Diagnosis and treatment of herpes encephalitis

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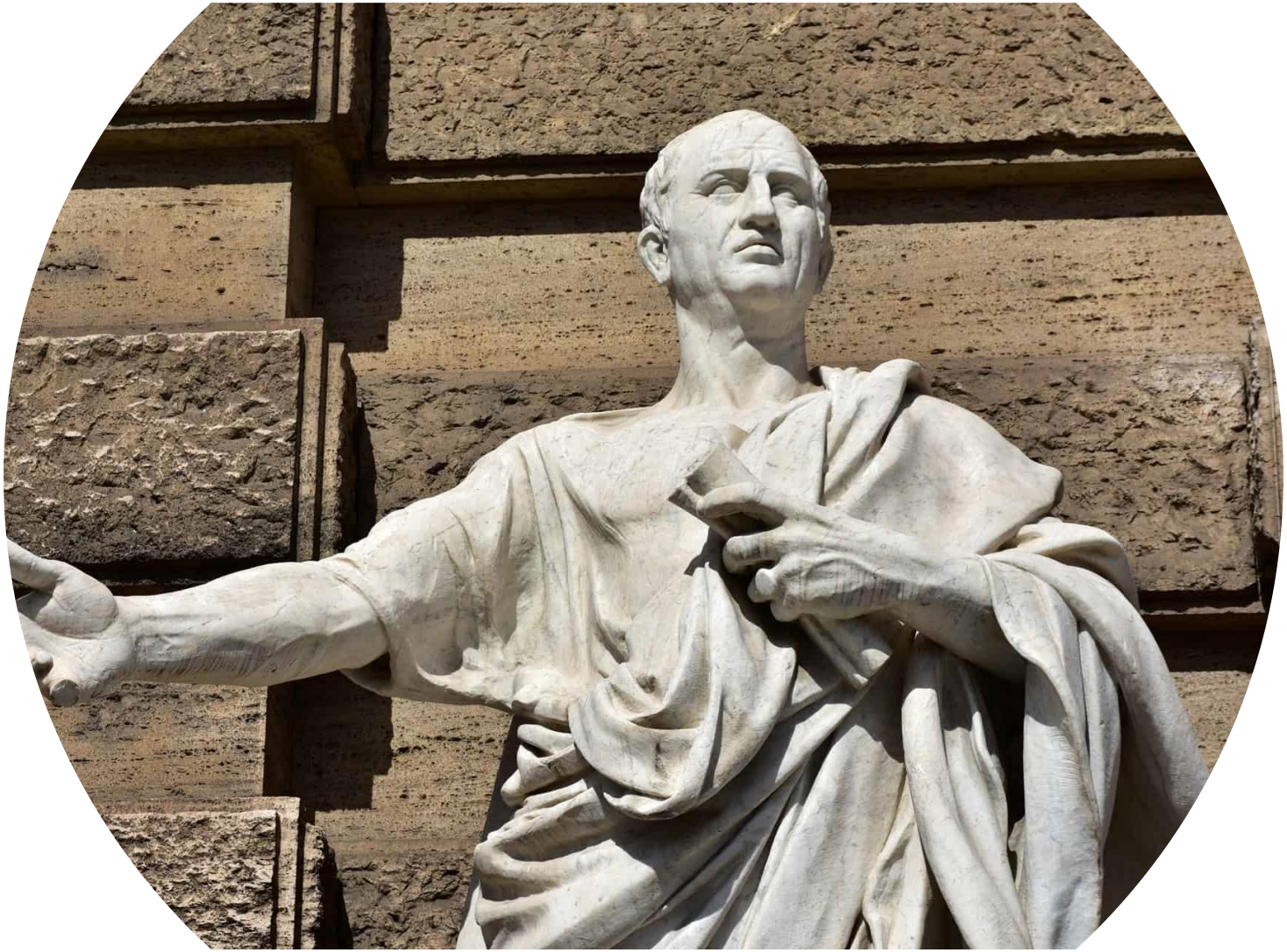
http://www.sipahi.tk

Conflict of interest

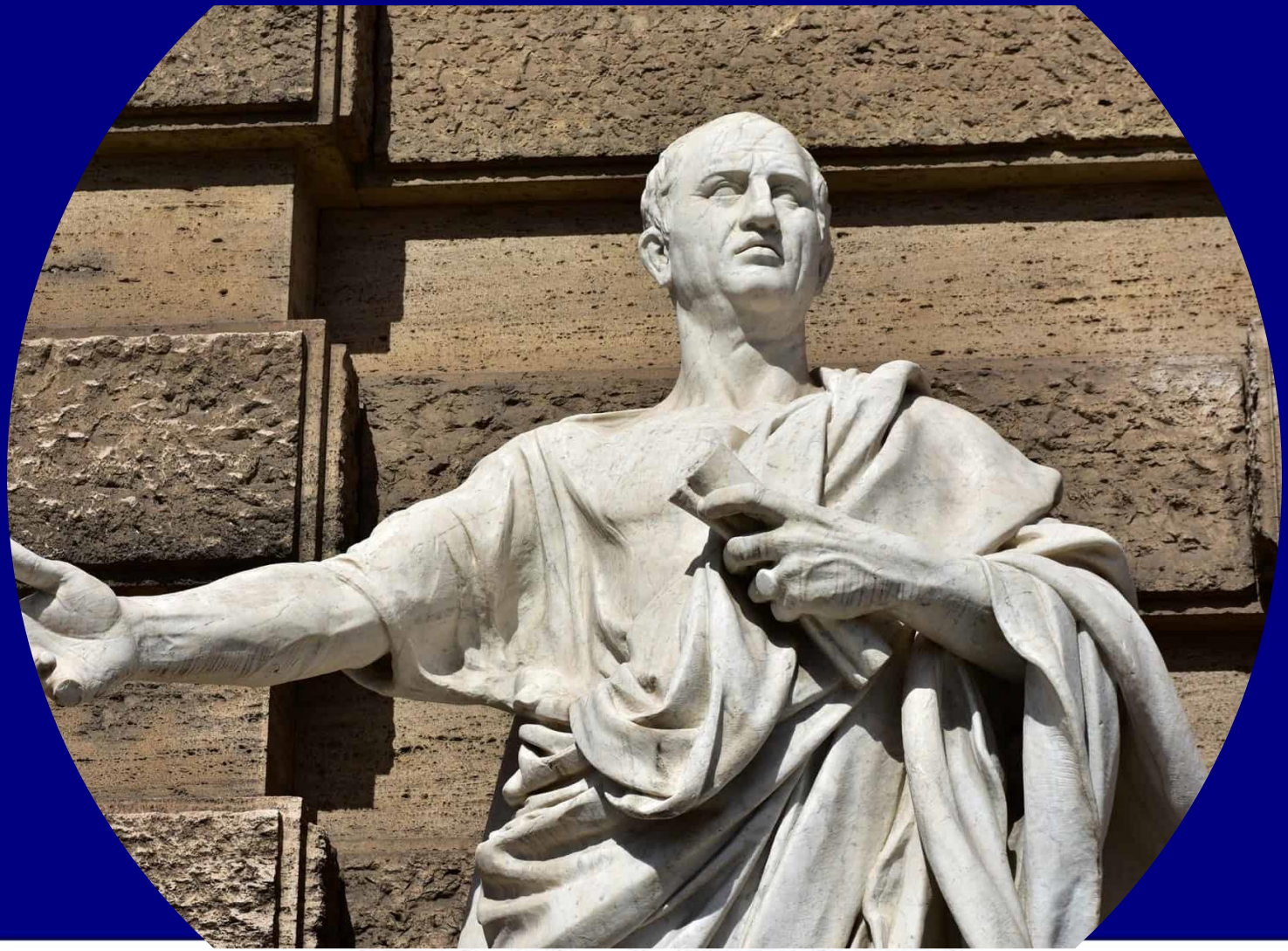
- MSD, Novartis, Pharma, Alkem, Astellas, Pfizer, Koçak (speaker's honorarium)
- Basilea research grant
- Turkish Society of Hospital Infections and Control (HIDER) current Executive Board member
- Biomed Research International (Academic Editor)
- Clinical Infectious Diseases (Editorial Advisory Board)
- Mediterranean Journal of Infection, Microbes and Antimicrobials Past Editor in Chief (2015 October-2020 February)
- European Study Group of Brain Infections past Executive board member and General Secretary (2014 May-2020 March)
- Case Reports in Infectious Diseases (past Academic Editor)
- World Health Organization consultant (2020-21)
- Infectious Diseases and Clinical Microbiology Specalty Society of Turkey (EKMUD) past Exedutive Board member (2010-12 2014-16)



HSV encephalitis: treatment update in 2022

J.P. Stahl
Infectiology
Grenoble Alpes University

Conflict of interest



Plan

- Clinical definitions
- Epidemiology
- Laboratory diagnosis
- Metagenomic analysis
- Treatment
- Ganciclovir
- Sequaleae
- Genetic background studies

Search for [herpes and encephalitis]
Time period: 2017-22
Web of science
Google scholar
Draft highly cited as well as interesting papers

Ensefalit

- Beyin parankiminin inflamasyonu
  - Doğrudan infeksiyon
  - Acute disseminated encephalomyelitis (ADEM) gibi enfeksiyon sonrası bir süreç veya
  - anti-N-metil-D-aspartat reseptörü (NMDAR) ensefaliti gibi non-infeksiyöz bir durum

Clin Infect Dis. 2013 Oct;57(8):1114-28. doi: 10.1093/cid/cit458. Epub 2013 Jul 15.

Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium.

Venkatesan A[1], Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, Stahl JP, Mailles A, Drebot M, Rupprecht CE, Yoder J, Cope JR, Wilson MR, Whitley RJ, Sullivan J, Granerod J, Jones C, Eastwood K, Ward KN, Durrheim DN, Solbrig MV, Guo-Dong L, Glaser CA; International Encephalitis Consortium.

Ensefalit ve Enfeksiyöz veya Otoimmün Etiyolojiye bağlı olası Ensefalopati için Tanı Kriterleri

- Major kriter (zorunlu)
  - Alternatif bir nedene bağlanamayan ve ≥24 saat süren mental durum değişikliği (bilinçte bozulma düzeyi, letarji veya kişilik değişikliği olarak tanımlanmış) ile başvuru
- Minör Kriterler (olası/possible ensefalit için 2; probable ya da konfirme ensefalit için ≥3 kriter)
  - Başvurudan önceki veya sonraki 72 saat içinde belgelenmiş ≥38˚ C (100.4˚ F) ateş
  - Önceden var olan bir nöbet bozukluğuna tam olarak bağlanamayan jeneralize veya kısmi nöbetler
  - Yeni başlangıçlı fokal nörolojik bulgular
  - BOS lökosit sayısı ≥5/mm^3
  - Nörogörüntülemede beyin parankiminde akut başlangıçlı ensefaliti düşündüren anormalliler
  - Elektroensefalografide ensefalit ile uyumlu ve başka bir nedene bağlanamayan

Clin Infect Dis. 2013 Oct;57(8):1114-28. doi: 10.1093/cid/cit458. Epub 2013 Jul 15.

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Konfirme ensefalit

- (1) Ensefalit ile uyumlu beyin iltihabının patoloji ile gösterilmesi
- (2) Uygun bir klinik örnekte, ensefalit ile ilişkili bir mikroorganizmaya ait akut enfeksiyonunun patolojik, mikrobiyolojik veya serolojik kanıt ile gosterilmesi
- (3) Ensefalit ile güçlü bir şekilde ilişkili bir otoimmün durumun laboratuvar kanıtının gösterilmesi (anti-NMDA reseptör antikorları)

Clin Infect Dis. 2013 Oct;57(8):1114-28. doi: 10.1093/cid/cit458. Epub 2013 Jul 15.

