Infection Triggered Encephalopathy Syndrome

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Disclosures

Consultation fees from CSL Behring, Roche, Novartis and Octapharma
Travel grants from Merck Serono
Educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono and Bayer

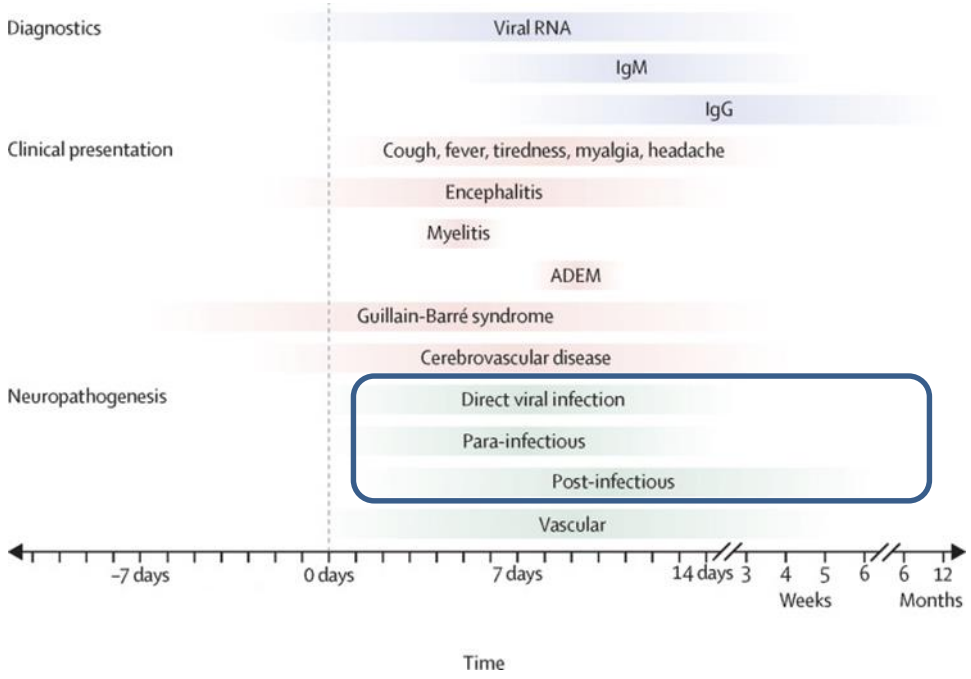
Summary

Infection associated neurological syndromes

The spectrum of infection triggered encephalopathy syndromes

Genetic (and environmental) determinants

The spectrum of infection-associated neurological syndromes



Lancet Neurol. 2020 Sep; 19(9): 767–783

Table 1. The child with acquired encephalopathy with focal neurological deficits of infectious/immune origin (subgroups, pathogenesis and immunotherapeutics)

Subgroup	Examples	Likely pathogenesis	Therapeutic options
Infectious encephalitis	Herpes simplex virus encephalitis	Direct invasion of the CNS by bacteria, viruses, or other microorganisms	Antibacterials
	Enterovirus encephalitis	Secondary inflammation and even autoimmunity may occur after some infections	Antivirals
			Probable role for immune suppression or immune modulation in some cases
Infection-associated encephalopathy	Clinico-radiological syndromes such as	General lack of inflammatory cell infiltration[a]	Unclear, possible role of targeted immune modulation of innate immune system or cytokines[a]
	Acute necrotizing encephalopathy (ANE), mild encephalopathy with reversible splenium involvement (MERS), fever induced refractory epilepsy syndrome (FIRES), acute encephalopathy with biphasic seizures and diffusion restriction (AESD)	More likely genetic vulnerability associated 'cytokine storm' of the CNS, with cytotoxic injury	
Autoimmune encephalitis	Cell surface auto-antibodies (anti-NMDAR antibodies, see Table 2)	Predominantly neuronal disease	Immune suppression
		Expansion of auto-reactive lymphocyte and production of auto-reactive antibodies, and access to CNS with or without intrathecal auto-antibody production	Immune modulation

