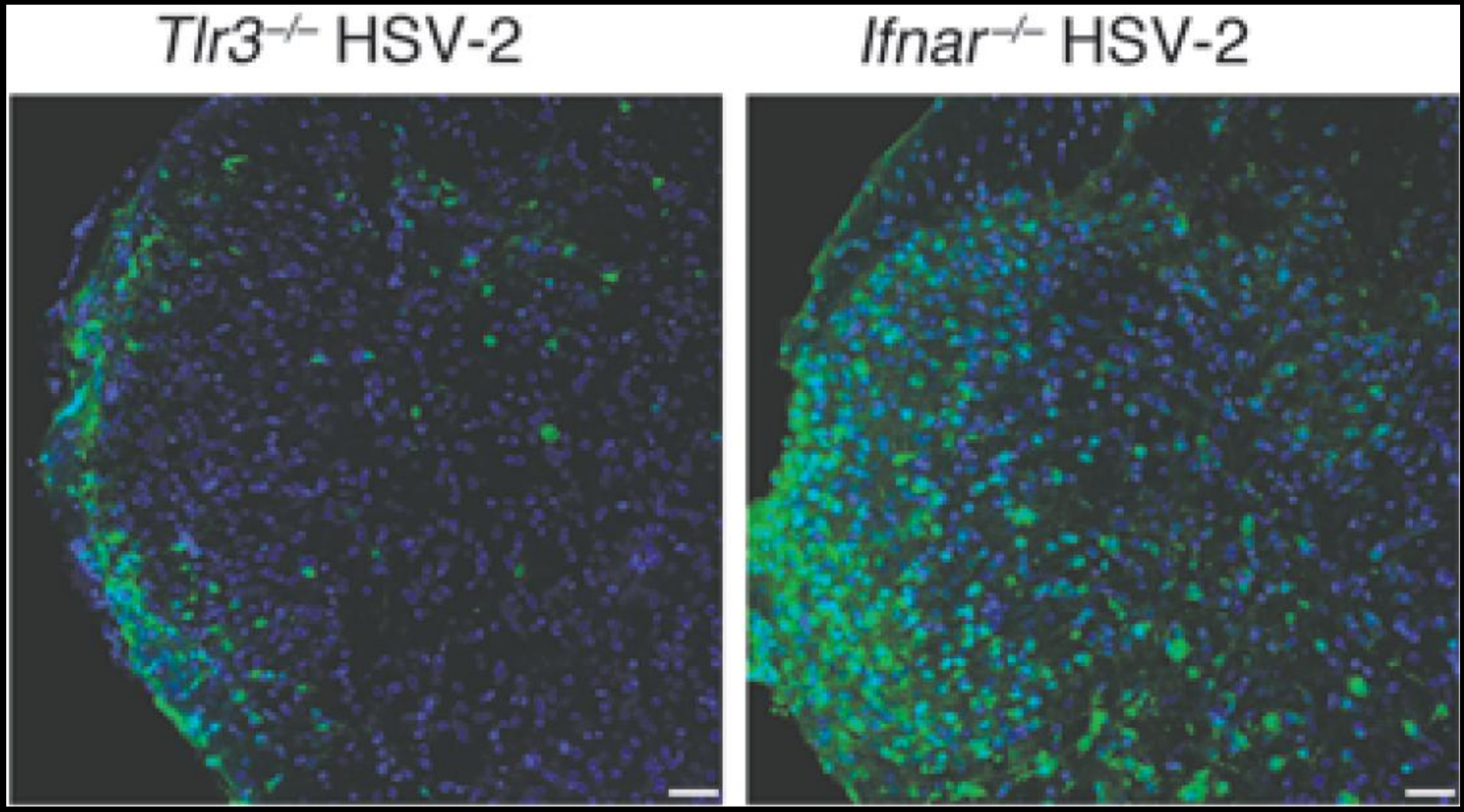
J Clin Invest. 2012;122(4):1368–1376.

WT TLR3 deficiency Ifn-α receptor def.