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- Herpetic infections recognized since the time of ancient Greece/Anatolia
- The word herpes translates as “creeping” or “crawling”, and is a reference to herpetic skin lesions
- Goodpasture (1929) and others demonstrated that material from herpetic lip and genital lesions produced encephalitis when introduced into the scarified cornea or skin of rabbits
- HSV-1 infection is common, with seropositivity among older adults estimated to be 60–90 % worldwide
- The annual incidence of HSVE worldwide varies between 1 and 4 cases per 100000
- There is a bimodal distribution with peak incidence in the very young (up to 3 years of age), and again in adults aged > 50 years

Neurotherapeutics. 2016 Jul; 13(3): 493–508.
Published online 2016 Apr 22. doi: 10.1007/s13311-016-0433-7
PMCID: PMC4965403
PMID: 27106239

Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management

Michael J. Bradshaw[1] and Arun Venkatesan[✉2]

Factors associated with increased probability of Herpes encephalitis

- Neonates
- Person to person transmission
- Cranial nerve abnormalities
- Rhombencephalitis

IDSA GUIDELINES

The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Allan R. Tunkel,[1] Carol A. Glaser,[2] Karen C. Bloch,[3] James J. Sejvar,[4] Christina M. Marra,[5] Karen L. Roos,[6] Barry J. Hartman,[7] Sheldon L. Kaplan,[8] W. Michael Scheld,[9] and Richard J. Whitley[10]

[1]Monmouth Medical Center, Long Branch, New Jersey; [2]California Department of Health Services, Richmond; [3]Vanderbilt University School of Medicine, Nashville, Tennessee; [4]Centers for Disease Control and Prevention, Atlanta, Georgia; [5]University of Washington School of Medicine, Seattle; [6]Indiana University School of Medicine, Indianapolis; [7]Weill Cornell Medical Center, New York, New York; [8]Baylor College of Medicine, Houston, Texas; [9]University of Virginia School of Medicine, Charlottesville; and [10]University of Alabama at Birmingham

- A total of 2583 patients with CA-CNS infections were included
  - from 37 referral centers in 20 countries
- 3.21% HSV

	Total	Meningitis	Encephalitis	Meningoencephalitis
HSV-1	48	7	21	19
HSV-2	34	17	6	10
HSV-1/2	1	1	0	0

doi: 10.1007/s10096-017-2973-0. Epub 2017 Apr 10.

The burden and epidemiology of community-acquired central nervous system infections: a multinational study

H Erdem [1 2], A Inan [3], E Guven [4], S Hargreaves [5], L Larsen [6], G Shehata [7], E Pernicova [8 9], E Khan [10], L Bastakova [11], S Namani [12], A Harxhi [13], T Roganovic [14], B Lakatos [15], S Uysal [16], O R Sipahi [17], A Crisan [18], E Miftode [19], R Stebel [11], B Jegorovic [20], Z Fehér [21], C Jekkel [15], N Pandak [22], A Moravveji [23], H Yilmaz [24], A Khalifa [25], U Musabak [26], S Yilmaz [27], A Jouhar [25], N Oztoprak [28], X Argemi [29], M Baldeyrou [29], G Bellaud [30], R V Moroti [31], R Hasbun [32], L Salazar [32], R Tekin [33], A Canestri [30], L Čalkić [34], L Praticò [35], F Yilmaz-Karadag [36], L Santos [37], A Pinto [37], F Kaptan [38], P Bossi [39], J Aron [39], A Duissenova [40], G Shopayeva [40], B Utaganov [40], S Grgic [41], G Ersoz [42], A K L Wu [43], K C Lung [43], A Bruzsa [15], L B Radic [44], H Kahraman [17], M Momen-Heravi [45], S Kulzhanova [46], F Rigo [47], M Konkayeva [46], Z Smagulova [46], T Tang [48], P Chan [49], S Ahmetagic [50], H Porobic-Jahic [50], F Moradi [51],

- ID-IRI study on 35 referral centres in 10 countries
- 496 patients with PCR-proven HME (herpes meningoencephalitis)
  - HSV-1 DNA in 351 patients (70.8%)
  - HSV-2 DNA in 83 patients (16.7%)
  - Undefined HSV DNA type in 62 patients (12.5%)
- Encephalitis presentation
  - At least one clinical finding compatible with encephalitis

  at hospital admission such as changes in conscious, disorientation, convulsions, amnesia, personality changes, speech disorders, hallucinations, abulia, history of unconsciousness or syncope, hemiparesis, dizziness, facial and hypoglossal cranial nerve palsies
- Others non encephalitic presentation

Multicenter Study > Clin Microbiol Infect. 2016 Jun;22(6):568.e9-568.e17.
doi: 10.1016/j.cmi.2016.03.027. Epub 2016 Apr 13.

Managing atypical and typical herpetic central nervous system infections: results of a multinational study

Y Cag [1], H Erdem [2], S Leib [3], S Defres [4], S Kaya [5], L Larsen [6], M Poljak [7], D Ozturk-Engin [8], B Barsic [9], X Argemi [10], S M Sørensen [11], A L Bohr [12], P Tattevin [13], J D Gunst [14], L Baštáková [15], M Jereb [16], I S Johansen [6], O Karabay [17], A U Pekok [18], O R Sipahi [19], M Chehri [20], G Beraud [21], G Shehata [22], R Fontana [23], M Maresca [23], H Karsen [24], G Sengoz [25], M Sunbul [26], G Yilmaz [27], H Yilmaz [26], A Sharif-Yakan [28], S Kanj [28], E Parlak [29], F Pehlivanoglu [25], F Korkmaz [30], S Komur [31], S Kose [32], M Ulug [33], S Bolukcu [8], S A Coskuner [34], J P Stahl [35], N Ince [36], Y Akkoyunlu [37], G Halac [38], E Sahin-Horasan [39], H Tireli [40], G Kilicoglu [41], A Al-Mahdawi [42], S A Nemli [43], A Inan [8], S Senbayrak [8], H Vahaboglu [44], N Elaldi [45]

- 379 patients (76.4%) had at least one of the specified characteristics of encephalitis placed these patients into the encephalitis presentation group
- 117 patients (23.6%) had none of these findings placed in the nonencephalitis presentation group
- Abnormalities suggestive of encephalitis in the encephalitis vs non encephalitis presentation group
  - MRI 83.9% vs. 33.3% of the patients
  - EEG in 91.0% vs. 61.9% of patients
  - MRI or EEG 96.3% vs 87.5%
- Considering the subtle nature of HME, clinical, CSF, HSV PCR, EEG and MRI data should be collected for all patients with a central nervous system infection

Multicenter Study > Clin Microbiol Infect. 2016 Jun;22(6):568.e9-568.e17.
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- ≥18 years of age with an admitting or discharge diagnosis (primary and/or secondary) of meningitis or encephalitis determined by ICD-9
  - 1 January 2011 and 31 December 2014
- Overall 26429 cases
  - Enterovirus (13463 [51.6%])
  - Unknown (4944 [21.4%])
  - Bacterial meningitis (3692 [14.1%])
  - Herpes simplex virus (2184 [8.3%])
  - Noninfectious (921 [3.5%])
  - Fungal (720 [2.7%])
  - Arboviruses (291 [1.1%])
  - Other viruses (214 [0.8%])

> Clin Infect Dis. 2017 Aug 1;65(3):359-363. doi: 10.1093/cid/cix319.

Epidemiology of Meningitis and Encephalitis in the United States, 2011–2014

Rodrigo Hasbun [1], Ning Rosenthal [2], J M Balada-Llasat [3], Jessica Chung [2], Steve Duff [4], Samuel Bozzette [5 6], Louise Zimmer [5], Christine C Ginocchio [5 7]

Etiology (No.)	Antibiotic Therapy		Antiviral Therapy		Antifungal Therapy	
	No. (%)	Median Days (IQR)	No. (%)	Median Days (IQR)	No. (%)	Median Days (IQR)
Overall sample	22684 (89.7)	4 (5)	13791(57.2)	3 (3)	2042 (8.5)	4 (7)
Enterovirus (13463)	10490 (89.0)	3 (2)	6673 (56.6)	3 (2)	412 (3.5)	2 (3)
Unknown etiology (4944)	3838 (86.9)	5 (6)	2510 (56.8)	4 (4)	470 (10.6)	4 (6)
Bacterial meningitis (3692)	3611 (99.1)	8 (7)	1529 (41.9)	2 (3)	370 (10.1)	4 (6)
Herpes viruses[a] (2184)	1827 (84.7)	3 (3)	2042 (94.6)	5 (5)	101 (4.7)	3 (4)

> Clin Infect Dis. 2017 Aug 1;65(3):359-363. doi: 10.1093/cid/cix319.

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- Nationwide prospective observational study of all cases of proven community-acquired infectious meningitis and encephalitis in adults
- Treated in all infectious diseases departments in Denmark
  - 1 January 2015 to 30 June 2016 (1.5 years)
- International encephalitis consortium definitions

Observational Study > Clin Microbiol Infect. 2018 Oct;24(10):1102.e1-1102.e5.
doi: 10.1016/j.cmi.2018.01.016. Epub 2018 Mar 1.

Infectious meningitis and encephalitis in adults in Denmark: a prospective nationwide observational cohort study (DASGIB)

J Bodilsen [1], Merete Storgaard [2], L Larsen [3], L Wiese [4], J Helweg-Larsen [5], A-M Lebech [6], C Brandt [7], C Østergaard [8], H Nielsen [9], DASGIB study group

- 252 cases of viral meningitis (3.6/100 000/year)
- 214 cases of bacterial meningitis (3.1/100 000/year)
- 96 cases of encephalitis (1.4/100 000/year)

Observational Study > Clin Microbiol Infect. 2018 Oct;24(10):1102.e1-1102.e5.
doi: 10.1016/j.cmi.2018.01.016. Epub 2018 Mar 1.

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Table 2
Causative pathogens of infectious meningitis and encephalitis in adults treated in departments of infectious diseases in Denmark

Central nervous system infection	Observed patients (*n*)	Causative pathogen
Bacterial meningitis		
Proven aetiology	214	183 (86)
Streptococcus pneumoniae	–	101 (47)
Staphylococcus aureus	–	24 (11)
β-haemolytic streptococci	–	14 (7)
Neisseria meningitidis	–	11 (5)
α-haemolytic streptococci	–	8 (4)
Escherichia coli	–	8 (4)
Listeria monocytogenes	–	7 (3)
Encephalitis		
Proven aetiology	96	64 (67)
HSV-1	–	37 (39)
VZV	–	20 (21)
HSV-2	–	3 (3)
HIV	–	2 (2)
TBEV	–	1 (1)
EBV	–	1 (1)
Viral meningitis		
Proven aetiology	252	163 (65)
VZV	–	61 (24)
Enterovirus	–	50 (20)
HSV 2	–	46 (18)
EBV	–	2 (1)
Chikungunya (traveller)	–	1 (1)
HIV	–	1 (1)
Influenza virus	–	1 (1)
TBEV	–	1 (1)

Encephalitis
94 cases
64 (microb. proven)
HSV-1 37 cases (39%)
HSV-2 2 cases (3%)

Observational Study > Clin Microbiol Infect. 2018 Oct;24(10):1102.e1-1102.e5.
doi: 10.1016/j.cmi.2018.01.016. Epub 2018 Mar 1.