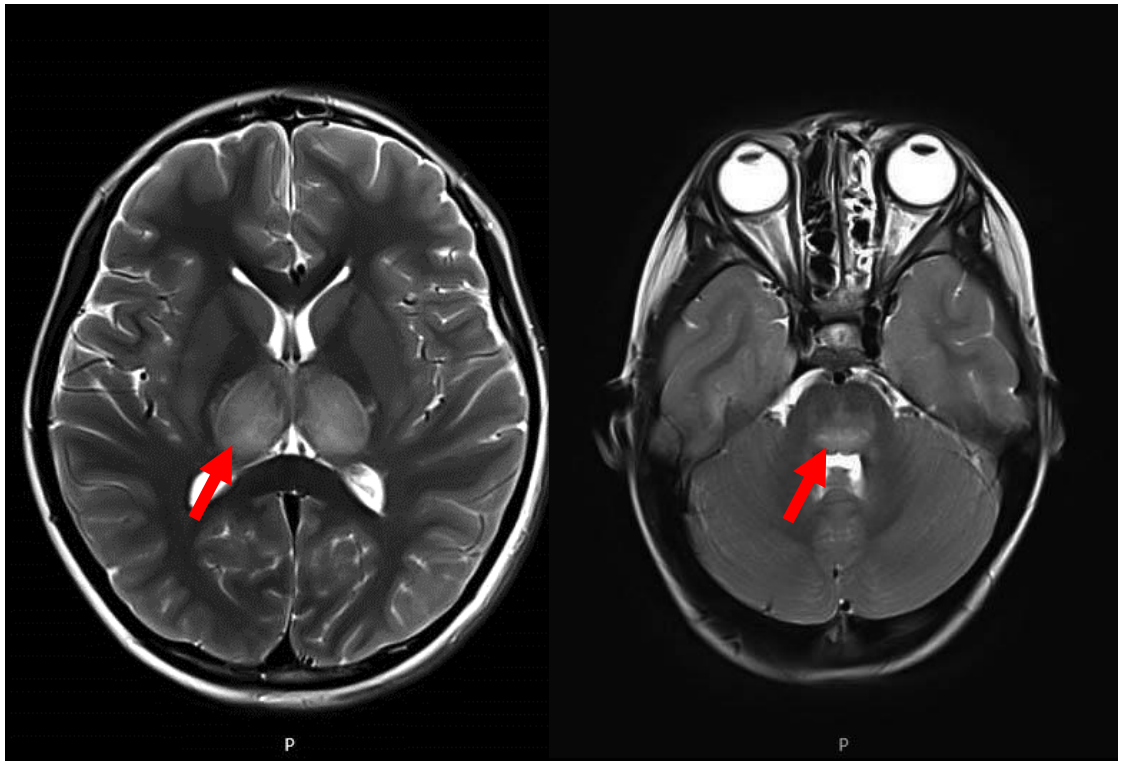
Curr Opin Neurol. 2017 30(3):334-344

Case 1

10y Boy
Febrile URTI
Status epilepticus on Day 2
then Encephalopathic

- AST 5152 IU/L
- ALT 2899 IU/L

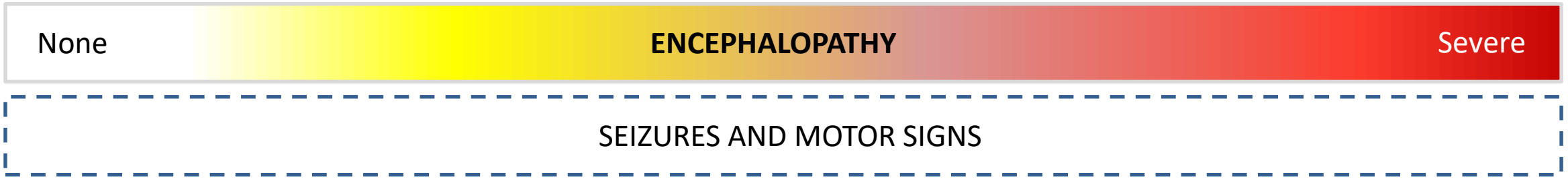
Imaging



Influenza A H1N1 pdm09

Surana et el., 2011 ***Eur J Pediatr.*** 170(8):1007-15

Infection triggered encephalopathy A severity spectrum