(**C**) Viral load in the cerebellum on day 6 p.i. (**D**) Viral load in the cerebrum on day 6 p.i. The dashed line indicates the detection limit. (**E**) Confocal images of the dorsal part of lumbar medulla spinalis from uninfected or infected mice (6 day p.i.). Positive anti–HSV-2 antibody staining is shown in green and nuclear staining with DAPI is shown in blue. Scale bar: 50 μm. The data are presented as mean of 3 independent experiments (n = 4–6 mice in each group per experiment). *$P < 0.05$.

J Clin Invest. 2012;122(4):1368–1376.


Tlr3$^{-/-}$ HSV-2
Ifnar$^{-/-}$ HSV-2

HSV encephalitis

Can be caused by ”bad genes”
but can also be just bad luck !

Other viral CNS infections may
also be linked to receptor deficiencies
Tick borne encephalitis TBE CCR5d32
West nile virus WNV CCR5d32, CCR2

Supplemental reading if ……

Human genetics of infectious diseases: between proof of principle and paradigm

Alexandre Alcaïs,[1,2] Laurent Abel,[1,2,3] and Jean-Laurent Casanova[1,2,3,4]

[1]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U550, Paris, France. [2]University Paris Descartes, Necker Medical School, Paris, France. [3]Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, New York, USA. [4]Pediatric Hematology-Immunology Unit, Necker Hospital, Paris, France.

The observation that only a fraction of individuals infected by infectious agents develop clinical disease raises fundamental questions about the actual pathogenesis of infectious diseases. Epidemiological and experimental evidence is accumulating to suggest that human genetics plays a major role in this process. As we discuss here, human predisposition to infectious diseases seems to cover a continuous spectrum from monogenic to polygenic inheritance. Although many studies have provided proof of principle that infectious diseases may result from various types of inborn errors of immunity, the genetic determinism of most infectious diseases in most patients remains unclear. However, in the future, studies in human genetics are likely to establish a new paradigm for infectious diseases.

