Altered mental status (AMS)

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Inhoudstafel

- Casus
- Interpretatie
- Aciclovir
- Referenties

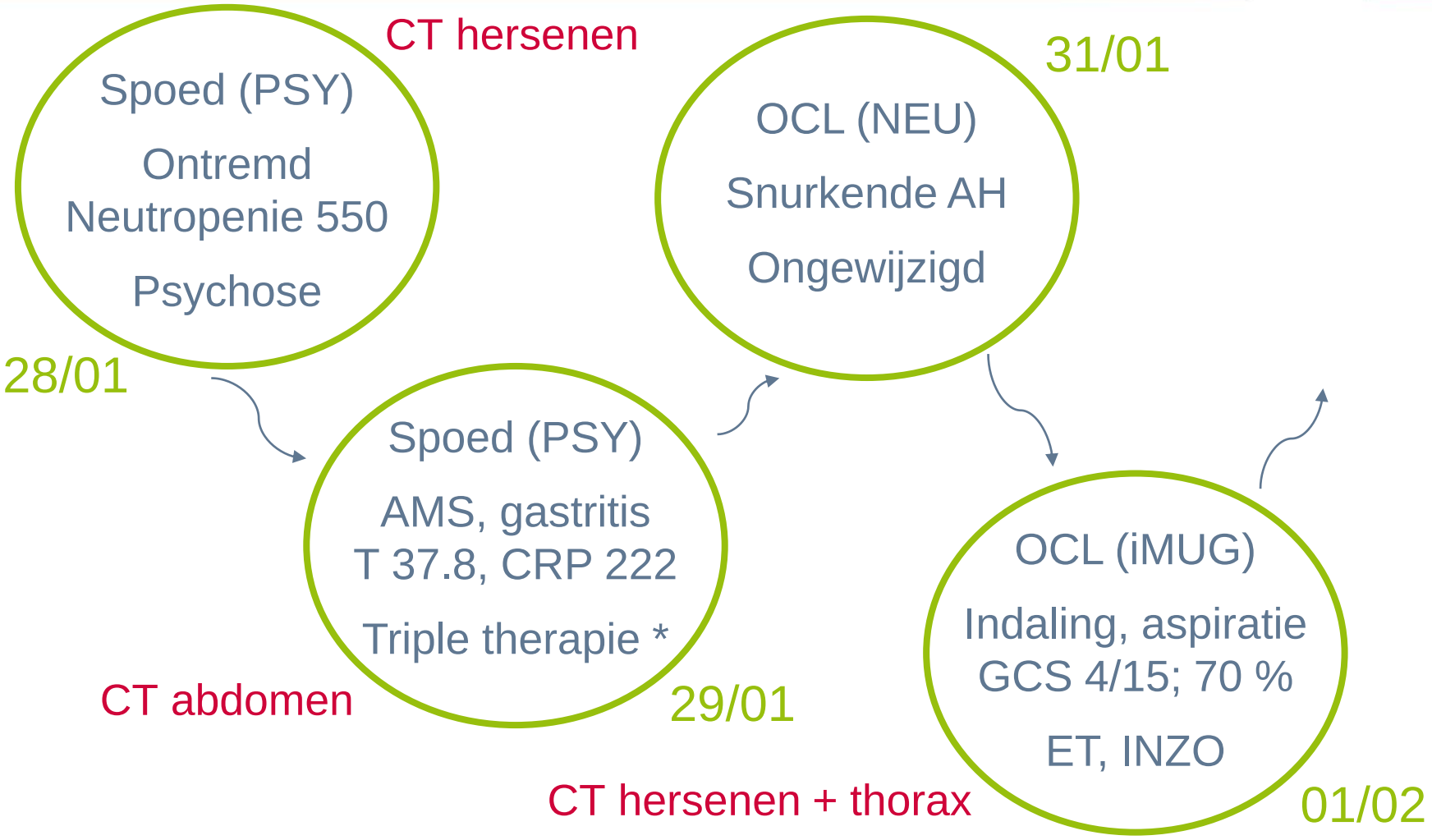
Casus

Casus (49 j, ♀)

- Invasief mammacarcinoom rechts
  - cT2N1 Luminal B **invasief adenocarcinoom** (12/2023)
  - Curatieve intentie: neo-adjuvant **paclitaxel** (PTX C2 24/01)