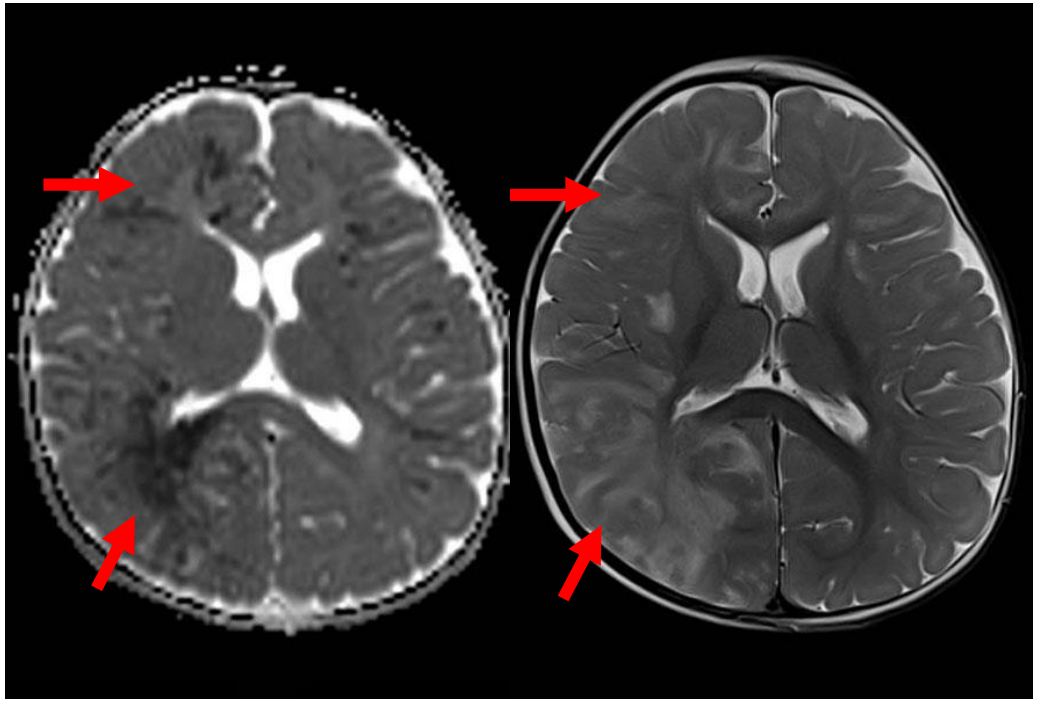


ANE Acute Necrotising Encephalopathy

Case 2

8m Girl
Normal development
Febrile URTI with seizure
Status epilepticus on Day 3
Encephalopathic
GI Bleeding
Retinal haemorrhage

- CSF protein 0.43 g/L
- Leukopenia



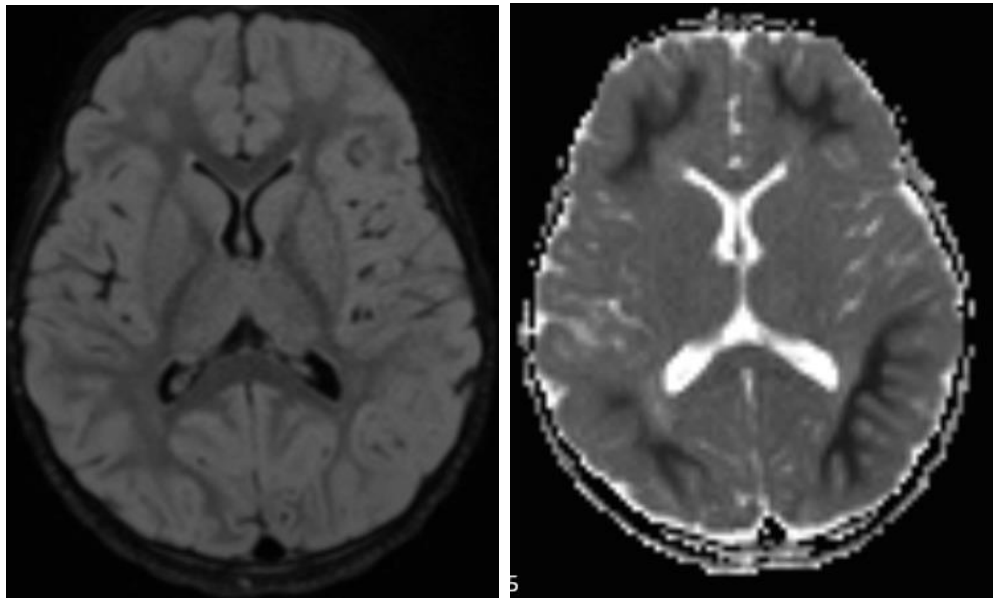
Influenza B virus

Acute encephalopathy with Biphasic Seizures and Subcortical restricted Diffusion (AESD)