J. Clin. Invest. **119**:2506–2514 (2009).

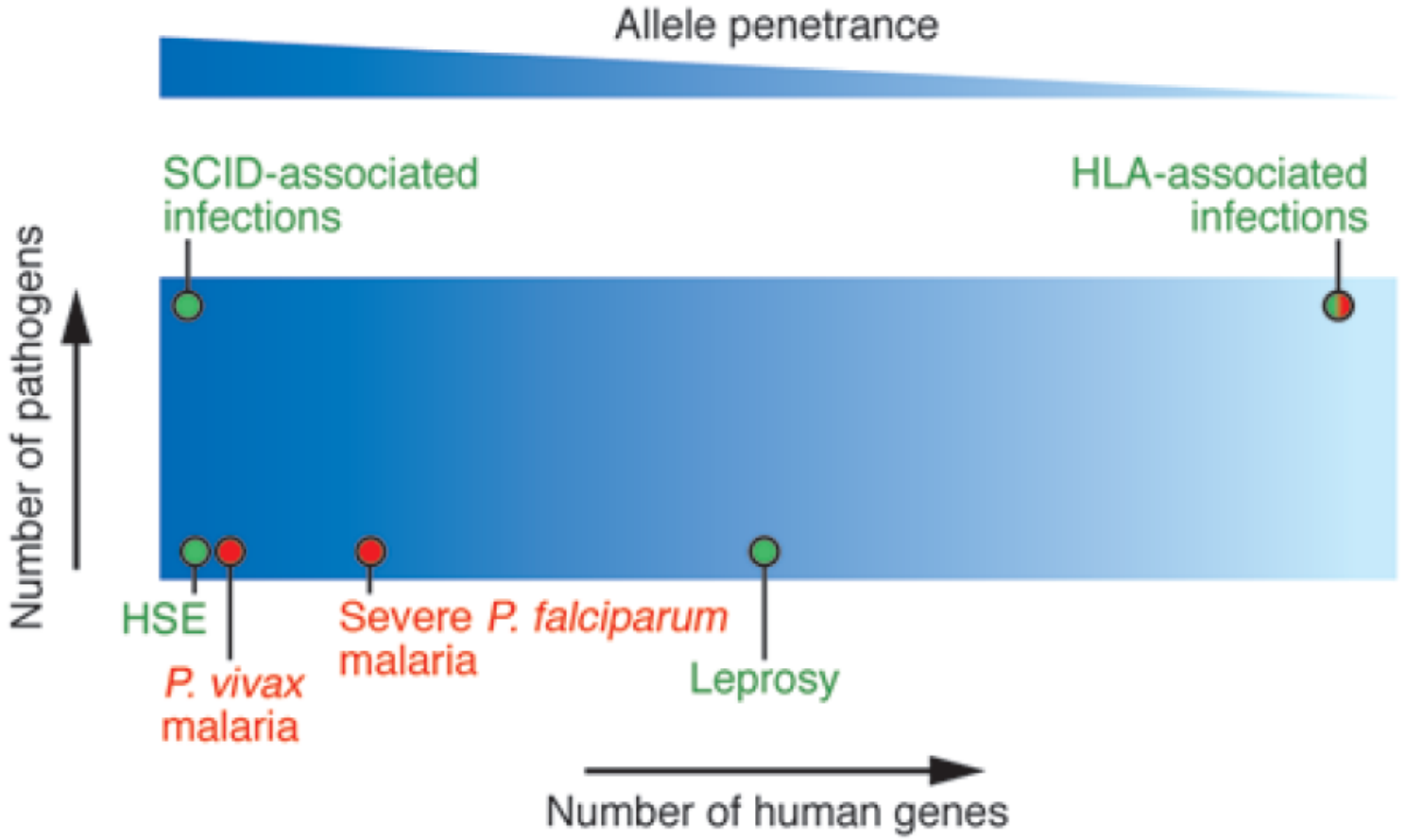
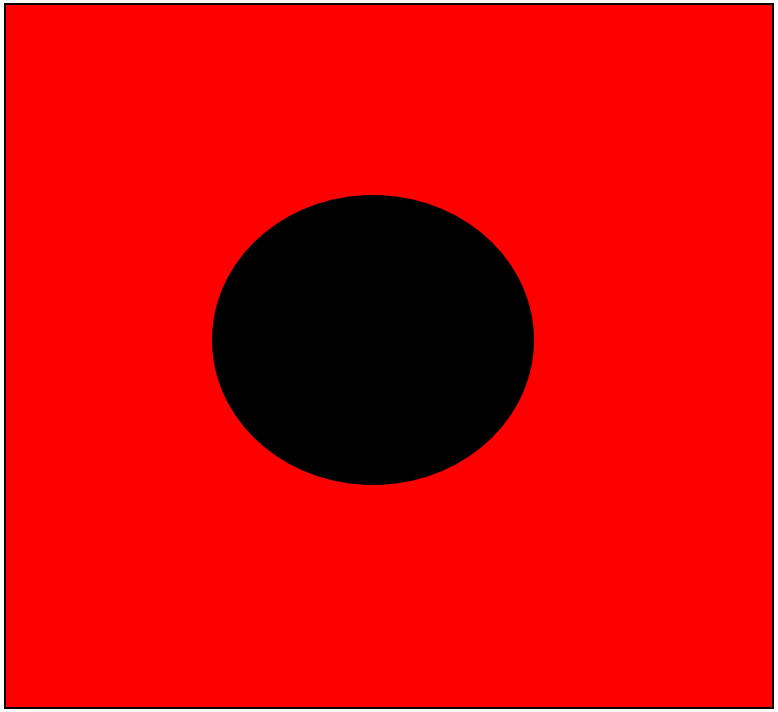


