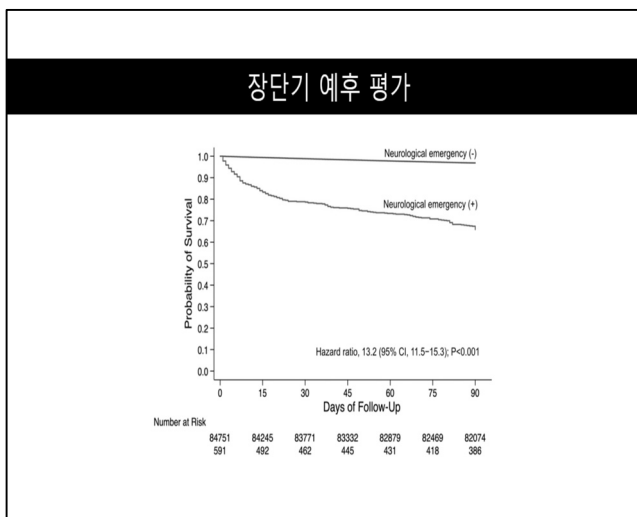
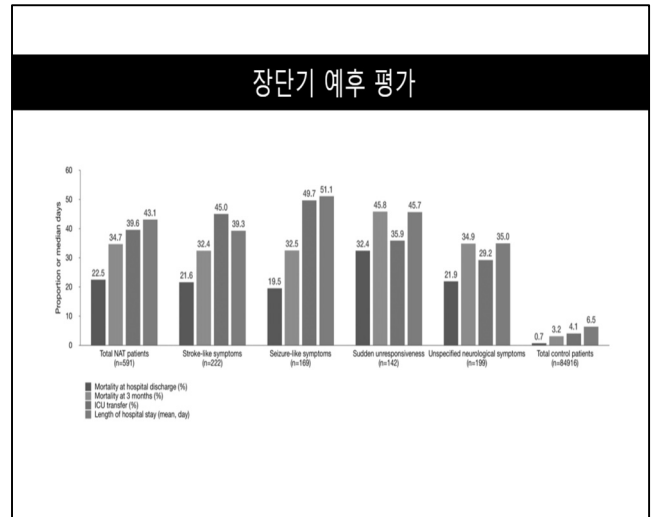
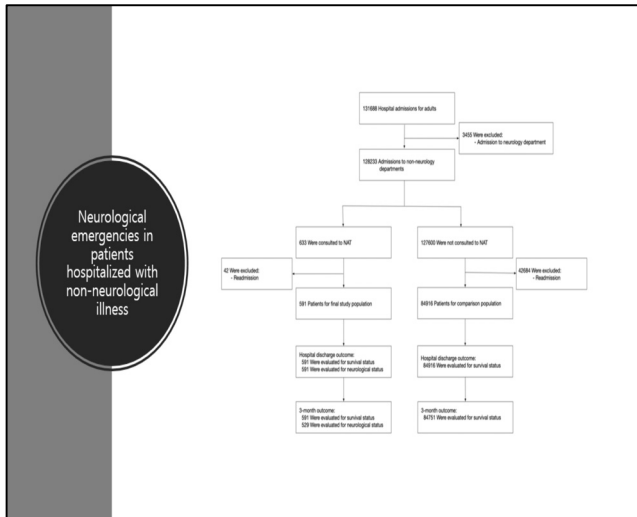


입원환자의 의식변화 및 신경학적 응급

서울아산병원 신경과 조기대응팀

이 한 빈



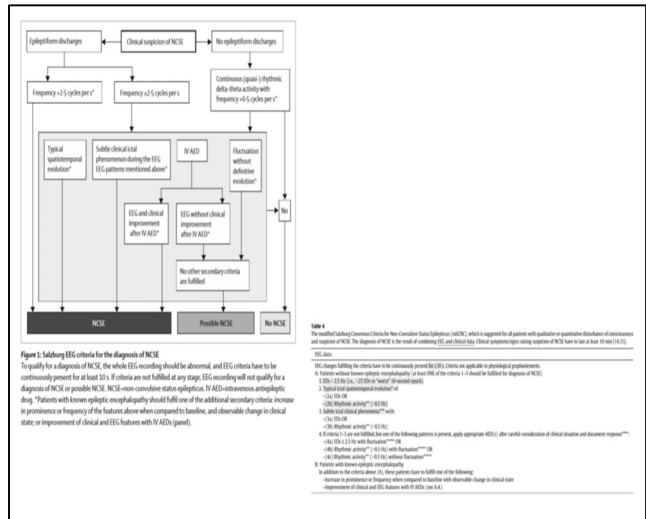
Case 1

57/F
C.C> Disorientation (19.03.13)