Case 3

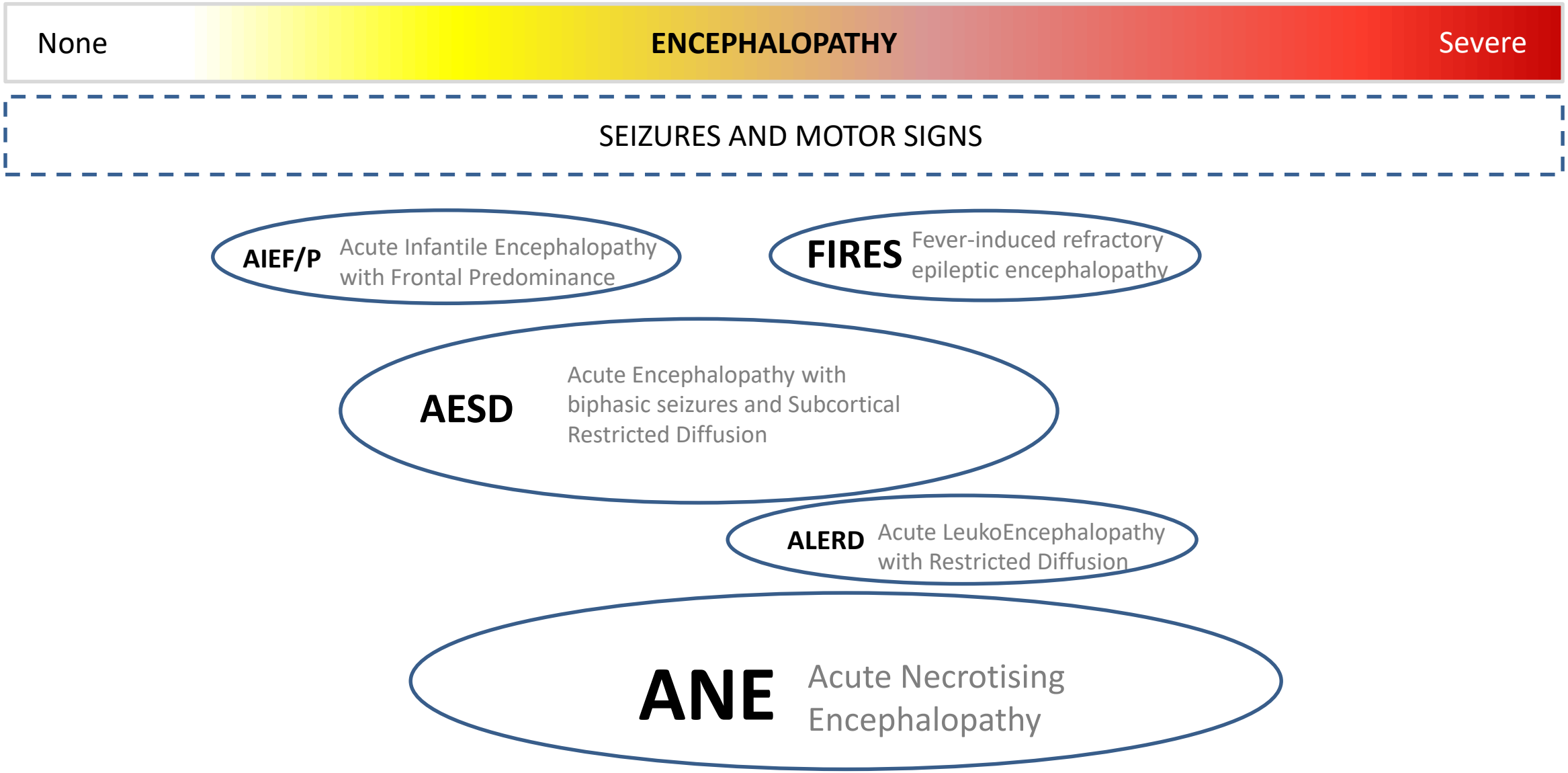
2.7yr Girl
Prolonged febrile illness
Diarrhoea & vomiting 2 days prior
Progressive encephalopathy
Clinically I&V; hypotensive

- CSF no cells, normal protein
- EEG reactive encephalopathy
- No liver/renal involvement
- Serum antibodies -ve
- Infective screen -ve



Acute LeukoEncephalopathy with Restricted Diffusion (ALERD)