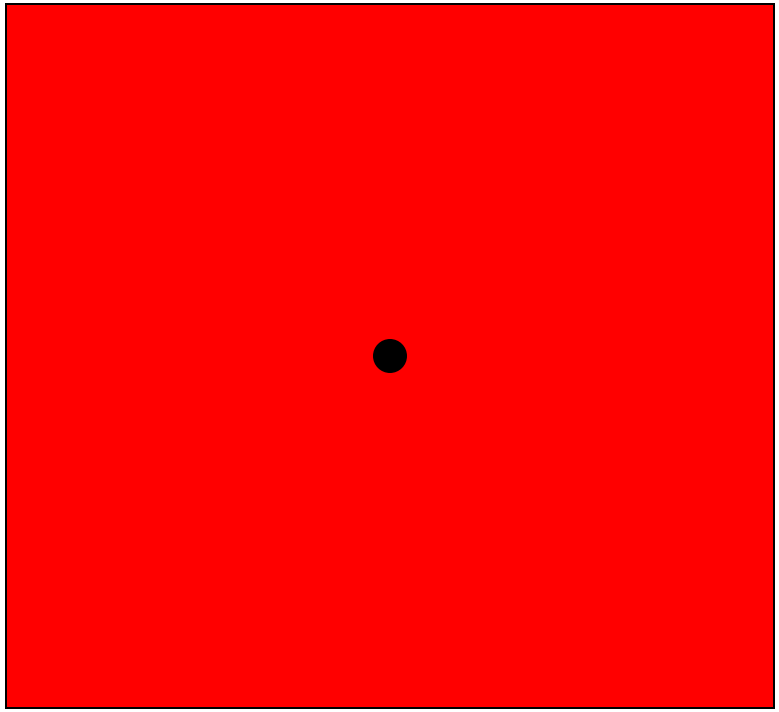
Figure 2
Schematic representation of the continuous genetic models underlying human infectious diseases.

J. Clin. Invest. **119**:2506–2514 (2009).

SCID



TLR3 deficiency



Duration of treatment after HSV infection in neonates

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes

David W. Kimberlin, M.D., Richard J. Whitley, M.D., Wen Wan, Ph.D., Dwight A. Powell, M.D., Gregory Storch, M.D., Amina Ahmed, M.D., April Palmer, M.D., Pablo J. Sánchez, M.D., Richard F. Jacobs, M.D., John S. Bradley, M.D., Joan L. Robinson, M.D., Mark Shelton, M.D., Penelope H. Dennehy, M.D., Charles Leach, M.D., Mobeen Rathore, M.D., Nazha Abughali, M.D., Peter Wright, M.D., Lisa M. Frenkel, M.D., Rebecca C. Brady, M.D., Russell Van Dyke, M.D., Leonard B. Weiner, M.D., Judith Guzman-Cottrill, D.O., Carol A. McCarthy, M.D., Jill Griffin, R.N., Penelope Jester, R.N., M.P.H., Misty Parker, M.D., Fred D. Lakeman, Ph.D., Huichien Kuo, M.S., Choo Hyung Lee, M.S., and Gretchen A. Cloud, M.S., for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

N Engl J Med 2011;365:1284-92.