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- A total of 79 patients (28 female, 51 male, aged 42.1 ± 18.5)
  - 46 patients were classified in purulent meningitis group
  - 33 (42%) were in meningoencephalitis group
- Pathogens were detected by multiplex PCR in 41 patients (52%)
- In the meningoencephalitis group, pathogens were detected in 14 (42%) out of 33 patients
  - HSV 1 and 2 comprised 10% meningoencephalitis subgroup
  - All three cases fullfilling international encephalitis consortium

Multicenter Study > Mikrobiyol Bul. 2017 Jul;51(3):277-285. do

[Investigation of bacterial and viral etiology in community acquired central nervous system infections with molecular methods]

[Article in Turkish]

Hasip Kahraman [1], Alper Tünger, Şebnem Şenol, Hörü Gazi, Meltem Avcı, Bahar Örmen, Nesrin Türker, Sabri Atalay, Şükran Köse, Sercan Ulusoy, Meltem Işıkgöz Taşbakan, Oğuz Reşat Sipahi, Tansu Yamazhan, Zeynep Gülay, Sema Alp Çavuş, Hüsnü Pullukçu

Turk Mikrobiyol Cemiy Derg 2021;51(1):70-85
doi:10.5222/TMCD.2021.74508

Araştırma / *Research Article*

Türkiye'de Son On Yılda Saptanan Santral Sinir Sistemi Enfeksiyonlarında Viral Etkenlerin Değerlendirilmesi ve Bibliyometrik Analizi*

Evaluation and a Bibliometric Analysis of Viral Factors in Central Nervous System Infections Detected in the Last Ten Years in Turkey

Berke Gökkılıç*, Candan Çiçek, Ayşın Zeytinoğlu**, Ekin Kartal***

* Ege Üniversitesi Tıp Fakültesi, İzmir, Türkiye
** Ege Üniversitesi Tıp Fakültesi, Tıbbi Mikroiyoloji Anabilim Dalı, İzmir, Türkiye

- A total of 12669 CSF samples from 33 studies (2010-19)were included in the analysis
- The highest number of CSF samples was published from Izmir (n=5566)
- 2.58% HSV

Ege University Medical Faculty CSF panel results

- **2020 484 samples 7 positive (1.44%) for HSV 1-2**
- **2021 283 samples 2 positive cases (0.7%) for HSV 1-2**
  - **– Could not be tested for a period for lack of kits**

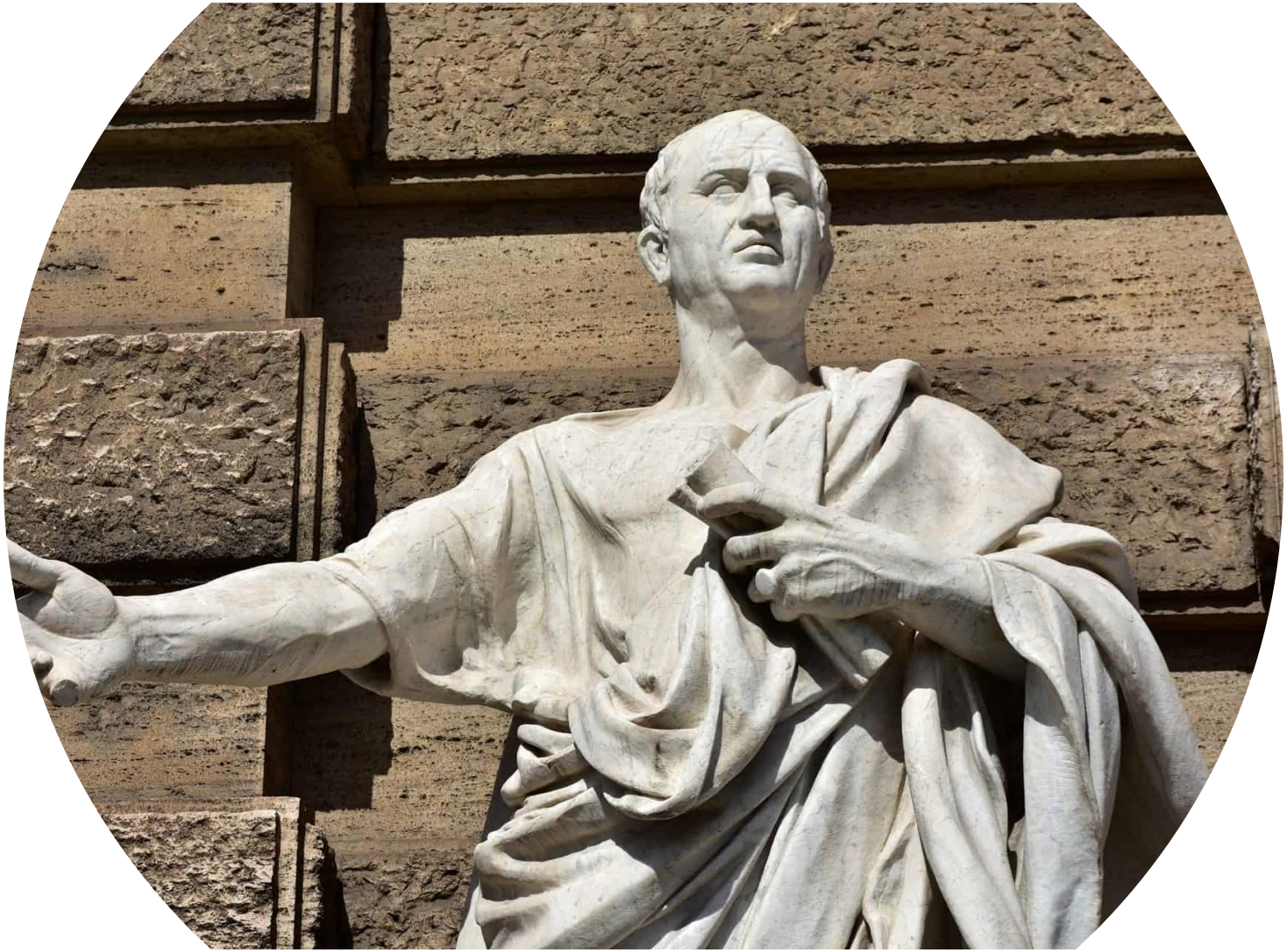
via Candan Cicek

KHUH CSF Panel results

- January 2021-April 2022
- 185 cases (1.1% + for HSV)
  - One case HSV-1
  - One case HSV-2

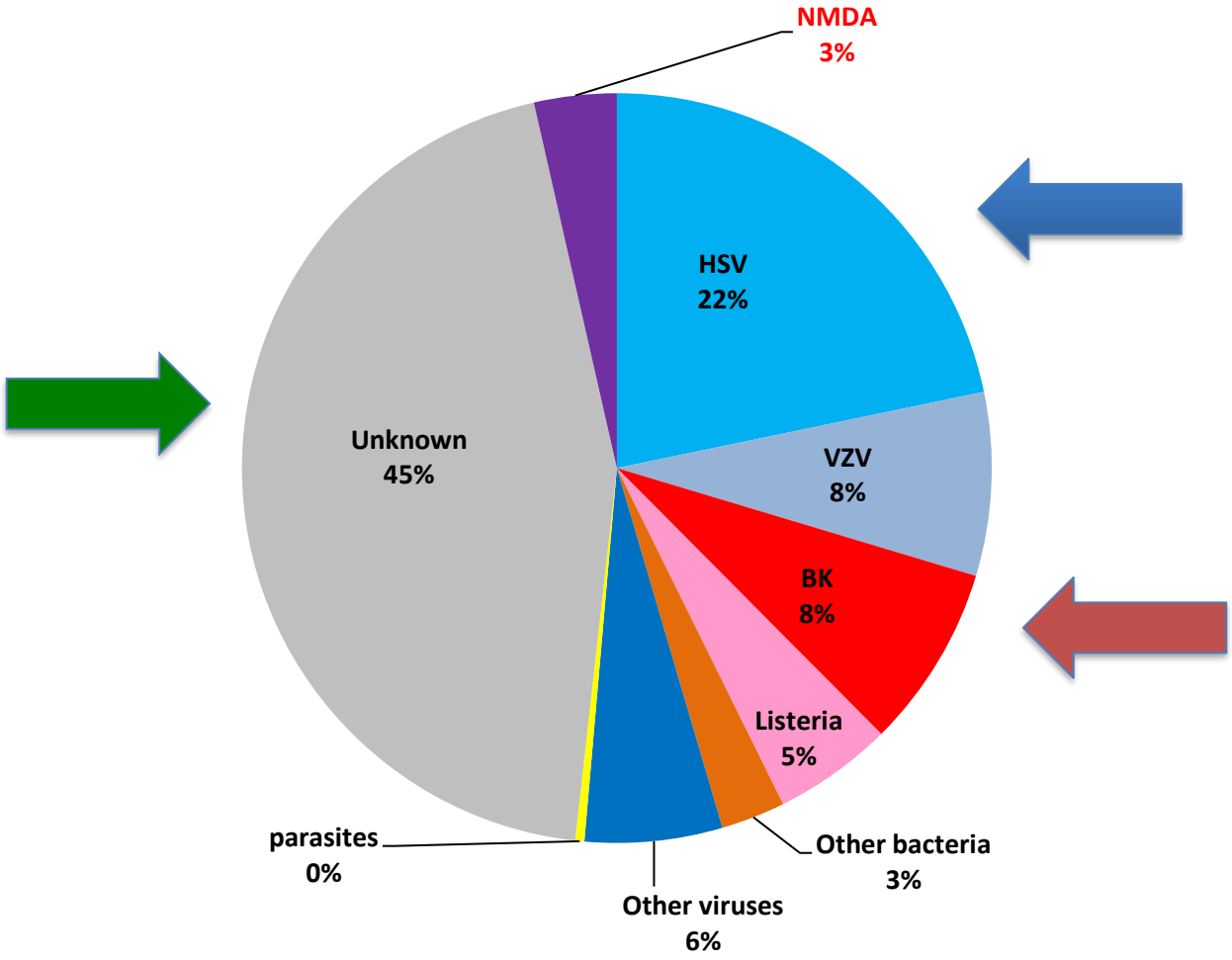
KING HAMAD UNIVERSITY HOSPITAL
مستشفى الملك حمد الجامعي

Via Amira Khairy



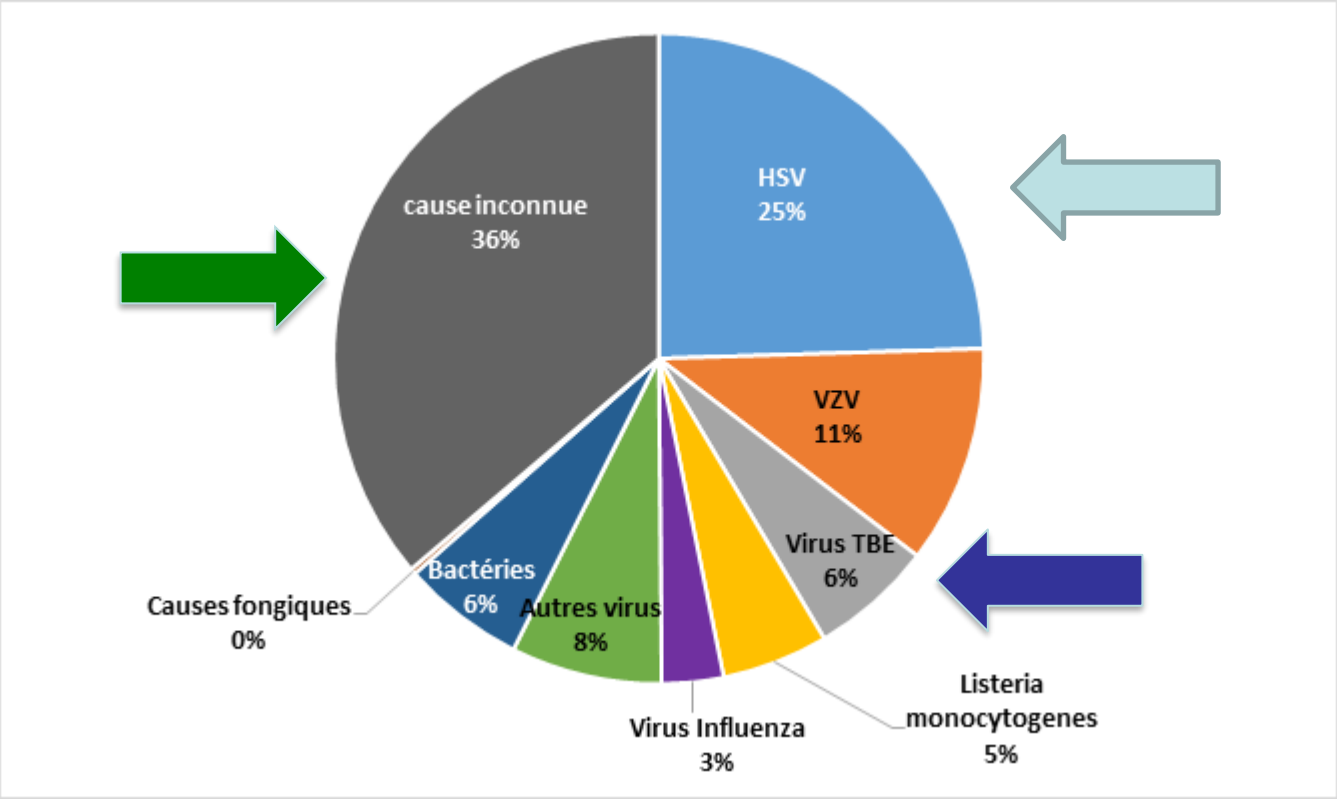
Evolving epidemiology: the French example