Patient information

Imp>

- #1. non-convulsive status epilepticus
r/o cancer related paraneoplastic encephalitis
r/o metabolic cause such as Hepatic encephalopathy



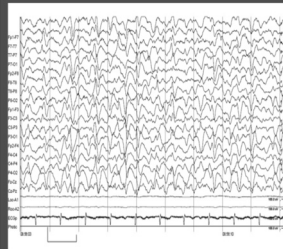
EEG finding:

1. Background
 - Abnormal
 - Theta rhythm frequency: 6-7 Hz
 - Reactivity to eye opening: partial
 - Reactivity to pain stimulation: partial
2. Epileptiform discharge
 - Abundant 2-2.5 Hz generalized periodic discharge
3. No abnormal non-epileptiform discharge
4. No abnormal discharge during photic stimulation
5. Hyperventilation
 - Not performed due to poor cooperation
6. No developed sleep stage

Degree of abnormality : Abnormal II

- These findings suggest moderate diffuse cerebral dysfunction.

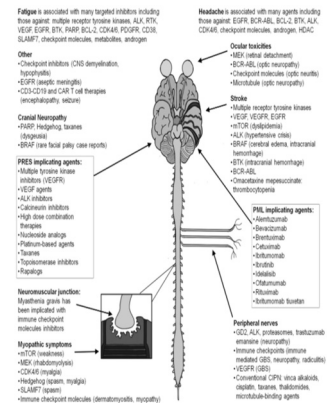
Comment)
- Status epilepticus 의 가능성이 있습니다.



CNS toxicity of Chemotherapy

- Nervous system is vulnerable
- Immediate vs Delayed
 - Encephalopathy
 - Seizures
 - Cerebellar ataxia
 - Focal symptoms
 - Aseptic meningitis
 - Spinal cord toxicity

→ Early recognition is vital to avoid irreversible neurological injury



CNS toxicity of Chemotherapy

- **DDX**
 - Parenchymatous and/or leptomeningeal metastatic disease: *MRI/CSF*
 - CNS infection: *MRI/CSF*
 - Metabolic causes: infectious complications, electrolytic imbalances, disturbances of osmolality, renal and hepatic failures, thiamine deficiency, endocrine disturbances, and tumor lysis syndrome
 - Non-convulsive status epilepticus: *EEG monitoring* + *ifosamide*
 - Paraneoplastic neurological syndrome: *specific antibodies*

Signs/symptoms	Recommended diagnostic testing
Sensory loss	Glucose, high A1c, vitamins B12, SPEP, UPEP, EMG/NCs
Cognitive deficits	Vitamin B12, UPE/urine, TTP, creatinine-BUN, EEG (if episodic), CT head and/or MRI brain
Seizures	Glucose, sodium, EEG, CT head and/or MRI brain, U/P (if suspicion for infection)

UPEP, urinary function test; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; EMG/NCs, electromyogram nerve conduction studies; UTP, liver function test; BUN, blood urea nitrogen; EEG, electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; U/P, urinalysis.

- **Treatment**
 - Limited / Discontinuation of chemotherapy
 - Prevention is necessary
 - Requires knowledge of neurotoxic side effects
 - Careful monitoring of patients at risk.

- Prognosis
 - Complete or partial recovery
 - Irreversible damage, Death

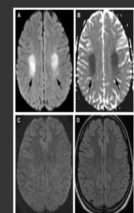
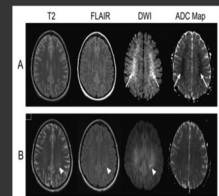
- Drug chosen: MTX, AraC, ifosfamide.
- Dose: Single and cumulative, escalation
- Duration of treatment
- Coexisting neurological morbidity
- Combination > monotherapy
- Stem cell transplantation
- Chemotherapy after irradiation (RT) of the brain

Acute Encephalopathy

- Few hours to days; confusion, agitation → coma, Sz, myoclonus
- DOX: NCSE, Encephalitis, Metabolic ds, Paraneoplastic syndrome

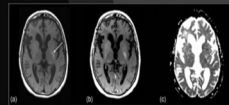
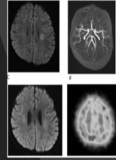
- Self-limiting – fetal
- 0.8-15%: High methotrexate: leucovorin ratio, simultaneous use of IT and i.v.
- Folate derivatives: MTR cofactor → SAM bioavailability
- S-adenosylmethionine (SAM) ↓, Homocysteine ↑ (toxic)
- G-allele of MTR c.2756A>G may play role (4% of general population)
- Tx: Oral SAM substitution. Folate-derivatives + Steroid?