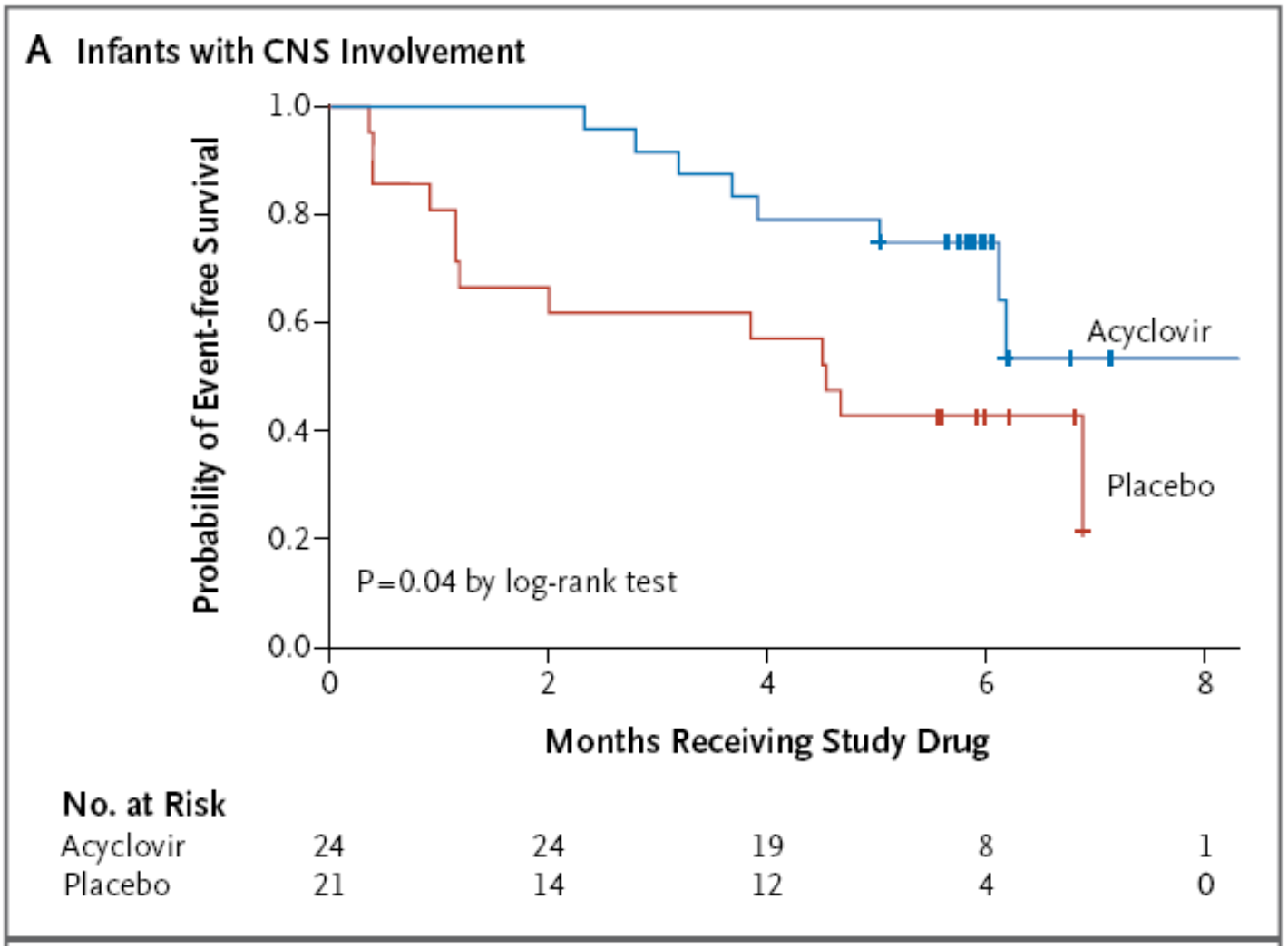
METHODS

We enrolled neonates with HSV disease in two parallel, identical, double-blind, placebo-controlled studies. Neonates with central nervous system (CNS) involvement were enrolled in one study, and neonates with skin, eye, and mouth involvement only were enrolled in the other. After completing a regimen of 14 to 21 days of parenteral acyclovir, the infants were randomly assigned to immediate acyclovir suppression (300 mg per square meter of body-surface area per dose orally, three times daily for 6 months) or placebo. Cutaneous recurrences were treated with open-label episodic therapy.