2007 epidemiology



Infectious Encephalitis in France in 2007: A National Prospective Study A. Mailles, J.P. Stahl Clin. Infect. Dis. 2009; 49:1838–47

Current epidemiology



Changing profile of encephalitis: Results of a 4-year study in France
A. Mailles et al. Infect. Dis. Now 2022, 1:

In 2022 diagnosis of HSV is still an emergency

New tools for pathogens identification

Old school

VS

Modern school

All in one

FilmArray is Comprehensive

FilmArray detects 14 pathogens including bacteria, viruses and fungi—something no other diagnostic on the market can do.

ME Panel Menu

Bacteria

Escherichia coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae

Yeast

Cryptococcus neoformans/gattii

Viruses

Cytomegalovirus (CMV)
Enterovirus
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Human herpesvirus 6 (HHV-6)
Human parechovirus
Varicella zoster virus (VZV)

See how you can get faster results at BioFireDX.com.

It looks simple, but you have to analyze the result and interpret it

Multiplex performances

- Lack of sensitivity: 27% false negative for HSV1, 13% for HSV2 *(Vetter, CMI 2020)*

→ **never** rule out HSV diagnosis in case of negative result

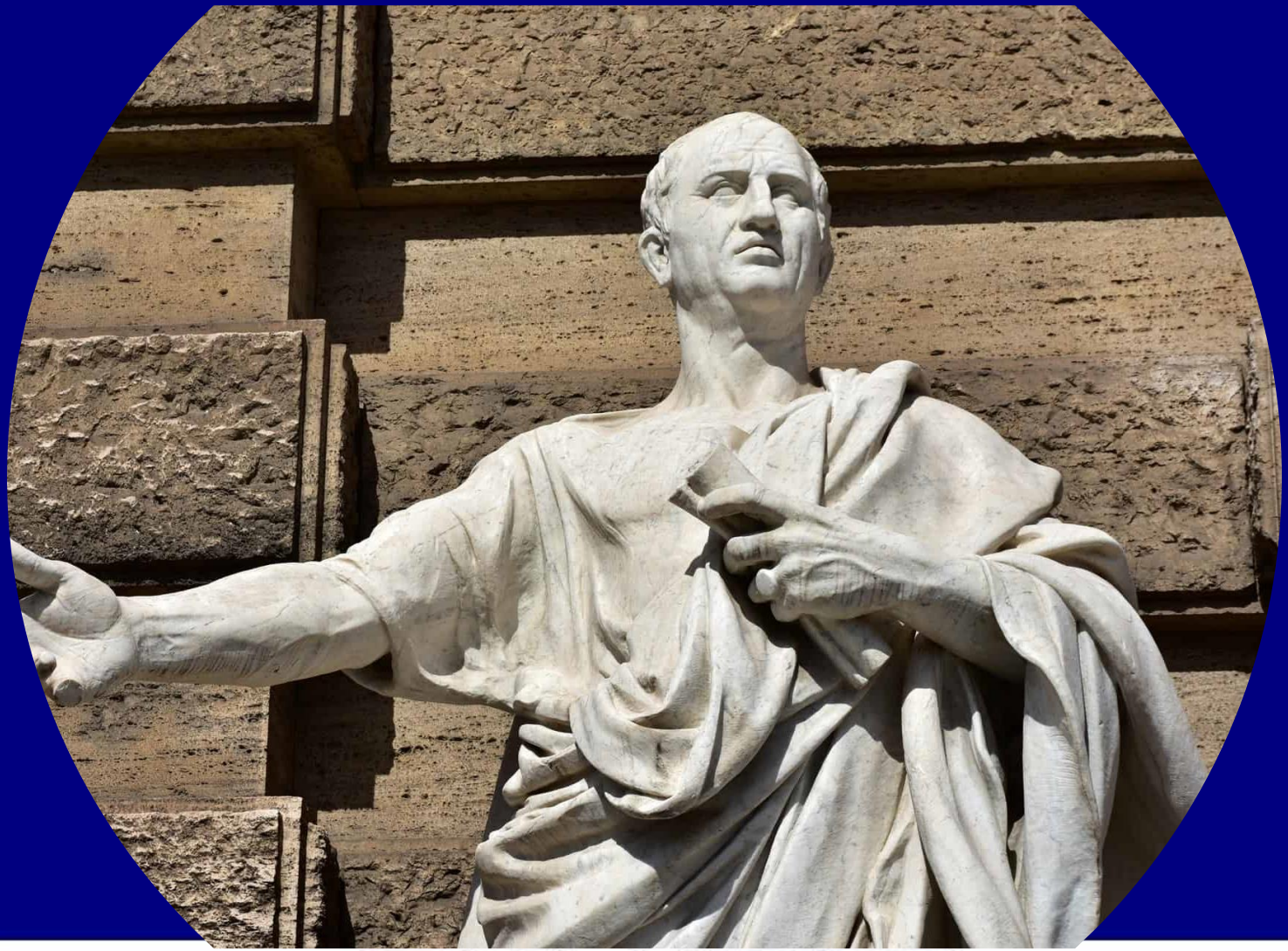
- Sensitivity for the target HSV1 sub-optimal *(Graf et al.Diagn Microbiol Infect Dis 2017; Lee et al. J Microbiol Immunol Infect 2019; Piccirilli et al. New Microbiol 2018)*

- False positive results are ~~also~~ reported, also rare (*Gomez et al. Open Forum Infect Dis 2017)*

Interpretation of early negative HSV PCR (mono- and multiplex)

- Possible negative PCR if test performed before D4 after the onset of neurological symptoms: 24%.
- Limit of the study: children, 33 patients, retrospective study, 2003
- The risk/benefit ratio is in favor of maintaining acyclovir, up to a second PCR at or after D4.

De Tiege X. et al. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis 2003;36(10):1335–9.



Untargeted metagenomic next generation screening

- Shotgun sequencing of clinical samples or pure microbial cultures in which random samples of analyte DNA or RNA are surveyed en masse
  - In contrast to targeted approaches that utilize singleplex or multiplex PCR, primer extension, or bait probe enrichment methods
    - Not restricted to detecting a list of specific targets

Review > Annu Rev Pathol. 2019 Jan 24;14:319-338.
doi: 10.1146/annurev-pathmechdis-012418-012751. Epub 2018 Oct 24.

Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection

Wei Gu [1], Steve Miller [1], Charles Y Chiu [1 2]

Metagenomic analysis

- PROS
- Hypothesis-free, or unbiased, testing
- Discovery of new or unexpected organisms
- Potential for quantitation
- Ability to detect any portion of genome

- CONS
- Must also sequence human host background
- Expensive
- Time consuming
- Not all genomes are available
- Prone to contamination with environmental species

Review > Annu Rev Pathol. 2019 Jan 24;14:319-338.
doi: 10.1146/annurev-pathmechdis-012418-012751. Epub 2018 Oct 24.

Clinical Metagenomic Next-Generation Sequencing for Pathogen Detection

Wei Gu [1], Steve Miller [1], Charles Y Chiu [1 2]

- A 1-year, multicenter, prospective study
- Investigated the usefulness of metagenomic NGS of CSF for the diagnosis of infectious meningitis and encephalitis in hospitalized patients
- All positive tests for pathogens on metagenomic NGS were confirmed by orthogonal laboratory testing
- Physician feedback was elicited by teleconferences with a clinical microbial sequencing board and by surveys
- Clinical effect was evaluated by retrospective chart review

Multicenter Study > N Engl J Med. 2019 Jun 13;380(24):2327-2340.
doi: 10.1056/NEJMoa1803396.

Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

Michael R Wilson [1], Hannah A Sample [1], Kelsey C Zorn [1], Shaun Arevalo [1], Guixia Yu [1], John Neuhaus [1], Scot Federman [1], Doug Stryke [1], Benjamin Briggs [1], Charles Langelier [1], Amy Berger [1], Vanja Douglas [1], S Andrew Josephson [1], Felicia C Chow [1], Brent D Fulton [1], Joseph L DeRisi [1], Jeffrey M Gelfand [1], Samia N Naccache [1], Jeffrey Bender [1], Jennifer Dien Bard [1], Jamie Murkey [1], Magrit Carlson [1], Paul M Vespa [1], Tara Vijayan [1], Paul R Allyn [1], Shelley Campeau [1], Romney M Humphries [1], Jeffrey D Klausner [1], Czarina D Ganzon [1], Fatemeh Memar [1], Nicolle A Ocampo [1], Lara L Zimmermann [1], Stuart H Cohen [1], Christopher R Polage [1], Roberta L DeBiasi [1], Barbara Haller [1], Ronald Dallas [1], Gabriela Maron [1], Randall Hayden [1], Kevin Messacar [1], Samuel R Dominguez [1], Steve Miller [1], Charles Y Chiu [1]

- 204 pediatric and adult patients at eight hospitals
- International consortium encephalitis criteria
- Isolated meningitis (70 patients [34.3%]) or encephalitis (130 patients (63.7%]), with only 2.0% presenting with myelitis
- Patients were severely ill: 48.5% had been admitted to the ICU
- The 30-day mortality among all study patients was 11.3%
- A total of 58 confirmed infections of the nervous system were diagnosed in 57 patients (27.9%) (mean test time 90 h)
- Among these 58 infections
  - Metagenomic NGS identified 13 (22%) (none Herpes) that were not identified by clinical testing at the source hospital

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- Among the remaining 45 infections (78%), metagenomic NGS made concurrent diagnoses in 19 (42.2%) including herpes
- Of the 26 infections not identified by metagenomic NGS
  - 11 were diagnosed by serologic testing only
  - Seven were diagnosed from tissue samples other than CSF
  - 8 were negative on metagenomic NGS owing to low titers of pathogens in CSF
- **A total of 8 of 13 diagnoses made solely by metagenomic NGS had a likely clinical effect, with 7 of 13 guiding treatment (12%)**

Multicenter Study > N Engl J Med. 2019 Jun 13;380(24):2327-2340.
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Definite (one or more of i, ii, iii plus either a or b)

i Virus-positive culture of CSF, brain biopsy, throat, stool, or genital swab.

ii ⩾four-fold increase in virus-specific antibody titre or detection of virus-specific IgM antibody in serum.

iii Virus-specific rash (herpes genitalis or shingles).

(a) CSF white-cell count ⩾5/μL and ⩾1 of meningism, headache, or fever (with no other explanation).

(b) Clouding of consciousness or focal neurological signs and fever or headache (with no other explanation).