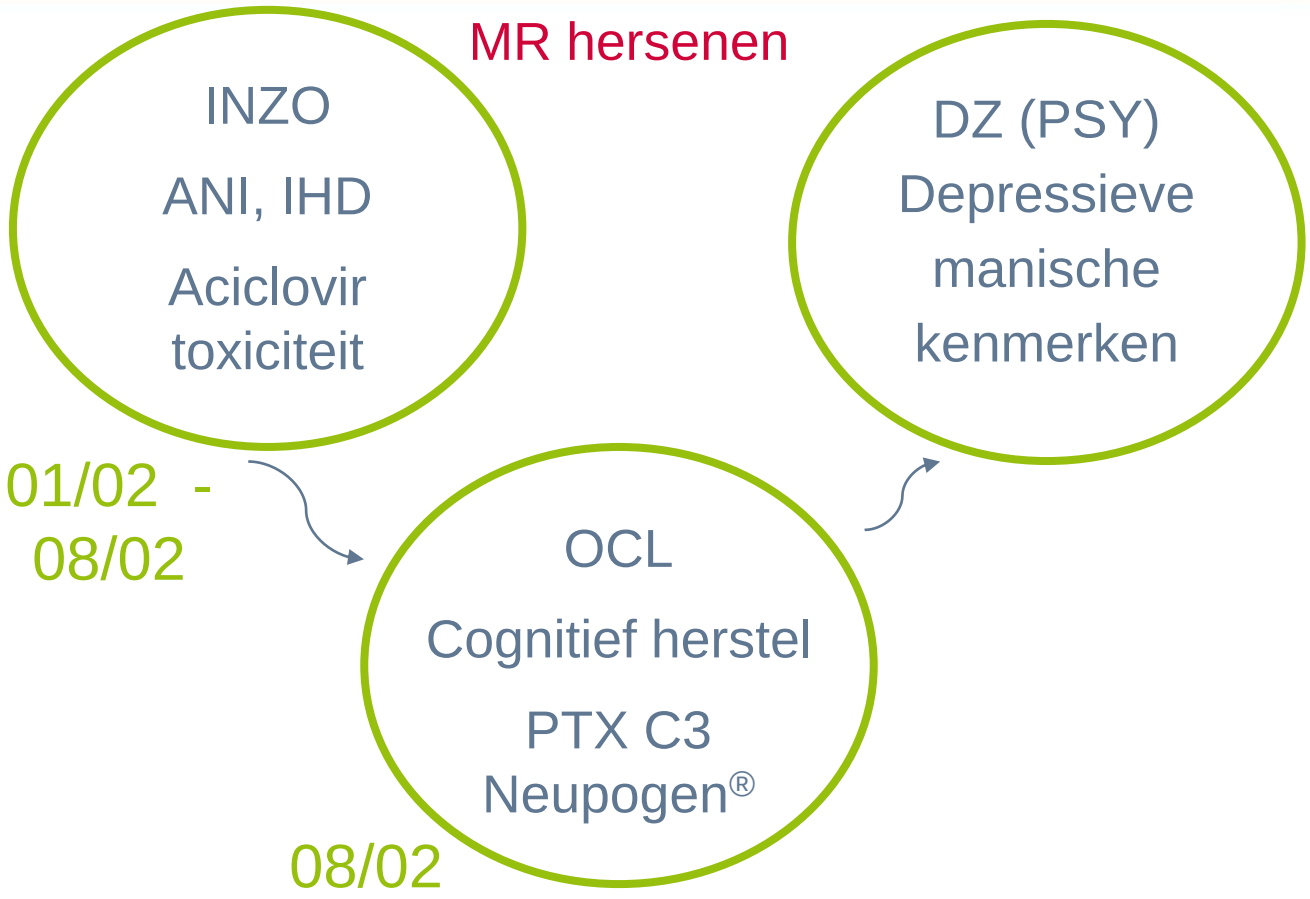
- Comorbiditeiten:
  - **Spastische paraplegie** t.g.v. **perinatale asfyxie**
  - **Depressies** met **psychotische symptomen**
  - Crisisopname UPC Duffel (2017): **hypomanie**
  - **Sinustachycardie**

Casus (49 j, ♀)



** Aciclovir, amoxicilline, ceftriaxon*

Casus (49 j, ♀)


MR hersenen
INZO
ANI, IHD
Aciclovir toxiciteit
DZ (PSY)
Depressieve manische kenmerken
01/02 - 08/02
OCL
Cognitief herstel
PTX C3 Neupogen®
08/02