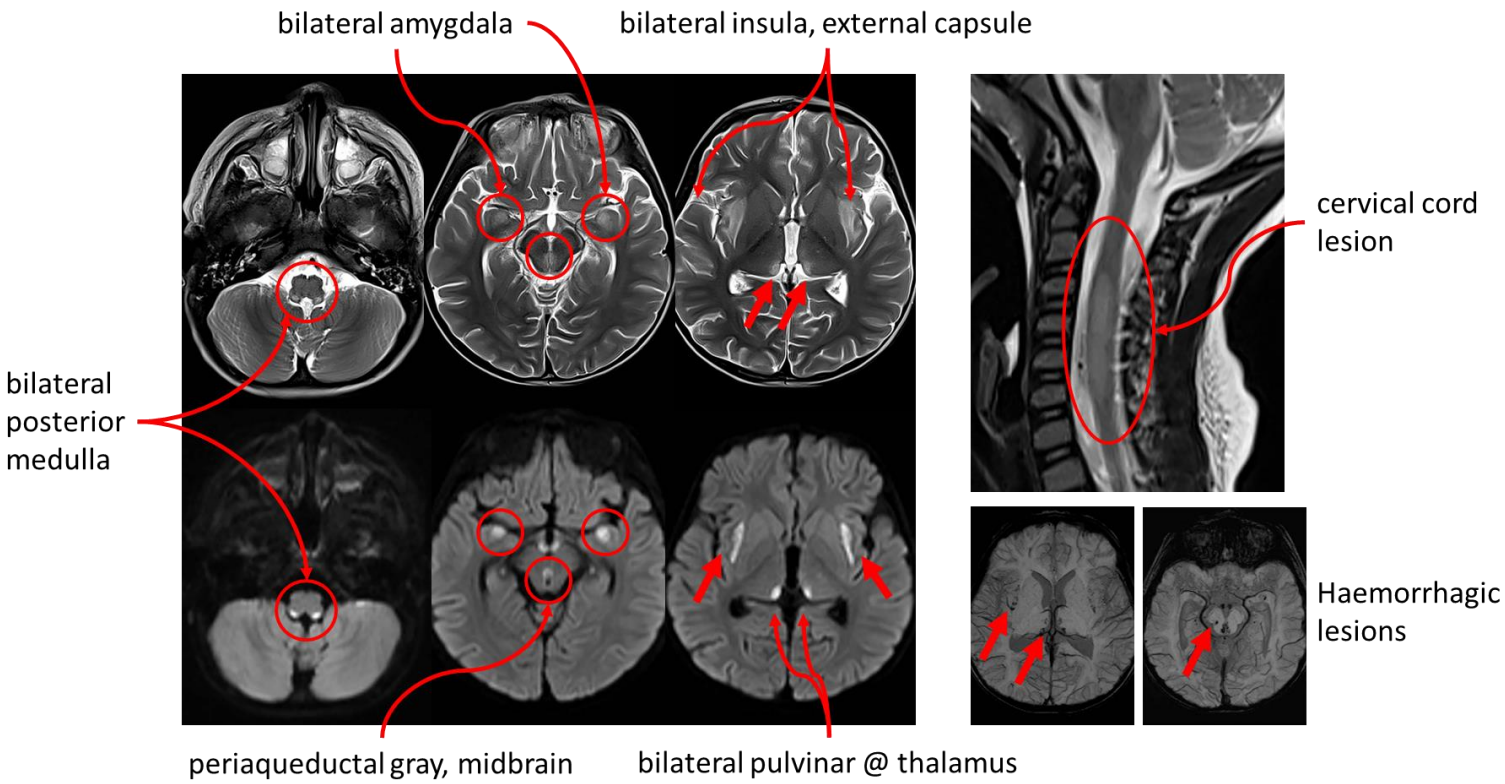
Infection triggered encephalopathy A severity spectrum



Case 4

2y Boy
Febrile URTI
Encephalopathy Day 5
Recurrent vomiting
Left hemiplegia
Neurogenic bladder