Multicenter Study > Front Cell Infect Microbiol. 2020 Mar 5;10:88.
doi: 10.3389/fcimb.2020.00088. eCollection 2020.

Metagenomic Next-Generation Sequencing for Diagnosis of Infectious Encephalitis and Meningitis: A Large, Prospective Case Series of 213 Patients

Xiao-Wei Xing [1], Jia-Tang Zhang [2 3], Yu-Bao Ma [2], Mian-Wang He [2], Guo-En Yao [4], Wei Wang [5], Xiao-Kun Qi [6], Xiao-Yan Chen [2], Lei Wu [2], Xiao-Lin Wang [2], Yong-Hua Huang [7], Juan Du [8], Hong-Fen Wang [2], Rong-Fei Wang [2], Fei Yang [2], Sheng-Yuan Yu [2 3]

- 213 patients treated in six hospitals were finally enrolled
  - including 75 (35.2%) with presumed viral encephalitis and/or meningitis
  - 44 with presumed TBM
  - 43 with presumed bacterial meningitis
  - 18 with fungal meningitis
  - 33 with presumed non-infectious CNS diseases

Multicenter Study > Front Cell Infect Microbiol. 2020 Mar 5;10:88.
doi: 10.3389/fcimb.2020.00088. eCollection 2020.

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- For the 54 patients with definite viral encephalitis and/or meningitis, if an (species-specific read number SSRN ≥2) was considered positive, the AUC was 0.659
  - 95% confidence interval [CI] = 0.566–0.751
- All herpes subgroup cases n: 10 was positive in metagenomic analysis (SSRN>2)

Table 3

Positive mNGS results of the four types of CNS infection (73/180).

Results of mNGS				Confirmatory data
Pathogen	**SSRN**	**Coverage, %**	**Depth**	
Viral encephalitis and/or meningitis (*n* = 23), SSRN ≥ 2				
Herpes simplex virus 1 (*n* = 9)	2,764 (2–27639)	57.9066 (0.0412–91)	2.99 (1–7.5)	PCR (*n* = 5), Positive HSV antibody (CLIA) (*n* = 9)
Herpes simplex virus 2 (*n* = 1)	4,311	90	6.5	Positive HSV antibody (CLIA)

doi: 10.3389/fcimb.2020.00088. eCollection 2020.

Metagenomic Next-Generation Sequencing for Diagnosis of Infectious Encephalitis and Meningitis: A Large, Prospective Case Series of 213 Patients

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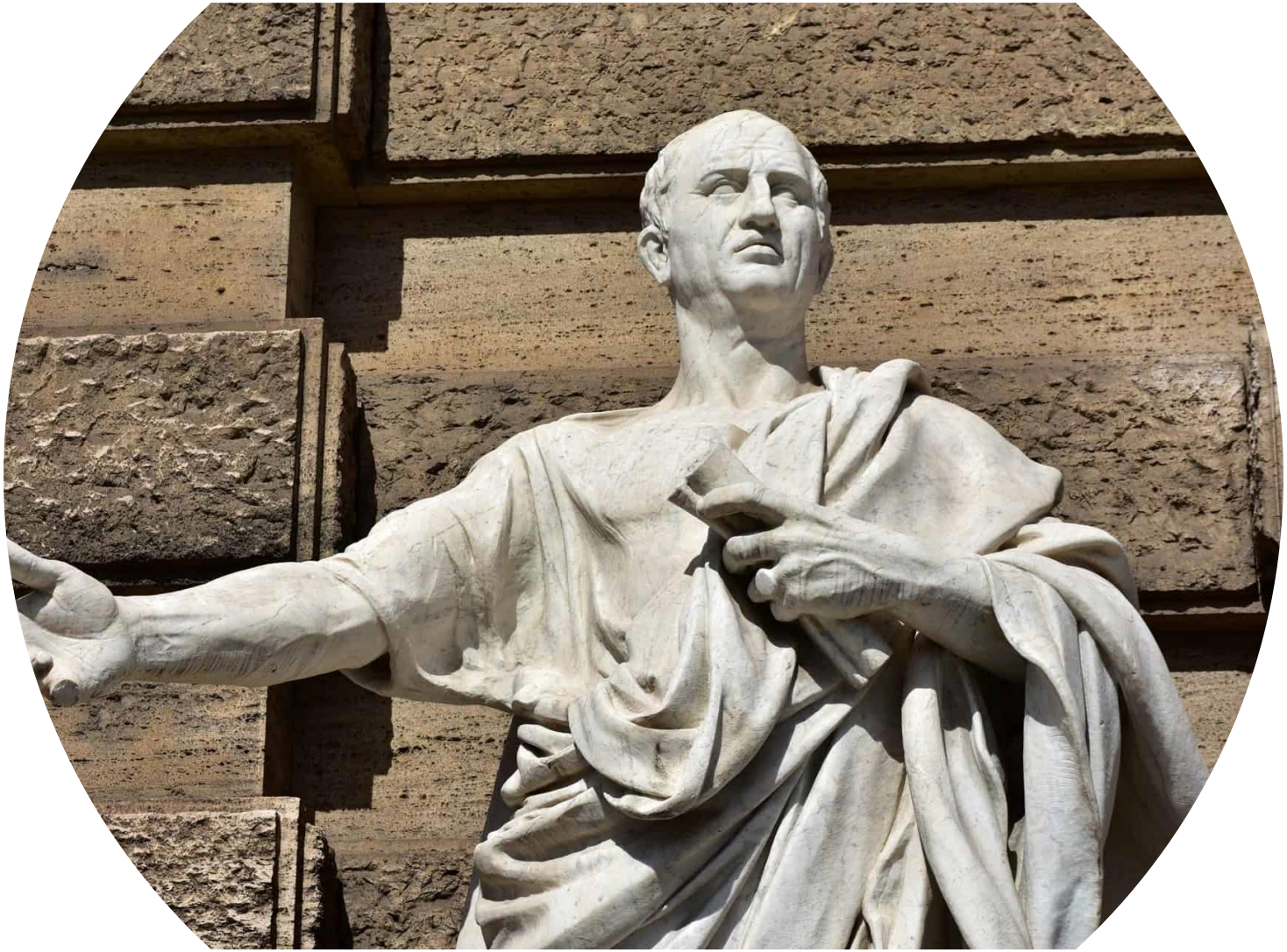


Antiviral treatment

Various guidelines (IDSA, France, UK), same recommendations:

- Acyclovir I.V.: 10 mg/Kg every 8 hours for 14 days in immunocompetent patients, 21 days in immunocompromised patients
- Oral acyclovir or valacyclovir is not recommended: insufficient distribution in CSF

Acyclovir (ACV) distribution in CSF

- *In vitro* IC_{50} of HSV: 0.1 to 3.9 μM
- After oral administration of valaciclovir (1000 mgx3/day)*: 2.5 μM/L of ACV in CSF. The AUCs ratio in CSF and serum: 20%
- After oral administration of valaciclovir (2000 mgx 4/day)**: 4.9 to 8 μM/L ACV in CSF, but **high risk of neurotoxicity**

**Lycke et al. AAC 2003*

*** Smith et al. AAC 2010*

Resistance to aciclovir ? data is still scarce

Specific study in 12 patients with HSV encephalitis:

- No detection of intrathecal ACVR-associated TK mutations in HSV isolates
- Short-term ACV therapy did not induce emergence of detectable ACVR-associated TK mutations

Mitterreiter JG, et al. (2016) Prevalence of Intrathecal Acyclovir Resistant Virus in Herpes Simplex Encephalitis Patients. PLoS ONE 11(5): e0155531. doi:10.1371/journal. pone.0155531

ACV-resistant HSV in CSF

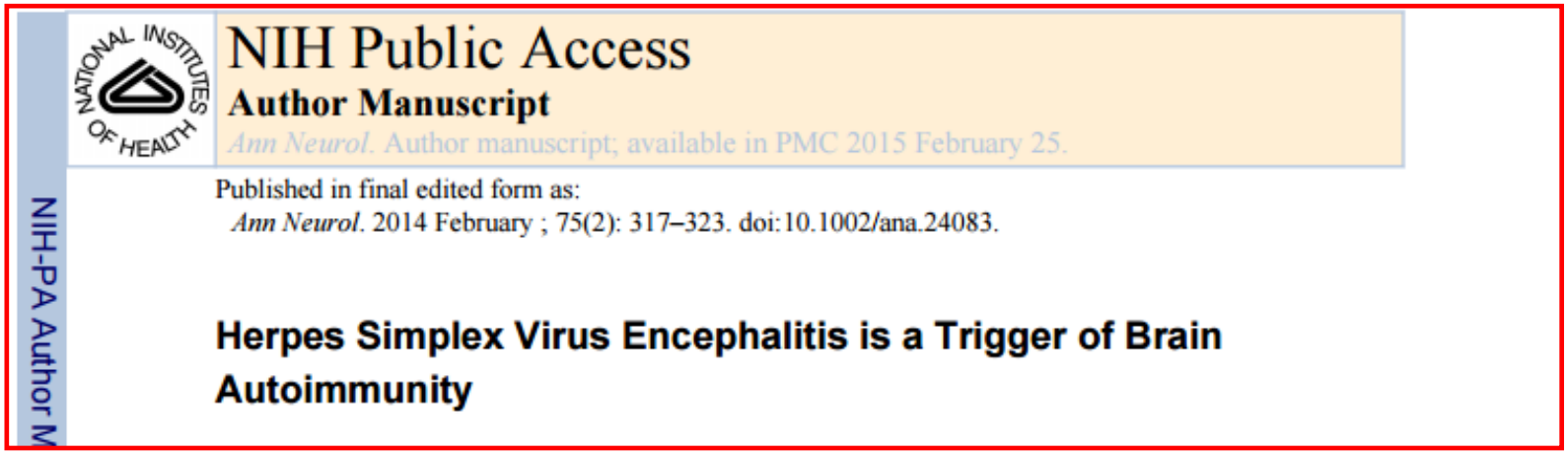
- 3 cases reported in literature, so far
  - All were immunocompromized patients

Schepers et al., JCV, 2014 (anti-TNF treatment), *Kakiuchi et al., JCM, 2013* (neonate), *Karrash et al., J Neurol Sci, 2018* (Chronic Lymphoid Leukemia).

- French Reference Center for *Herpesviridae* (*personnal communication D. Boutolleau*):
- 36 CSF with HSV-1 (25 different patients) over the 2008-2021 time period.
- 11 (30%) possible investigations for resistance: no mutation for resistance

HSV is a « trigger » for autoimmunity

T. Armangue et al. Ann. Neurol. 2014



Published in final edited form as:
Ann Neurol. 2014 February ; 75(2): 317–323. doi:10.1002/ana.24083.