- **Isosfamide**
 - More severe – fetal
 - 10-15% of > 1 g/m2: Low albumin
 - NCSE
 - Interfere TPP/TPP (phosphorylated thiamine)
 - Tx: Thiamine 100mg IV q4h, methylene-blue 50mg IV q4h (low evidence)



Subacute Encephalopathy

- Days – weeks
- Rare, Children-Adult
- Sudden confusion, Sx, focal signs
- MTX, Cis-platinum
- Symmetrical HSI in DWI + decreased ADC (cytotoxic edema of the WM)
- Reversible – Lethal
- Tx: dextromethorphan 1-2 mg/kg PO: Non-competitive antagonist of the NMDA R (low evidence)



Posterior Reversible Encephalopathy Syndrome (PRES)

- Headache, visual field deficits, cortical blindness, confusion, seizures, and eventually coma
- After chemotherapy with or without accompanying electrolytic imbalance
- Characteristic P-O HSI → Usually resolves within days after cessation of CTx
- Tx: symptomatic treatment of seizures and electrolytic imbalance

TABLE 2. Implicated Chemotherapeutic Agents in the Development of Posterior Reversible Encephalopathy Syndrome

Chemotherapeutic Agent	N
Cisplatin, carboplatin, oxaliplatin*	30
CMF/IF/AC/IF*	14
Doxorubicin	24
Vincristine, vinorelbine, irinotecan, vinorelbine, vindesine	27
Cyclophosphamide	10
Gemcitabine	14
Capecitabine, 5-fluorouracil*	13
Cytarabine	5
IF cytarabine	5
Etoposide	8
Methotrexate	7
IF methotrexate	5
Taxane	5
Ifosfamide	3
Bleomycin	2
Lomustine	1
Dacarbazine	1
Irinotecan	1

*IF/IF: 1:1

CMF indicates Cyclophosphamide, Hydroxycarbamide/Fluorouracil, Oxaliplatin/Vincristine, Procarbazine, IF/CMF, Etoposide, Cyclophosphamide, Hydroxycarbamide/Fluorouracil, Oxaliplatin/Vincristine, Procarbazine.

Seizures

- MTX + Ara-C, 5-FU, Gemcitabine, Irinotecan, Capecitabine, Vincristine
- Intrathecal any drug
- Seizure type:
 - GTCs clusters Drug ME, CNS meta/infection, Encephalitis, CVT
 - Myoclonic Bouts
 - Prolonged tonic-clonic Interim alpha
 - Multiple focal/epileptogenic: CNS meta, Multifocal infection, Paraneoplastic
 - SE: Cyclosporine, Toxic drug overdose/impairment clearance
 - NCSE: Irinotecan, Paraneoplastic, Herpes encephalitis, Cyclosporine
 - Epilepsia partialis continua: Paraneoplastic, CVT
 - Recurrent but easily controlled with AED: MTX, 5-FU, Leukoencephalopathy, CNS infection
 - Intractable epilepsy: Paraneoplastic, Delayed RT necrosis, Herpes encephalitis

- Amacrine
- Asparaginase
- Busulfan (high-dose)
- Carmustine
- Cisplatin
- Cytarabine
- Cyclosporine
- Dacarbazine
- Etoposide
- 5-Fluorouracil
- Fludarabine
- Gemcitabine
- Ifosfamide
- Methotrexate
- Nelarabine
- Paclitaxel
- Vincristine

- IDH:
 - Before Dx of cancer: paraneoplastic limbic encephalitis, CNS meta
 - During CTx: Metabolic/toxic
 - -w/o after CTx: CNS infection, CNS meta
 - -w/ after CTx: CNS meta/infection, RT necrosis, Paraneoplastic, Leukoencephalopathy
 - Several yrs after CTx: CNS meta, RT necrosis, RT-induced tumor, CNS infection, Paraneoplastic