Leukopenia
Mild liver transaminitis
Thrombocytopenia
CSF protein 0.60 g/L



Influenza A H3N2 virus

COVID-19: Radiological features

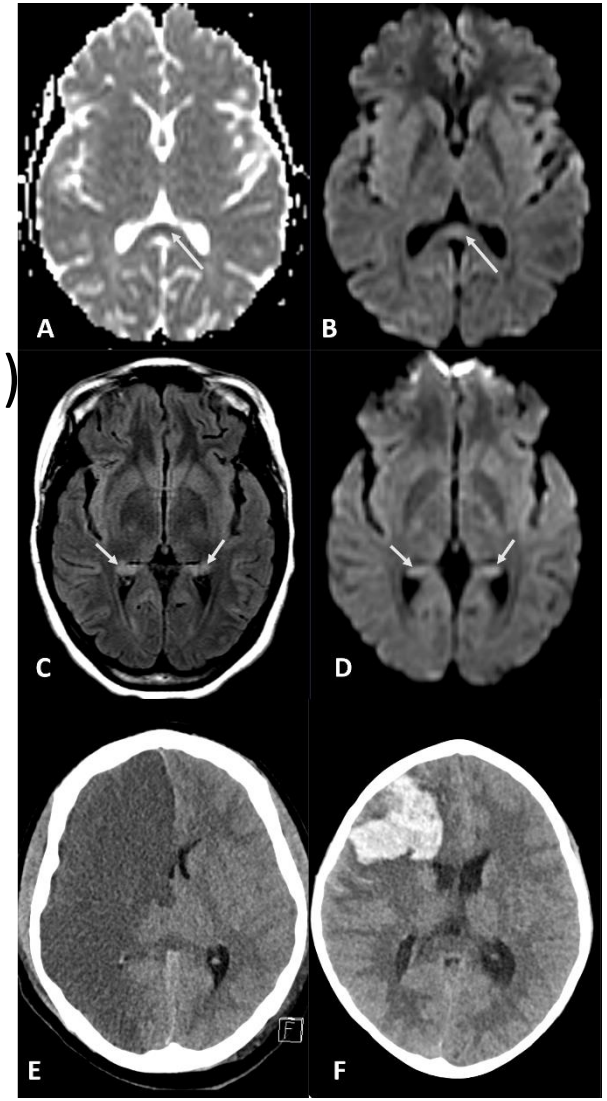
Post infectious

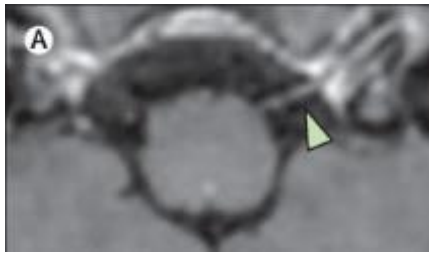
- ADEM
- Myelitis
- Cranial nerve enhancement (asymptomatic)