RESULTS

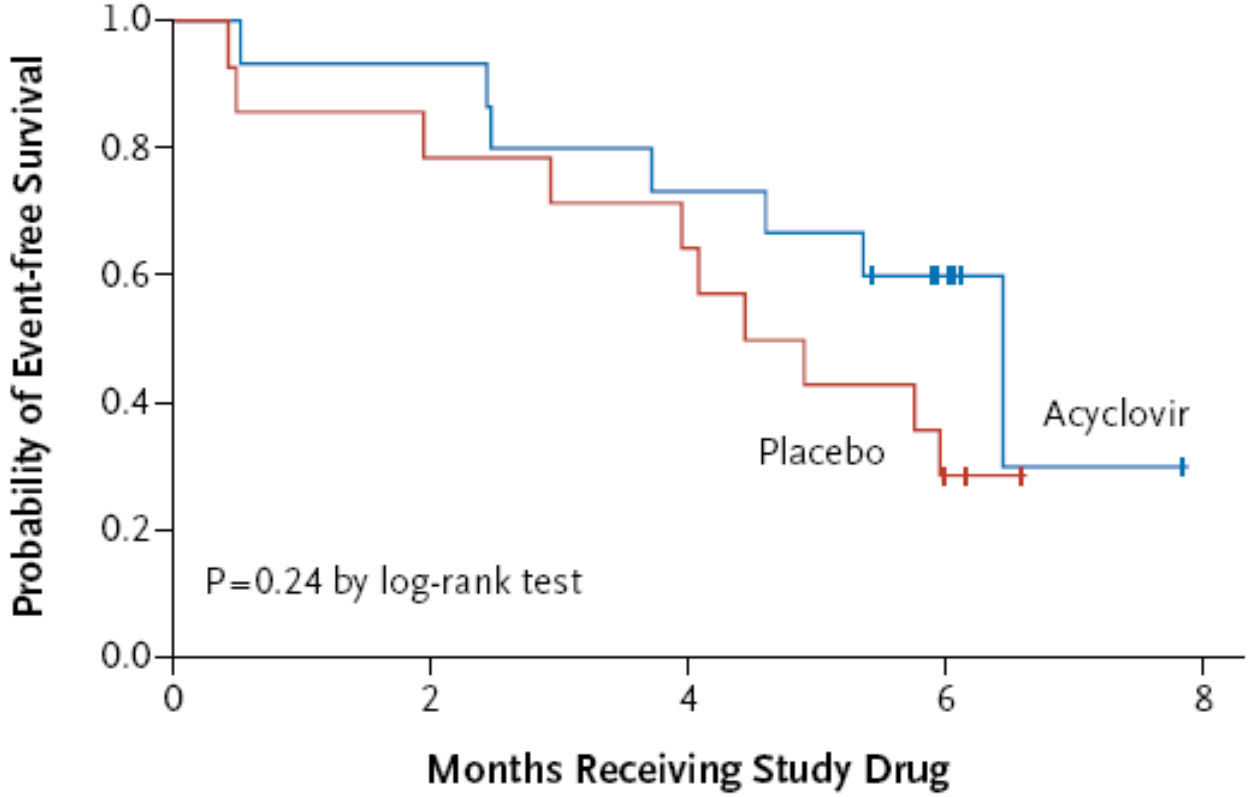
A total of 74 neonates were enrolled — 45 with CNS involvement and 29 with skin, eye, and mouth disease.

N Engl J Med 2011;365:1284-92.



N Engl J Med 2011;365:1284-92.

B Infants with Skin, Eye, and Mouth Involvement



No. at Risk					
Acyclovir	15	14	11	6	0
Placebo	14	11	9	3	0

N Engl J Med 2011;365:1284-92.

These data support the use of suppressive therapy with 300 mg of oral acyclovir per square meter per dose administered three times daily for skin recurrences, whereas babies with CNS disease may have additional benefit with respect to neurodevelopmental outcomes.

Give 6 months supportive treatment with aciclovir after neonatal HSV infection!

N Engl J Med 2011;365:1284-92.