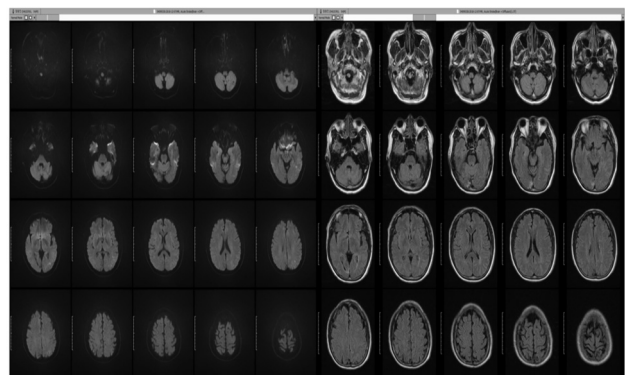
Clinical syndromes of CNS toxicity

Acute (reversible) Encephalopathy	MTX, 5-FU, Ara-C, Ifosfamide, Paclitaxel, Etoposide, VP16, Procarbazine, Nitrosoureas, Tamoxifen, Interferon- α , Interleukin-2, Steroid, Stem cell transplantation
Subacute E	MTX, Cisplatin
Chronic E	MTX, High-dose polychemotherapies
PRES	Cyclosporine, Cyclophosphamide, Ara-C, Cis-platinum, Ifosfamide, Vincristine, Gemcitabine, Other immunosuppressant
Multifocal leukoencephalopathy	Capecitabine
Thrombotic microangiopathy	Gemcitabine, Cyclosporine, Mitomycin-C
Cerebral infarctions	MTX, Cyclosporine, Platinum derivatives
Cortical blindness	Platinum derivatives, Fludarabine
Cerebellar dysfunction	Ara-C, 5-FU + Vincristine, Cyclosporine
Seizures	MTX, Ara-C, 5-FU, Cisplatin, Cyclosporine, Busulfan, Paclitaxel, Vincristine, Asparaginase, Etoposide, VP-16, Dacarbazine, Amacrine, Misondazole, Ifosfamide
Aseptic meningitis	MTX, Ara-C (IT)

Case 2

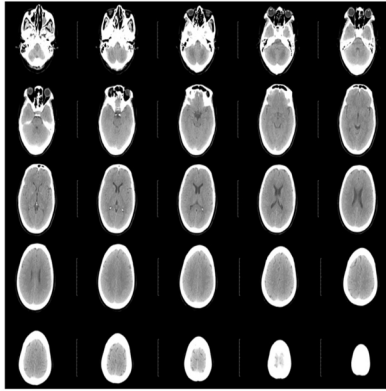
54/M
C> aphasia
last normal time: 20181206 1455(마취 시작 시간)
first abnormal time: 20181207 2140

MR Acute stroke

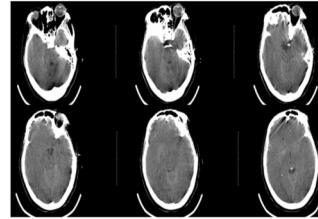


Hospital course

NE>
Coma, obey –
pupil 5.72mm/5.66mm NP(3.5/3.3)
Lt side extension response to pain
Rt side minimal withdrawal to pain
DTR+/-
Babinski's sign +/-



Hospital course



[Video EEG monitoring (32Ch)]
3-4 Hz delta to theta activities -> low attenuated background activity
Abundant 1 Hz generalized periodic discharge

Hyperammonemia

- Plasma ammonia level >50 micromol/L (>100micromol/L in newborns)
- Hyperammonemia + Clinical symptoms → regarded as emergency!
- Production of ammonia
 - intestinal bacterial overgrowth
 - neurogenic bladder
 - infections of other catabolic states (→ endogenous protein degradation)
- Ammonia detoxification
 - decreased urea cycle flux
 - portosystemic shunts

Hyperammonemia

- Classification
 - Primary hyperammonemia
 - Secondary hyperammonemia
- However, both type of hyperammonemia may result in encephalopathy and irreversible brain damage if not treated early and thoroughly.
- Prognostic factor
 - the duration of a hyperammonemic coma
 - peak ammonia concentration

Neuropathology of HE

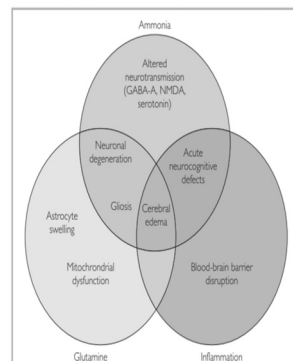


FIGURE 1. The neuropathology of hepatic encephalopathy reflects the interplay of ammonia, glutamine, and inflammation. GABA-A = γ -aminobutyric acid type A; NMDA = N-methyl-D-aspartate receptor.