Herpes Simplex Virus Encephalitis is a Trigger of Brain Autoimmunity

First data from Sweden

- Cohort of 49 HSV encephalitis
  - 12/49 (24%) patients positive for IgG anti-NMDAr,
  - 3 weeks to 3 months after the encephalitis episode

G. Westman et al. N-methyl-D-aspartate receptor autoimmunity affects cognitive performance in herpes simplex encephalitis

Further data from Spain

- Cohort of 51 patients with HSV encephalitis
- 14 /51 (27%) patients presented with an auto-immune encephalitis after the HSV encephalitis (9 with anti-NMDAR, 5 with other antibodies)
- 11/37 (30%) patients *without* an immune encephalitis had auto-antibodies (NMDAR n=3, other antibodies n=8)

Thais Armangue, et al. Autoimmune Encephalitis Post-herpes Simplex Encephalitis: Frequency, Syndromes, Risk Factors, and Outcome. Lancet Neurol. 2018

HSV and immune mechanisms, a tricky situation

- RNA-sensing receptor TLR3 is necessary for the innate immunity efficacy toward HSV, in neurons.
- Experimental infection is worsened if TLR3 deficit
- Peripheral lymp nodes don’t have this pathway, but neurons have

Sato R, et al. Combating herpesvirus encephalitis by potentiating a TLR3-mTORC2 axis. Nat. Immunol. 2018, 19:1071-1082

Zimmer B, et al.Human iPSC-derived trigeminal neurons lack constitutive TLR3-dependent immunity that protects cortical neurons from HSV-1 infection. Proc Natl Acad Sci U S A. 2018; 115: E8775-E8782

Compleasomes

- Interaction between complement and proteasomes => complex named compleasomes
- Important increase of compleasomes levels in CSF, in case of HSV encephalitis.
- These complexes are probably important defense mechanisms as they decrease the intracranial pressure in animals

Johansson E.,et al. Increased level of compleasomes in cerebrospinal fluid of patients with herpes simplex encephalitis. J. NeuroVirol. 2018, 24:702–711

A matter of balance

Increase immune mechanisms

Decrease inflammatio

Steroids or not steroids, that is the question

HSV encephalitis in animal models

- ***Meyding-Lamade UK, et al. Journal of Neurovirology. 2003***

  Steroids + aciclovir

  - Improved longterm lesions on MRI
  - Did not decrease the viral clearance
  - Improved the decrease of the viral load

- ***Sergerie Y, et al. The Journal of infectious diseases. 2007***

Steroids administered 3 days after HSV inoculation to mice, on top of aciclovir

- Significant longer survival in steroid-treated mice
- Less severe symptoms in steroid-treated mice

Reports in human

- No clinical trial published yet
- Some case reports, observational cohorts including few patients, or retrospective studies suggest a clinical benefit
- The largest cohort: 45 patients
  - Higher age, initial low Glasgow coma score, and absence of steroid are the best predictors for a poor outcome

Kamei S, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry. 2005;76(11):1544-9

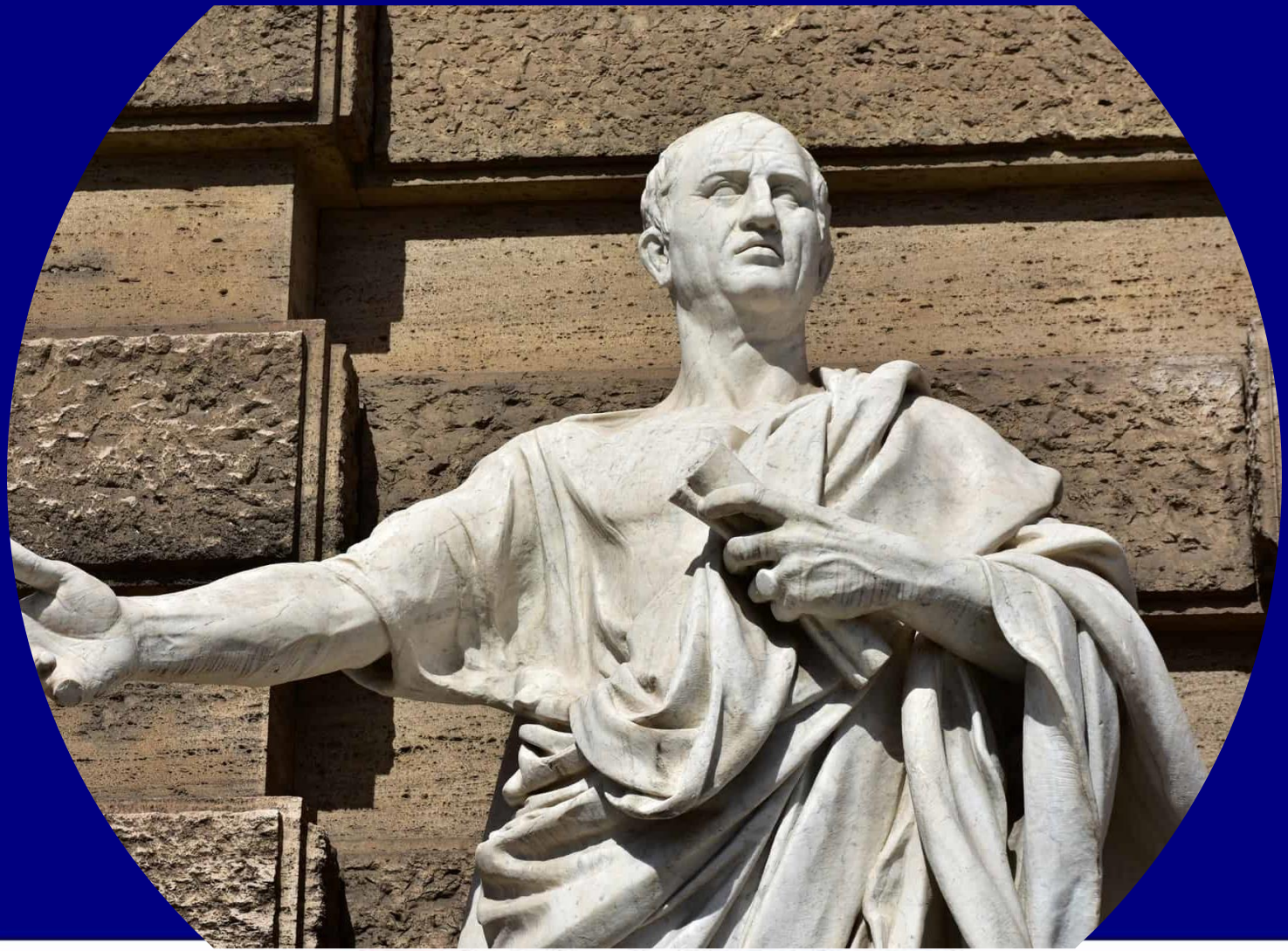
DexEnceph: an ongoing randomized trial

- Dexamethasone 10 mg x 4 /day for 4 days vs no steroids, on top of acyclovir treatment
- Endpoints: rate of auto-immune encephalitis, neuropsychological outcome
- Results expected in 2023 ?

Whitfield T, Fernandez C, Davies K, et al.

Protocol for DexEnceph: a randomised controlled trial of dexamethasone therapy in adults with herpes simplex virus encephalitis.

BMJ Open 2021;11:e041808. doi:10.1136/ bmjopen-2020-041808



- 1 Temmuz 2009-Clinical/Infectious Diseases uyerısı
- Foskarnet yan etki profili nedeniyle
  - renal bozukluk, hipokalsemi, hipofosfatemi, hipomagnezemi, hipokalemi
- Gansikloir HSV/VZV infeksiyonlarında birinci seçenek

Gansiklovir

- Asiklovir gibi deoksiguanozin analoğu
- Dna sentezini inhibe ediyor
- Asiklovir etkinliğine benzer şekilde gansiklovir fosforilizasyonunda ilk basamak virüs tarafından kodlanan enzimle sonraki basamaklar hücresel enzimlerle
- Asiklovir etkinliğine benzer HSV-1, HSV-2 ve VZV etkinliiği
  - Asiklovirden farklı olarak CMV etkinliği en yüksek
- Yan etki profili pratikte biraz daha kötü

Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis.

Show details

Arvin A, Campadelli-Fiume G, Mocarski E, et al., editors.
Cambridge: Cambridge University Press; 2007.

Contents

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Chapter 64 Antiviral therapy of HSV-1 and -2

David W. Kimberlin and Richard J. Whitley.

TABLE 1. Susceptibilities of all tested HSV-1 strains to nucleoside analogs and PFA determined by flow cytometry and by CPE inhibitory assay

HSV-1 strain	IC_{50} (μM) of[a]: ACV		GCV		PFA	
		CPE		CPE	FC	CPE
K1	0.45 ± 0.13	0.37	0.23 ± 0.08	0.20	213 ± 11	65
3210	1.17 ± 0.68	0.36	0.36 ± 0.07	0.29	220 ± 30	ND[b]
2890	1.47 ± 0.25	0.32	1.28 ± 0.28	0.44	296 ± 50	ND
1588	1.09 ± 0.45	0.51	0.98 ± 0.18	ND	243 ± 11	ND
2323	1.37 ± 0.18	0.55	0.77 ± 0.15	ND	270 ± 26	ND
1439	1.12 ± 0.23	0.26	0.55 ± 0.18	ND	220 ± 26	ND
K1r	2,233 ± 991	20	467 ± 135	80	423 ± 48	60
1912	3,134 ± 116	07	2,100 ± 819	33	247 ± 134	29
3186	140 ± 53	77	3.37 ± 1.11	38	190 ± 36	160
9940	700 ± 229	02	120 ± 25	65	310 ± 78	27
8411	500 ± 123	62	202 ± 28	100	320 ± 26	45

[a] I… lard d… ained 18 h postinfection at a MOI of 1 by flow cytometric analysis (FC) of at least three separate experiments or by standard CPE inhibitory assay.
[b] ND, not done.

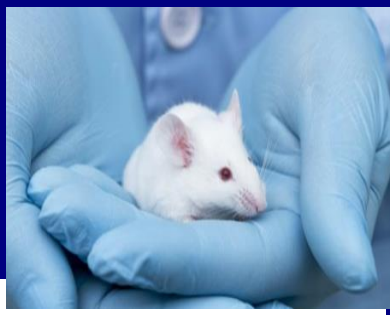
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1997, p. 2686–2692 Vol. 41, No. 12
0066-4804/97/$04.00+0

Flow Cytometric Analysis of Herpes Simplex Virus Type 1 Susceptibility to Acyclovir, Ganciclovir, and Foscarnet†

IVICA PAVIĆ, ANKE HARTMANN,‡ ALBERT ZIMMERMANN, DETLEF MICHEL, WALTER HAMPL, INGRID SCHLEYER, AND THOMAS MERTENS*
Abteilung Virologie, Institut für Mikrobiologie, Universität Ulm, Ulm, Germany

Received 25 February 1997/Returned for modification 13 May 1997/Accepted 30 September 1997

- 50% etkin doz (ED50) değeri plak redüksüyon testi ile (Balb/C 3T3 hüceelrinde)
- 0.02 microgram ml $^{-1}$ PCV
- 0.01 microgram ml^{-1} ACV
- 0.001 microgram ml^{-} GCV
- Tedavide GCV>PCV ya da ACV



Treatment[a]	Survivors (%)[b]	Mean (s.d.) survival time (days) of mice that died	Explanted ganglia yielding virus/No. survivors tested (%)[f]
None	0/8	6.6 (0.4)	—
ACV[c]	7/8 (87)	16	3/7 (43)
ACV[d]	5/8[e] (63)	10.7 (0.5)	3/5 (60)
GCV[c]	8/8 (100)	—	0/8 (0)
GCV[d]	8/8 (100)	—	2/8 (25)
PCV[c]	7/8 (87)	8	3/7 (43)
PCV[d]	4/8 (50)	8.25 (0.4)	4/4 (100)

[a] Drugs were administered in drinking water *ad libitum* at 1 mg ml^{-1}.
[b] Proportion of mice surviving for more than 28 days.
[c] Treatment commenced at time of infection and continued until day 8.
[d] Treatment commenced 1 day after infection and continued until day 8.
[e] Two of the three mice that did not survive in this group were killed on day 11 p.i. suffering from severe bilateral hindlimb paralysis.
[f] Proportion of left ganglia from survivors yielding infectious virus by the end of 9 days *in vitro* cultivation. The ganglia were explanted on day 87 p.i.

Antiviral Chemistry & Chemotherapy (1992) 3(1), 37–47

Effects of penciclovir and famciclovir in a murine model of encephalitis induced by intranasal inoculation of herpes simplex virus type 1

S. E. Goldthorpe,[1]* M. R. Boyd[2] and H. J. Field[1]
[1]Department of Clinical Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES.
[2]SmithKline Beecham Pharmaceuticals, Epsom, Surrey KT18 5XQ.