Casus (49 j, ♀)

	28/01	29/01	30/01	01/02	02/02	03/02	08/02	
WBC	**0.8**	**1.4**	**1.3**	**1.5**	**1.1**	**1.1**	8.1	x 10^9/L (4.2-10.3)
ANC	**0.06**	**0.32**	**0.26**	**0.40**	**0.16**	**0.15**	5.1	x 10^9/L (2.0-6.7)
CRP	**36**	**181**	**162**	**222**	**142**	**124**	**50**	mg/L (<10)
Creatinine	0.43	0.42	0.49	**4.64**	**2.24**	**1.91**	0.64	mg/dL (0.55-1.02)
eGFR	119	112	112	**10**	**25**	**30**	105	mL/min/1.73m^2
Ureum				**64**	22	30		mg/dL (13-43)
Aciclovir (piek)				**32.2**	8.4	1.7		µg/mL (5-15)
Aciclovir (dal)				**12.0**	2.2	0.6		µg/mL (0.5-1.5, toxisch: >3)
Quetiapine				41	15	/		ng/mL (100-500)
RBC (csv)		**1000**						/µL
WBC (csv)		2						/µL
Glucose (csv)		69						mg/dL (40-70)
Eiwit (csv)		**448**						mg/dL (15-45)

Casus (49 j, ♀)

- Beeldvorming
  - CT hersenen (28/01, 01/02): geen ICB
  - MR hersenen (02/02): geen metastasen

  - CT abdomen (30/01): **leversteatose**, aberrante morfologie lever met **afwezigheid linker leverlob**
  - CT thorax (01/02): geen LE, **mucus** distaal van ETT, **consolidaties** *(DD aspiratie pneumonitis, DD infectieus, DD atelectase)*

Casus (49 j, ♀)

- Microbiologie
  - CSV (29/01): kweek neg. (incl. virale PCR)
  - Urine (29/01): kweek neg.
  - PCR COVID-19, INF A/B, RSV (30/10): neg.
  - HK (01/02): neg.
  - BAL (01/02): neg.
  - Faeces (03/02, 05/02, 08/02): kweek neg.
  - Serologie (08/02): bof IgG/IgM pos., CMV IgM neg., EBV IgM neg.

Casus (49 j, ♀)

- Toxicologie
  - Urine (29/01): zeer hoge hoeveelheid **quetiapine**
  - Serologie (01/02): **aciclovir** toxische spiegel

- Fase contrast (01/02): **kristalnefropathie**, secundaire **ATN**
- EEG (01/02): geen epilepsie

Casus (49 j, ♀)

- Interpretatie (1)

AMS (28/01)

DD neutropene sepsis

DD virale (meningo)encefalitis

DD NMS op quetiapine

DD andere

Casus (49 j, ♀)

- Interpretatie (2)

  Coma (01/01)

  Aciclovir nefrotoxiciteit **!**

  Aciclovir centrale neurotoxiciteit **!**

  Nevendiagnosen

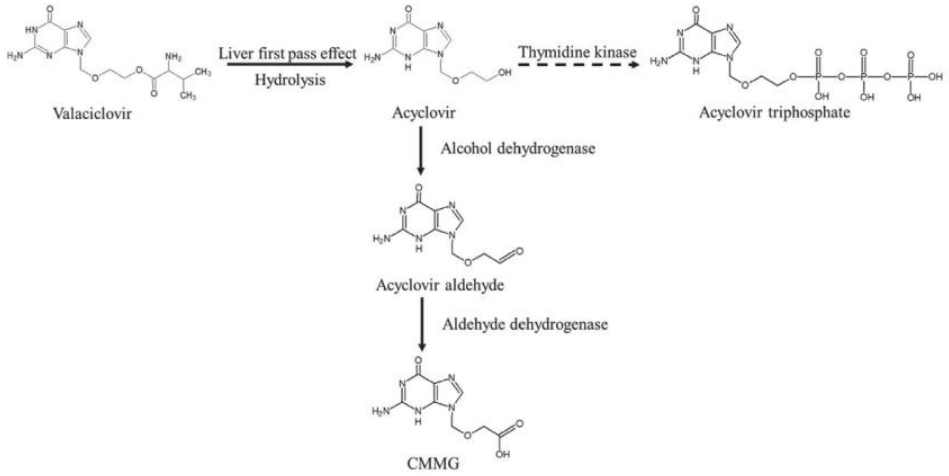
  Leversteatose, aberrante morfologie lever (30/01)