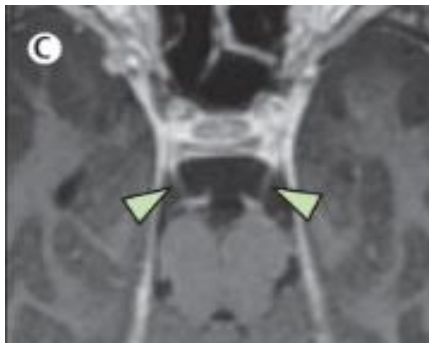
PIM-TS

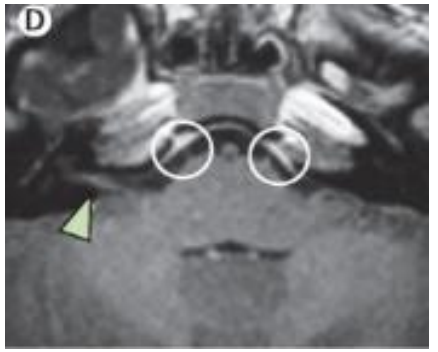
- Splenial changes
- Myositis

CVA





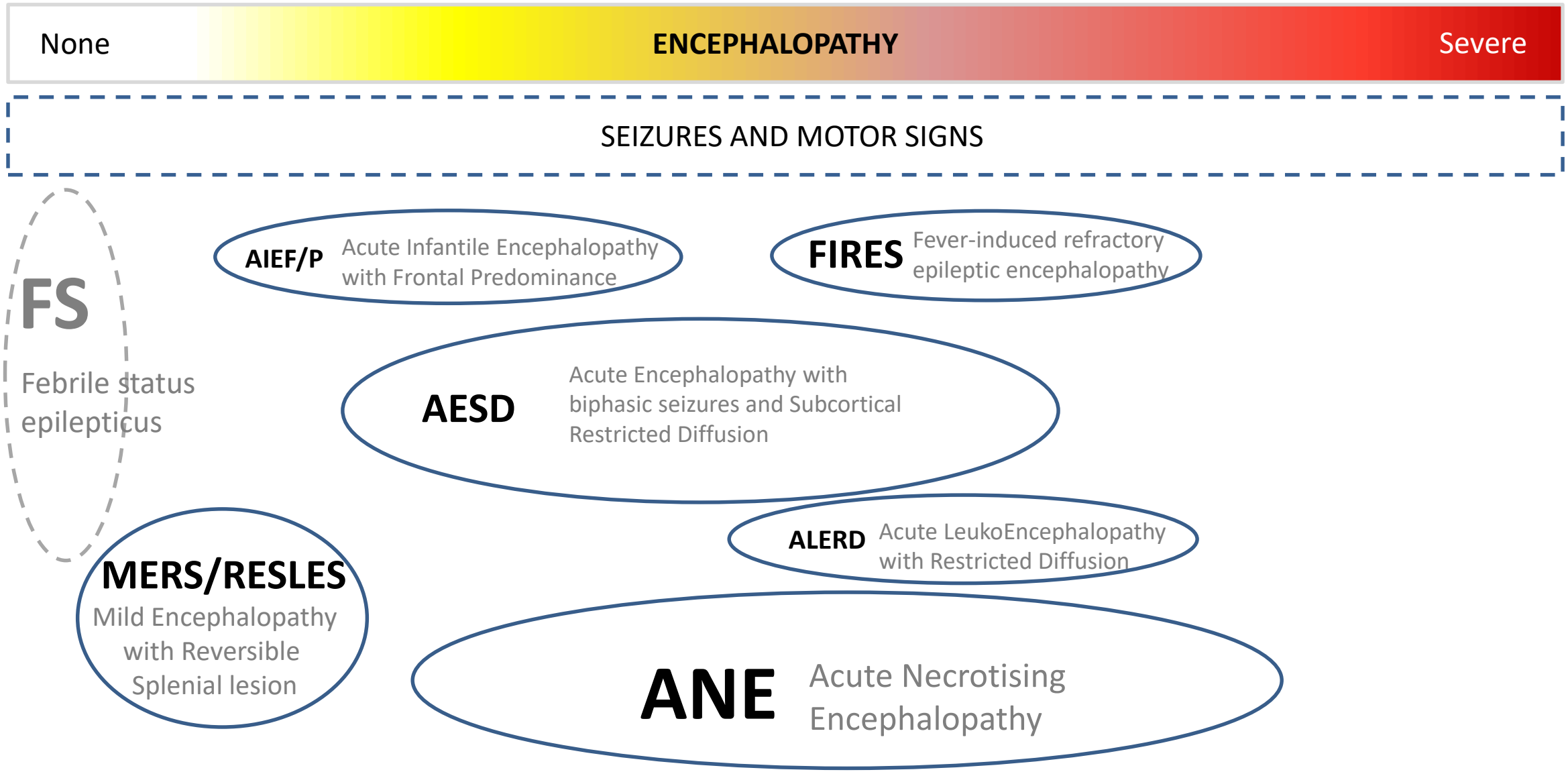




Lindan et al., 2021 ***Lancet Child Adolesc Health*** 5(3): 167–177

Sa, Mirza, Carter et al., 2021 ***Neurol Neuroimmunol Neuroinflamm***. 8(4):e999

Infection triggered encephalopathy A severity spectrum