Multiorgan mechanisms

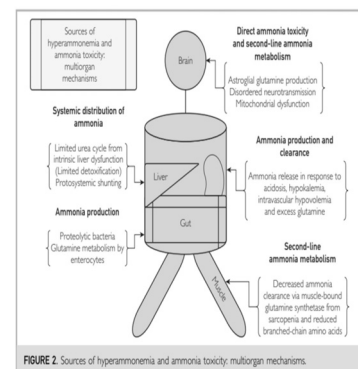


FIGURE 2. Sources of hyperammonemia and ammonia toxicity: multiorgan mechanisms.

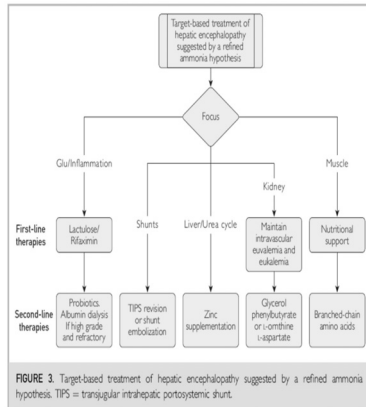


Table 1. Current treatments of hyperammonemia.

Name of Medicines	Pharmaceutical Name	Mechanism of Action	Drawbacks	Ref.
Lactulose ^a	Emulose	acidification of the colonic contents, increase in osmotic pressure, cathartic effect	customized drug dosage, abdominal cramping, bloating, flatulence, electrolyte imbalances	[20,21]
Rifaximin ^a	Xifaxan	inhibition of RNA synthesis in intestinal bacteria	high cost, nausea, bloating, diarrhea, antibiotic resistance	[22,23]
Sodium benzoate ^a	Ammonul	decrease glycine degradation, increase glycine elimination	headache, nausea, impaired mental status	[24,25]
Sodium phenylacetate/phenylbutyrate ^a	Bupenyl	decrease glutamine degradation, increase glutamine elimination	complication for patients with hypertension	[26-28]
L-arginine ^a /L-citrulline ^a	L-arginine/L-citrulline	activation of UC	gastrointestinal distress, increase plasma citrulline, diarrhea	[29,30]
Carbglutamic acid ^a	Carbglutamic acid	activation of UC through N-acetylglutamate restoration	chills, body aches, flu symptoms, sores in the mouth and throat	[31-33]
Albumin-based ^a dialysis	Prometheus®, Hepa Wash®, MARS	elimination of albumin-bound substances	mild thrombocytopenia	[34]
Peritoneal dialysis ^a		decrease of blood ammonia by transporting ammonia from vascular system to peritoneal cavity	mild to moderate nausea and vomiting	[35,36]
Neomycin ^b	Neomycin	inhibition of protein synthesis in intestinal bacteria	oto-, neuro-, nephrotoxicity	[37]

Dialytic Properties of Ammonia

- Compounds that have a high molecular weight or are highly protein bound to albumin or fat tissues (lipophilic) result in a high volume of distribution and accordingly, are less or poorly dialyzable.
- Furthermore, when intermittent HD is discontinued, there may be a rebound effect, where the drug that was initially distributed to the tissues may re-enter the vascular space.
- ammonia does not significantly bind proteins and is amenable to dialysis, because it is a small molecule (molecular mass is 17 g/mol).
- Because ammonia is similar to urea in terms of diffusive clearance, both modalities of continuous venovenous hemofiltration (CVVH) and intermittent HD should be effective in clearing ammonia, differing only by the rate of removal.

Dialytic Properties of Ammonia

- In adults, however, there are no established guidelines about the appropriate threshold to initiate dialysis in patients who present with hyperammonemia accompanied by cerebral edema
- The blood ammonia level is three times greater than the upper limit of normal or when the patient shows severe encephalopathy, it is worth considering RRT