  Aspiratie pneumonitis (01/01)

Aciclovir

Aciclovir

- Hepatische metabolisatie
  - Beperkt
  - ADH, ALDH2
  - 9-carboxymethoxymethylguanine (CMMG)
  - Genetische factor **?**

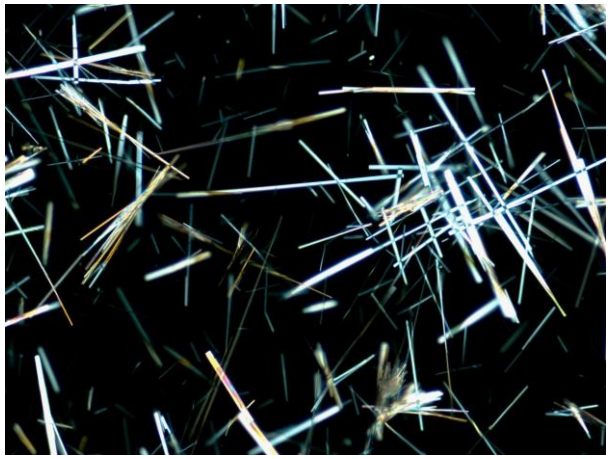


Abe K, Kaizaki-Mitsumoto A, Saito T, Sugiyama M, Honda H, et al. Time-dependent changes in serum concentrations of acyclovir and its metabolite, 9-carboxymethoxymethylguanine, in a patient with suspected acyclovir encephalopathy. Fundam. Toxicol. Sci. 2021 Jan;8(7):229-233.
Aboelezz A, Mahmoud SH. Acyclovir Dosing in Herpes Encephalitis: A Scoping Review. J Am Pharm Assoc (2003). 2024 Feb 14:S1544-3191(24)00043-8.

Aciclovir

- Renale eliminatie
  - Glomerulaire filtratie
  - Tubulaire secretie
  - T1/2: 3-5 u

- Nefrotoxiciteit
  - Kristalnefropathie
  - ATN, AIN
  - Incidentie: 5-18%



Aboelezz A, Mahmoud SH. Acyclovir Dosing in Herpes Encephalitis: A Scoping Review. J Am Pharm Assoc (2003). 2024 Feb 14:S1544-3191(24)00043-8.
Andrews AR, Yu D, Lyon AW. Diagnostic Challenges with Acyclovir Crystalluria - A Case Study. EJIFCC. 2020 Jun 2;31(2):157-163.

Aciclovir

- Neurotoxiciteit
  - AMS
    - Agitatie, verwardheid, hallucinaties
    - Tremor, clonus, dysartrie
    - Insult
  - CMMG **?**
  - Onset: 24-48 u
  - Incidentie: <0,01% (https://www.farmacotherapeutischkompas.nl)

Abuhelwa Z, Beran A, Venkataramany BS, Hinch BT, Assaly R. Concurrent Nephrotoxicity and Neurotoxicity Induced by Oral Valacyclovir in a Patient With Previously Normal Kidney Function. Cureus. 2022 Mar 31;14(3):e23693.
Marks D, De La Paz A, Walston BJ. Acyclovir-induced neurotoxicity in an immunocompromised patient. SAGE Open Med Case Rep. 2020 Aug 11;8:2050313X20946518.

Aciclovir

- Preventie
  - Dosisreductie (nierinsufficiëntie, gewicht)
  - Vullingsstatus
  - Toedieningssnelheid IV (≥1 u)
  - Oraal

CrCl	Dosing
>50	10 mg/kg q 8 h × 7 days
25–50	10 mg/kg q 12 h
10–25	10 mg/kg q 24 h
<10	5 mg/kg q 24 h
Hemodialysis	5 mg/kg post hemodialysis

CrCl: creatinine clearance.
Source: Acyclovir sodium injection; United States prescribing information (revised May 2014).[14]

Aboelezz A, Mahmoud SH. Acyclovir Dosing in Herpes Encephalitis: A Scoping Review. J Am Pharm Assoc (2003). 2024 Feb 14:S1544-3191(24)00043-8.
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Aciclovir

Zorginstituut Nederland

Obesitas: Bij obese patiënten die intraveneus aciclovir krijgen op basis van hun werkelijke lichaamsgewicht, kunnen verhoogde plasmaconcentraties worden gemeten. Bij hen moet daarom een dosisverlaging overwogen worden als ze een verminderde nierfunctie en/of een hogere leeftijd hebben. Bij doseren op basis van het ideale lichaamsgewicht waren in een onderzoek bij zeven morbide obese patiënten de piekconcentraties ca. 29% lager dan bij patiënten met een normaal lichaamsgewicht die een dosis kregen op basis van het totale lichaamsgewicht. De gevolgen van de lagere piekconcentraties voor de werkzaamheid zijn onbekend.