Enterovirus cases

Enterovirus cases #1

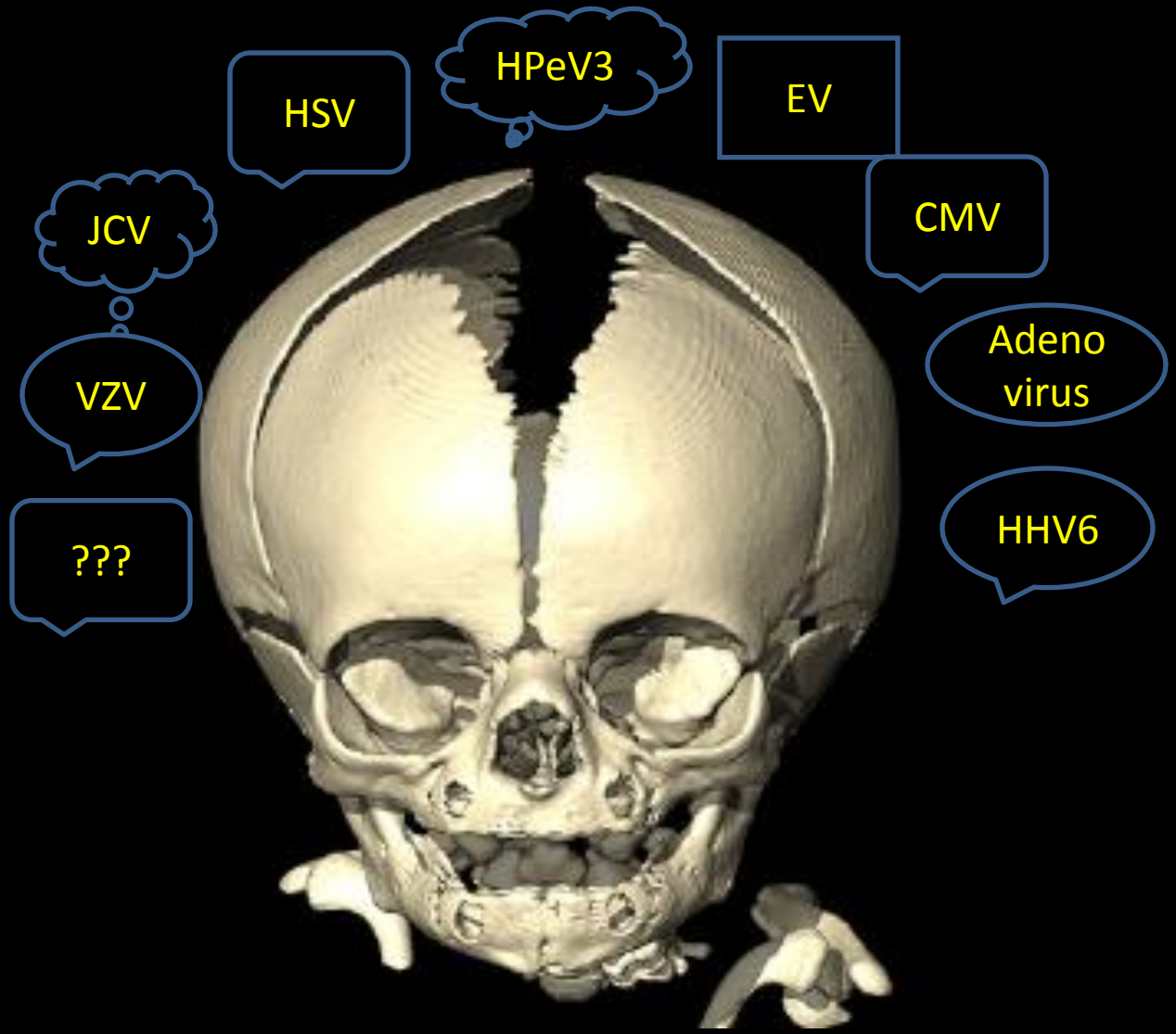
- 6 day old boy sleepy and vomiting
- Starting treatment for sepsis
- CRP 33 (>10) falling to CRP 22
- Normal leukocytes and trombocytes in blood
- No cells in CSF (<3)
- PCR Enterovirus PCR pos (result 36 hours after admission, 24 hour after lumbal puncture)
- Typed as ECHO11 (SSI)

Enterovirus cases #2

- 7 days old girl sleepy and not eating properly
- 4 days later seizures
- Lumbal puncture – Leuk 109, Eryt 5540, lymf 75 – not elevated if deduction for Erytrocytes
- Brother and father have had cataralia and blister in mouth
- CSF PCR pos for Enterovirus – Typed as Coxsackie B3 (SSI)

Summary

- What to do when you have a case of possible viral CNS infection ?
- Send more samples (SMS) with all possible clinical material (CSF, EDTA-blood, swabs, respiratory tract, feces) !!
- Test for HPeV3 if any suspecion = Parechovirus PCR
- Also test for viruses in CSF and blood if sepsis like illness only


HPeV3
HSV
EV
JCV
CMV
VZV
Adeno virus
???
HHV6