70% when untreated (Whitley, 1984). To date adenine arabinoside (AraA) and acyclovir (ACV) have been the compounds most frequently used in the treatment of HSE (Whitley *et al.*, 1977, 1981, 1983, 1986; Sköldenberg *et al.*, 1984). The therapeutic potential of other compounds, such as bromovinyldeoxyuridine (BVDU) and ganciclovir

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Case Report

First case of herpetic meningoencephalitis treated with ganciclovir

Anne Laure Blanc, Loubna El Mansouf & Xavier Lemaire

Pages 308-309 | Published online: 07 Jun 2016

Download citation https://doi.org/10.1080/1120009X.2016.1195070 Check for updates

- Kısa süreli oral ve lokal GCV ile herpes simpleks keratiti tedavisinde asiklovirle benzer sonuç (kür oranı ve relapsların engelllenmesi ve yan etkler benzer)
- 175 hasta (173 göz) rekürren herpes keratiti (stromal keratitis ve korneal endotel tutulumu)

Chin Med J (Engl). 2015 Jan 5; 128(1): 46–50.

doi: 10.4103/0366-6999.147808

PMCID: PMC4837818

PMID: 25563312

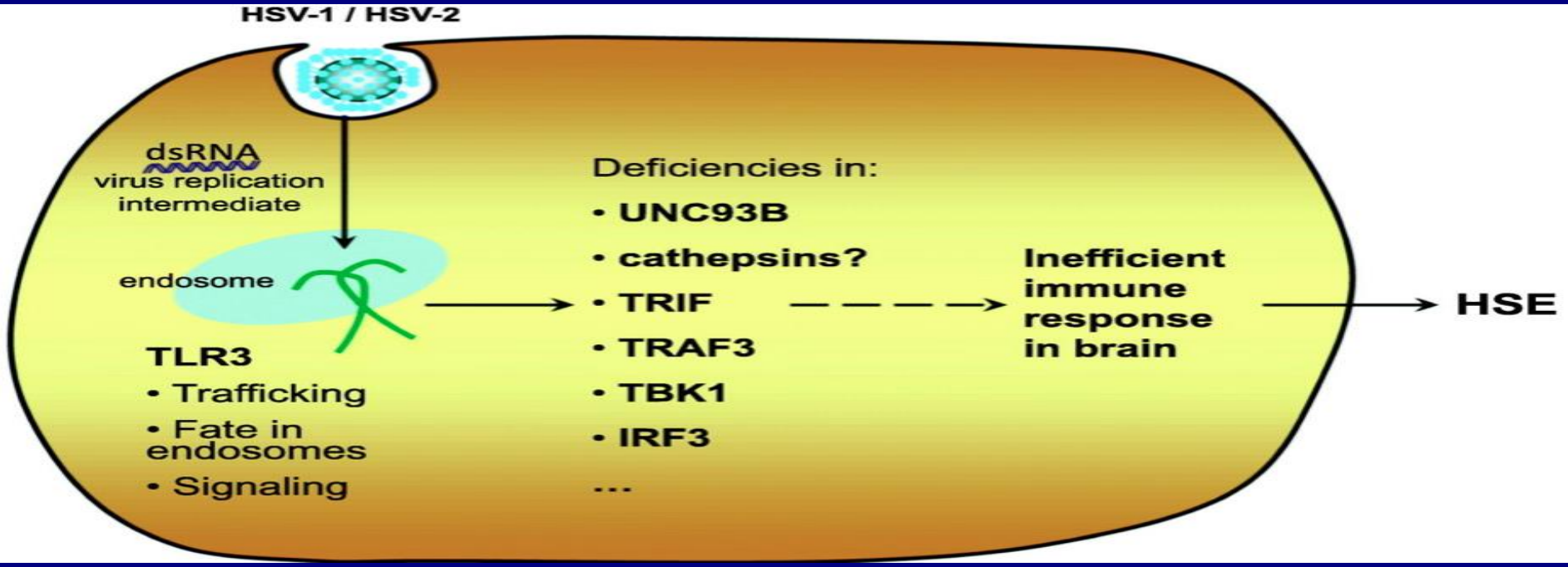
Clinical Efficacy of Oral Ganciclovir for Prophylaxis and Treatment of Recurrent Herpes Simplex Keratitis

Xin Wang,[1] Linnong Wang,[2] Nianlang Wu,[3] Xinjun Ma,[2] and Jianjiang Xu[1]

Davet

- Gansiklovir vs herpes ensefaliti çalışması katılma isteyenleri davet diyorum

Doğuştan genetik yapısal problemler



- TLR-3'deki ya da upstream ve downstream regülatör moleküllerindeki bu mutasyonlar, dermal fibroblastlarda ve uyarılmış pluripotent kök hücre türevli (iPSC türevli) kortikal nöronlarda dsRNA'ya yanıt olarak hem IFN-a/β hem de IFN-λ'nın TLR3'e bağlı indüksiyonunu bozmakta
- BU durum oligodendrositler HSV-1 enfeksiyonuna karşı artan duyarlılığa neden oluyor

Review > J Neuroimmunol. 2018 Mar 15;316:65-73. doi: 10.1016/j.jneuroim.2017.12.011. Epub 2017 Dec 18.

Functional failure of TLR3 and its signaling components contribute to herpes simplex encephalitis

Matylda Barbara Mielcarska [1], Magdalena Bossowska-Nowicka [2], Felix Ngosa Toka [3]

- Toll-like reseptörler (TLR'ler), doğal bağışıklık sistemde önemli rol oynayan bir protein sınıfı
- Genellikle makrofajlar ve dendritik hücreler gibi sentinel hücrelerde eksprese edilen ve mikroplardaki yapısal olarak korunmuş molekülleri tanıyan tek geçişli membran boyunca yerleşimli reseptörler
- TLR3 endozomlara yerleşmekte ve neredeyse evrensel bir viral replikasyon ara ürünü olan çift zincirli RNA'yı tanırmakta
- Alarm mekanizması IFN üretimini indükler, antiviral bağışıklıkta geniş bir rol oynar
- TLR3, insan SSS'de yerleşik hücrelerde en bol ve yaygın olarak ifade edilen TLR
- Çoğu viral enfeksiyon sırasında beyinde ve periferik sinirlerde eksprese edilmekte

Comparative Study > J Virol. 2005 Oct;79(20):12893-904.
doi: 10.1128/JVI.79.20.12893-12904.2005.

Virus infection switches TLR-3-positive human neurons to become strong producers of beta interferon

Christophe Préhaud [1], Françoise Mégret, Mireille Lafage, Monique Lafon

- Otozomal baskın modelde genetik homojenlik hipotezi test edilmiş
- Üç farklı grupta olası çok nadir heterozigoz varyantların tespiti için ekzomlar taranmış
  - Grup1:205 herpes simpleks ensefaliti olgu
  - Grup 2: 2,756 viral olmayan bulaşıcı hastalıkları olan diğer kurum içi hasta gruplarından hastalar
  - Grup 3: 1000 Genom Projesi (1KGP) veri tabanından 1.511 birey
- ExAC (The Exome Aggregation Consortium) veritabanındaki minör alel frekansları (MAF) <0,001 olan zararlı varyantlara bakmışlar
- Bu analiz, küçük bir nükleolar RNA (snoRNA) kodlayan gen olan SNORA31'i anlamlı bulmuş (P = 0.00029; OR: 11.4; %95 GA: 3.5-32.9)
- Biriktirme ve var olan bilgiyi kullanma açısından

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Article | Published: 05 December 2019

Human *SNORA31* variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis

Fabien G. Lafaille, Oliver Harschnitz, ... Shen-Ying Zhang ✉ + Show authors

Nature Medicine **25**, 1873–1884 (2019) | Cite this article

5438 Accesses | **45** Citations | **43** Altmetric | Metrics

- SnoRNA31, H/ACA box sınıfından bir 130 nükleotid (nt) snoRNA (small nucleolar rna)
- HACA box snoRNA'lar, çeşitli insan hücrelerinde yaygın olarak kullanılan bir transkripsiyon sonrası izomerizasyon reaksiyonu tipi olan psödoüridilasyon ile ilişkili
- Her biri farklı ülkelerde akraba olmayan ebeveynlerden doğan beş ilişkisiz hastada dört heterozigot tek nükleotid mutasyonu tespit edilmiş
- n.36T>C (hasta 1 Fas'tan hasta 2 Suudi Arabistan'dan)
- n.75C>G (hasta 3, Amerika Birleşik Devletleri'nden)
- 96T>G (hasta 4 Fransa'dan)
- n.111T>C (hasta 5, Portekiz'den)

nature medicine

Article | Published: 05 December 2019

Human *SNORA31* variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis

Fabien G. Lafaille, Oliver Harschnitz, ... Shen-Ying Zhang ✉ + Show authors

Nature Medicine **25**, 1873–1884 (2019) | Cite this article

- İndüklenmiş SNORA31 delesyonlarının
  - TLR3 veya STAT1 eksikliği olan hastalardan alınan hücre örneklerine benzer şekilde HSV-1'e duyarlı insan pluripotent kök hücre kaynaklı kortikal nöron oluşumuna neden olduğu gösterilmiş
  - Eksojen interferon (IFN)-β, SNORA31-negatif ve TLR3-negatif kökenleri HSV-1'e dirençli hale getirmiş-HSV-1 duyarlılığını ortadan kaldırmış
  - Buna karşı STAT1 mutasyonlu nöronlarda direnç interferon uygulamasıyla geri dönüşmemiş

nature medicine

Article | Published: 05 December 2019

Human *SNORA31* variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis

Fabien G. Lafaille, Oliver Harschnitz, ... Shen-Ying Zhang ✉ + Show authors

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- 11 İtalyan erişkin HSV ve VZV viral ensefalitii olgunun genetik analizi
- TLR3'te 2 nadir missense mutasyonu
- 1 HSE'li bir hastada (p.Leu297Val)
- 1 VZV ensefaliti hastasında (p.Leu199Phe)
- Her iki mutasyon da insan popülasyonlarında son derece nadir
- İşlevsel bir etkileri olma olasılıklarının yüksek olduğunu belirtmişler

Volume 215, Issue 9
1 May 2017

Article Contents

TLR3 Mutations in Adult Patients With Herpes Simplex Virus and Varicella–Zoster Virus Encephalitis FREE

Manuela Sironi, Anna Maria Peri, Rachele Cagliani, Diego Forni, Stefania Riva, Mara Biasin, Mario Clerici, Andrea Gori Author Notes

The Journal of Infectious Diseases, Volume 215, Issue 9, 1 May 2017, Pages 1430–1434, https://doi.org/10.1093/infdis/jix166
Published: 27 March 2017 **Article history**

- 2 yaşında HSV ensefalitinden kaybedilen bir çocuk olgu sunumu
- IFNAR1'in son eksonunun (interferon alfa ve beta reseptörü 1) tüm kodlama dizisinin ve 3′-UTR'sinin bir kısmının genomik olarak homozigot delesyonu saptanmış
- Daha büyük bir kuzeni 12 aylıkken kızamık, kabakulak ve kızamıkçık aşısının ardından kaybedilmiş
- Aynı varyant için homozigot olan 17 yaşındaki başka bir kuzeni daha az şiddette viral hastalık öyküsü+
- Hastadaki IFNAR1 proteini, hücre yüzeyinde eksprese ediliiyor, ancak uç kısmı eksik tirozin kinaz TYK2 ile etkileşime giremiyor
- Hastanın fibroblastları IFN-a2b veya IFN-β'ya yanıt vermemiş
- Ekzojen IFN-a2b veya IFN-p varlığında bile HSV-1 dahil olmak üzere virüslere duyarlı bulunmuş

Case Reports > J Clin Invest. 2021 Jan 4;131(1):e139980. doi: 10.1172/JCI139980.