Farmacotherapeutisch Kompas (https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/a/aciclovir).

UZA

Aciclovir

NOM DE LA SPECIALITE (DCI)	CONDITIONNEMENT CONSERVATION	RECONSTITUTION STABILITE APRES RECONSTITUTION
ACICLOVIR® LABATEC (aciclovir) Equivalent Zovirax®	Fiole sec. 250 mg **Ne pas mettre au frigo !**	Reconstitution avec 10 mL H_2O ppi ou NaCl 0.9% (conc : 25 mg/mL) Stable 8 h

DILUTION STABILITE APRES DILUTION	MODE D'ADMINISTRATION	PARTICULARITES pH, osmolarité/ osmolalité : si non spécifié, valeur de la solution non diluée.
Dilution avec NaCl 0.9% uniquement (conc : 2.5 à 5 mg/mL) **NE PAS DILUER AVEC GLUCOSE 5%** Stable 8 h	Perfusion IV sur 1 h **Si restriction hydrique :** non dilué (25 mg/mL) par VVC sur 1 h	pH 11 Osmolarité : 190 mOsm/L (25 mg/mL) **Incompatible avec Nutrition Parentérale Totale** Compatible avec G5% **en Y uniquement**

Pharmacie des HUG (https://pharmacie.hug.ch/infomedic/utilismedic/adulte_admin_medic_inj.pdf).

Aciclovir

- Monitoring (1)
  - GFR
  - Hematurie, proteïnurie
  - Fase contrast

“Laboratory staff should be aware and recognize acyclovir treatment as a possible cause of pathologic crystalluria.”

Andrews AR, Yu D, Lyon AW. Diagnostic Challenges with Acyclovir Crystalluria - A Case Study. EJIFCC. 2020 Jun 2;31(2):157-163.
Desrumaux MJ, Vanfraechem C, Mahieu E. Acyclovir-Induced Glomerulonephritis in a 40-year-old Woman Without Medical History: A Case Report. Eur J Case Rep Intern Med. 2023 Sep 15;10(10):003924.

Aciclovir

- Monitoring (2)
  - Serum
    - Aciclovir (dal/piek)
    - CMMG
  - CSV
    - CMMG

Abuhelwa Z, Beran A, Venkataramany BS, Hinch BT, Assaly R. Concurrent Nephrotoxicity and Neurotoxicity Induced by Oral Valacyclovir in a Patient With Previously Normal Kidney Function. Cureus. 2022 Mar 31;14(3):e23693.
Berry L, Venkatesan P. Aciclovir-induced neurotoxicity: Utility of CSF and serum CMMG levels in diagnosis. J Clin Virol. 2014 Dec;61(4):608-10.

Aciclovir

Referentiewaarden:

Therapeutisch:
Aciclovir intraveneus / Valaciclovir oraal (aciclovir wordt gemeten):
Dal: 0,5-2,5 mg/L (HSV/VZV)
Top: 5-15 mg/L (HSV/VZV)

Dal: 2,0-2,5 mg/L (Herpes encephalitis)
Top: 20-25 mg/L (Herpes encephalitis)

De gegevens hierboven zijn voor intraveneuze toediening. Na orale toediening van valaciclovir worden lagere topspiegels gemeten, dalspiegels zijn niet gerapporteerd.

Er zijn geen duidelijke toxische spiegels voor aciclovir. Een dalspiegel > 4,5 mg/L geeft mogelijk (neuro)toxiciteit, een tospiegel > 25 mg/L geeft mogelijk stijging van serum kreatinine waarden en gastro-intestinale bijwerkingen.

UMC Utrecht (https://www.umcutrecht.nl/nl/bepaling/aciclovir).

Aciclovir

- Behandeling
  - Dosisreductie / stopzetting
  - IVF
  - IHD **!**

Abuhelwa Z, Beran A, Venkataramany BS, Hinch BT, Assaly R. Concurrent Nephrotoxicity and Neurotoxicity Induced by Oral Valacyclovir in a Patient With Previously Normal Kidney Function. Cureus. 2022 Mar 31;14(3):e23693.