Herpes simplex encephalitis in a patient with a distinctive form of inherited IFNAR1 deficiency

Paul Bastard [1 2 3], Jeremy Manry [1 2], Jie Chen [3], Jérémie Rosain [1 2], Yoann Seeleuthner [1 2], Omar AbuZaitun [4], Lazaro Lorenzo [1 2], Taushif Khan [5], Mary Hasek [3], Nicholas Hernandez [3], Benedetta Bigio [3], Peng Zhang [3], Romain Lévy [1 2 6], Shai Shrot [7 8], Eduardo J Garcia Reino [3], Yoon-Seung Lee [3], Soraya Boucherit [1 2], Mélodie Aubart [1 9], Rik Gijsbers [10], Vivien Béziat [1], Zhi Li [11], Sandra Pellegrini [11], Flore Rozenberg [12], Nico Marr [5 13], Isabelle Meyts [14 15 16], Bertrand Boisson [1 2 3], Aurélie Cobat [1 2], Jacinta Bustamante [1 2 3 17], Qian Zhang [3], Emmanuelle Jouangy [1 2 3], Laurent Abel [1 2 3], Raz Somech [18 8], Jean-Laurent Casanova [1 2 3 6 19], Shen-Ying Zhang [1 2 3]

Randomized Controlled Trial > Eur J Med Res. 2005 Dec 7;10(12):527-31.

Therapy of focal viral encephalitis in children with aciclovir and recombinant beta-interferon - results of a placebo-controlled multicenter study

Uwe Wintergerst [1], K Kugler, F Harms, B H Belohradsky, T Pfluger

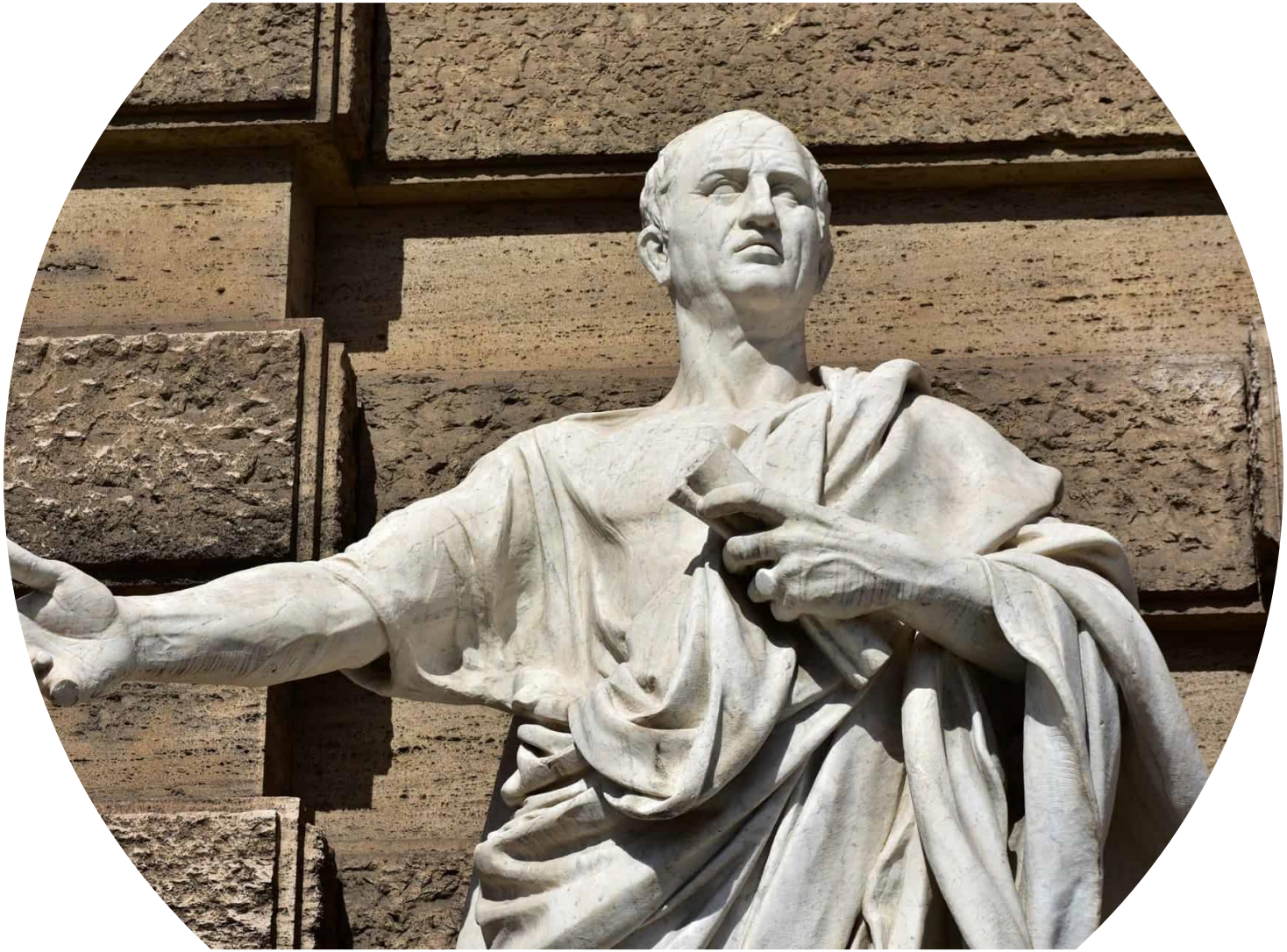
Affiliations + expand

PMID: 16356868

7şer iki kolda fark bulamamışlar (sayı az)

Abstract

Focal viral encephalitis in childhood is a rare but life-threatening disease. Animal experiments and case reports suggest a positive effect of an additional therapy with interferon-beta on the course of the disease. Therefore, we initiated a prospective, double-blind placebo-controlled study to investigate the benefit of a combination therapy of Aciclovir (ACV) and recombinant interferon-beta (rIFN-beta) in juvenile focal viral encephalitis. - Initial inclusion criterium was suspicion of focal viral encephalitis. Diagnosis was proven by demonstration of characteristic focal lesions in cerebral imaging or virological evidence of HSV in cerebrospinal fluid. Patients were treated with ACV plus rIFN-beta or ACV plus placebo. Neurological outcome was determined 21 days and 3 months after onset of the disease. - Initially 59 patients were enrolled in the study. Encephalitis was proven in 14 patients (7 ACV + rIFN-beta, 7 ACV + placebo). The study groups were balanced in terms of important prognostic criteria. 10 patients (5 ACV + rIFN-beta, 5 ACV + placebo) were cured or had slight defects, 4 patients (2 ACV + rIFN-beta, 2 ACV + placebo) showed moderate to severe defects. There was no significant difference in favour of the additive therapy with rIFN-beta.



Sequellae following HSE

- **France 2010**, 176 patients, 43 HSV, evaluated 3 years after discharge
- Poor outcome (GOS) : **39% of all patients**
  - 58% of HSV patients despite ACV treatment
    - 66% with decreased concentration/attention
    - 50% behavioral disorders
    - 30% memory impairment
    - 30% speech difficulties
  - Risk factors: age, education level, HSV, VZV, comorbidities

Mailles et al., CID 2012

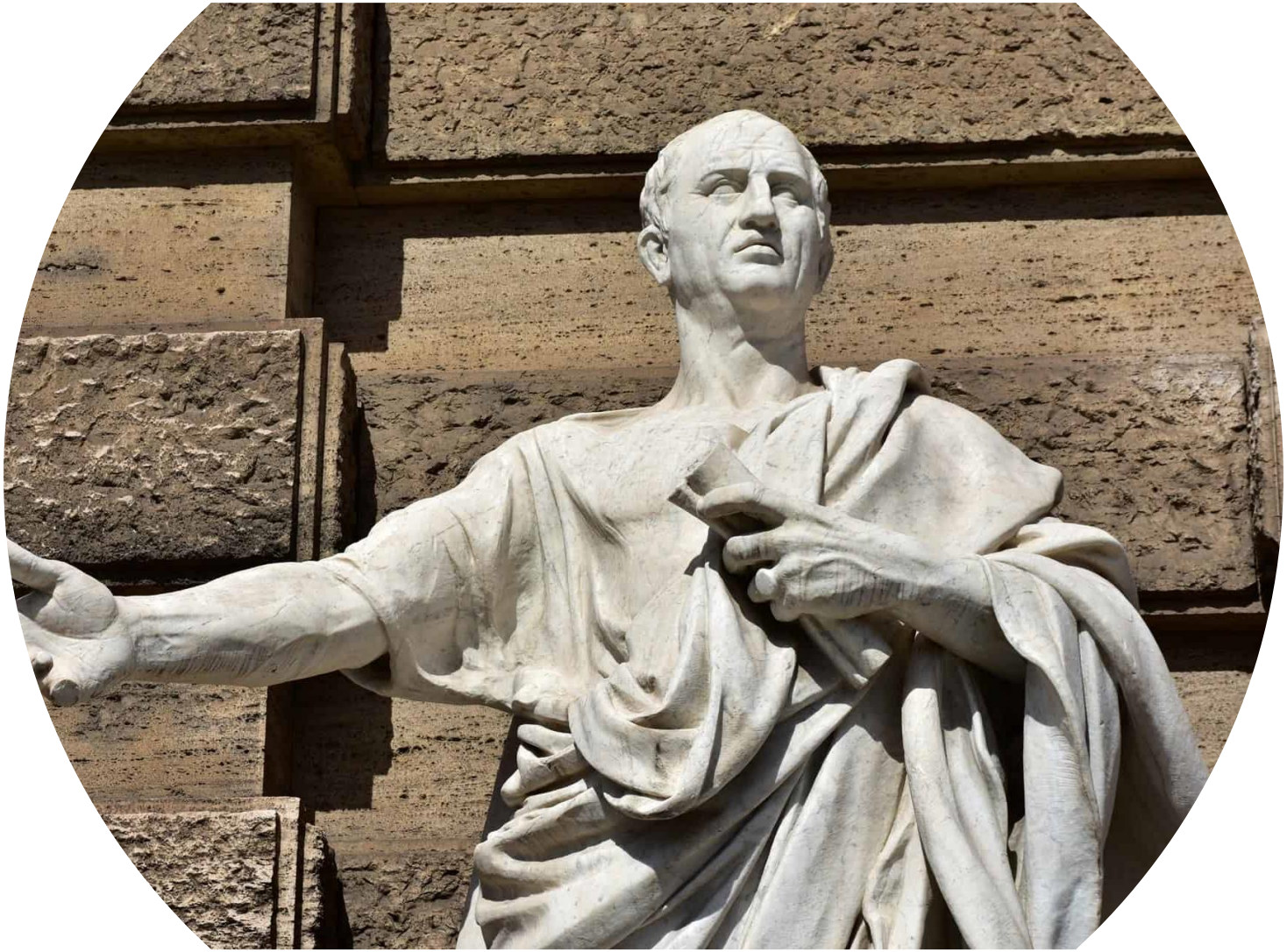
Sequellae: the future

- Longterm cognitive follow-up is important
- Hidden disability is a major issue
- The unmet need: guidelines for diagnosis and management of these sequellae

Aknowledgements

- Alexandra Mailles (Sante Publique France)
- David Boutolleau (French National Reference Center for *Herpesviridae*)
- ENCEIF (French cohort) investigators

Thank you for your attention



Conclusion

- Watching and accumulating your own data
  - What is the denominator?
    - All encephalitis meningoencephalitis ICD-10 ?
  - HSV-2/HSV-1 differs from country to country and definitions
- International consortium definitions
- Diagnosis
  - Clinical U CSF U Microbiological U MRI U EEG
- Metagenomics?
- Ganciclovir?
- Genetic background vs clinical approach aiming at interferon or TLR3 pathway

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  - King Hamad University Hospital Clinical Microbiology Labooratory

Sercan Ulusoy

Bilgin Arda

Tansu Yamazhan

Meltem Taşbakan

Hüsnü Pullukçu

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Thank you for your attention