Aciclovir

J Clin Pharm Ther. 2021 Aug;46(4):918-926. doi: 10.1111/jcpt.13464. Epub 2021 Jun 19.

Neurotoxicity associated with acyclovir and valacyclovir: A systematic review of cases

- Systematic review
- 119 cases

"In 83.3% of the cases, renal impairment was documented and 57.1% (n = 68) with end-stage renal disease. The administered dose was higher than the renal adjustment recommendations in 59.7% of the cases. The global mean of onset of symptoms was 3.1 days ± 4.3 (0.2-28) after the start of antivirals. The mean recovery time was 9.8 days ± 21.7 (0.2-180). 74.4% of the patients had a recovery of ≤7 days, 15.9% between 8 and 15 days and 9.8% > 15 days."

Brandariz-Nuñez D, Correas-Sanahuja M, Maya-Gallego S, Martín Herranz I. Neurotoxicity associated with acyclovir and valacyclovir: A systematic review of cases. J Clin Pharm Ther. 2021 Aug;46(4):918-926.

Conclusie

Conclusie

	VZV encephalitis	Acyclovir-induced neurotoxicity
Timing of onset	• Variable temporal association with cutaneous zoster and primary infection	• Close temporal association with initiation of acyclovir
Risk factors	• Immunocompromised state	• Impaired renal function
	• Can occur in previously health individuals	• Incorrect dosing
Clinical characteristics[a]	• Headache	• Acute encephalopathy
	• Acute encephalopathy	• Tremor, myoclonus
	• Fever	• Agitation
	• Nausea and vomiting	• Hallucinations
	• Cutaneous zoster may be present	• Dysarthria
CSF studies	• CSF pleocytosis	• Often normal
	• Positive CSF VZV PCR	• May have CSF pleocytosis [7] or positive VZV PCR [8]
	• Positive CSF anti-VZV IgM or IgG[b]	
	• Elevated serum or CSF CMMG[c]	
Treatment	• Acyclovir or valacyclovir	• Cessation of acyclovir
		• Hemodialysis
Clinical course	• Variable resolution	• Full resolution over 1–5 days
	• Chronic neurologic sequelae may occur	

Abbreviations: CMMG 9-Carboxymethoxymethylguanine, *CSF* Cerebrospinal fluid, *Ig* Immunoglobulin, *PCR* Polymerase chain reaction, *VZV* Varicella zoster virus

[a]These are more classic presentations. There is considerable clinical overlap in these two diagnoses.

[b]Positive CSF anti-VZV IgM and IgG may take several days or weeks to develop and would require repeat lumbar puncture.

[c]Elevated serum and CSF CMMG levels are suggestive of acyclovir-induced neurotoxicity [10].

Robertson KM, Harvey CL, Cunningham JM. Acyclovir-induced neurotoxicity with a positive cerebrospinal fluid varicella zoster PCR result creating a management dilemma: a case report. J Med Case Rep. 2020 Sep 18;14(1):156.

Bronvermelding

Bronvermelding

Referenties

1. Abe K, Kaizaki-Mitsumoto A, Saito T, Sugiyama M, Honda H, et al. Time-dependent changes in serum concentrations of acyclovir and its metabolite, 9-carboxymethoxymethylguanine, in a patient with suspected acyclovir encephalopathy. Fundam. Toxicol. Sci. 2021 Jan;8(7):229-233.
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Aanvullend

1. Gunness P, Aleksa K, Bend J, Koren G. Acyclovir-induced nephrotoxicity: the role of the acyclovir aldehyde metabolite. Transl Res. 2011 Nov;158(5):290-301.
2. Lim APW, Sung J, Ramburuth V, Oyibo SO. Acyclovir-Induced Nephrotoxicity and Neurotoxicity: A Report of Two Cases. Cureus. 2024 Jan 16;16(1):e52367.
3. Paluch Z, Trojánek M, Velíšková Z, Mlíchová J, Chrbolka P, et al. Neurotoxic side effects of acyclovir: two case reports. Neuro Endocrinol Lett. 2021 Oct;42(6):375-382.
4. Vonberg FW, Dawson A, Scott G, Davies N. Aciclovir-induced neurotoxicity. Pract Neurol. 2023 Apr;23(2):157-159.

Bedankt voor uw aandacht