Case 5

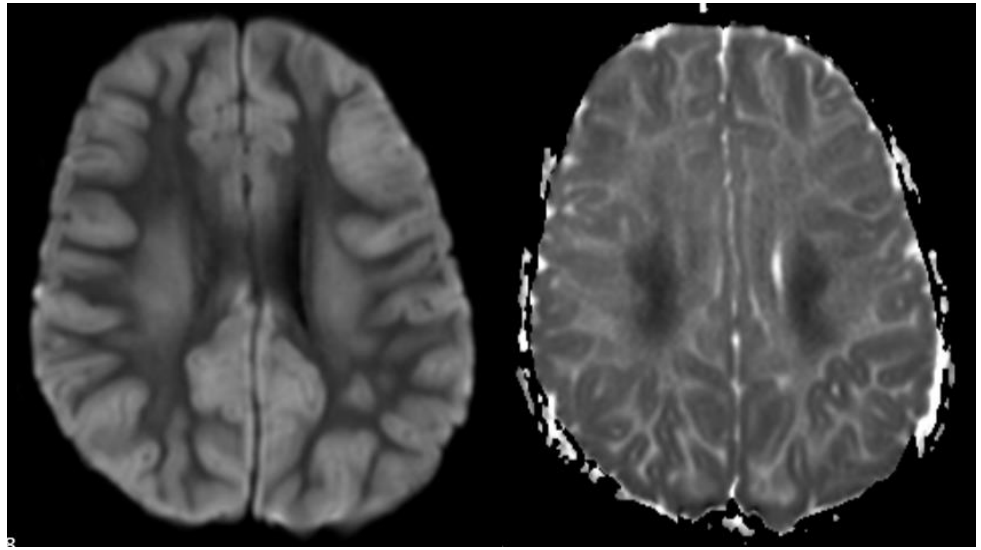
3yr Boy

Presented in status epilepticus

No clear prodrome/fever

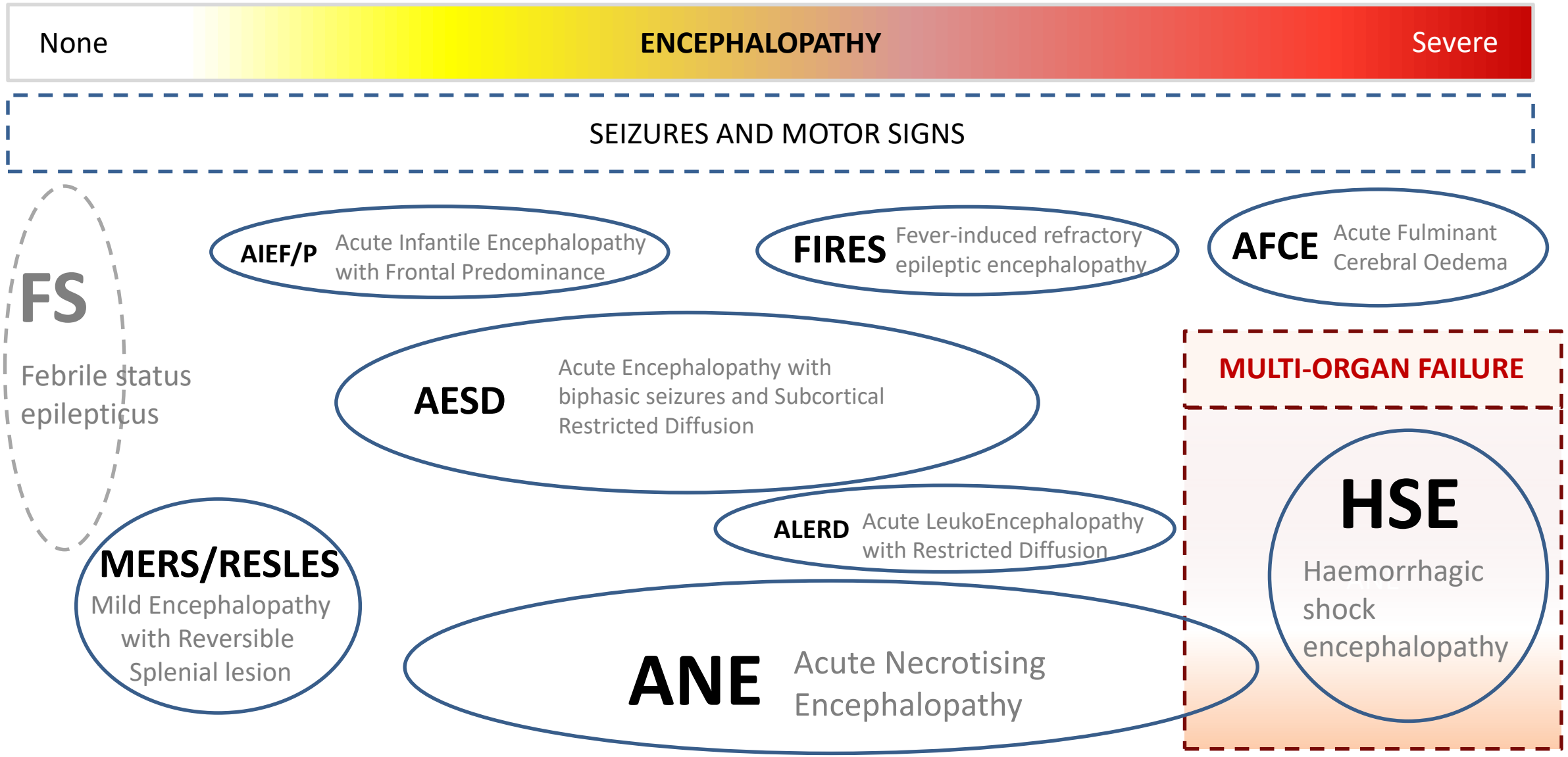
Clinically I&V ;UMN signs; hypotensive

- CSF prot 0.26/ cell count 1
- Oligoclonal band neg
- **Enterovirus detected**
- Hypernatremia
- Prolonged PT/ Fibrinogen 3.9
- LDH 1513/ ALT 1058/ CK 1235

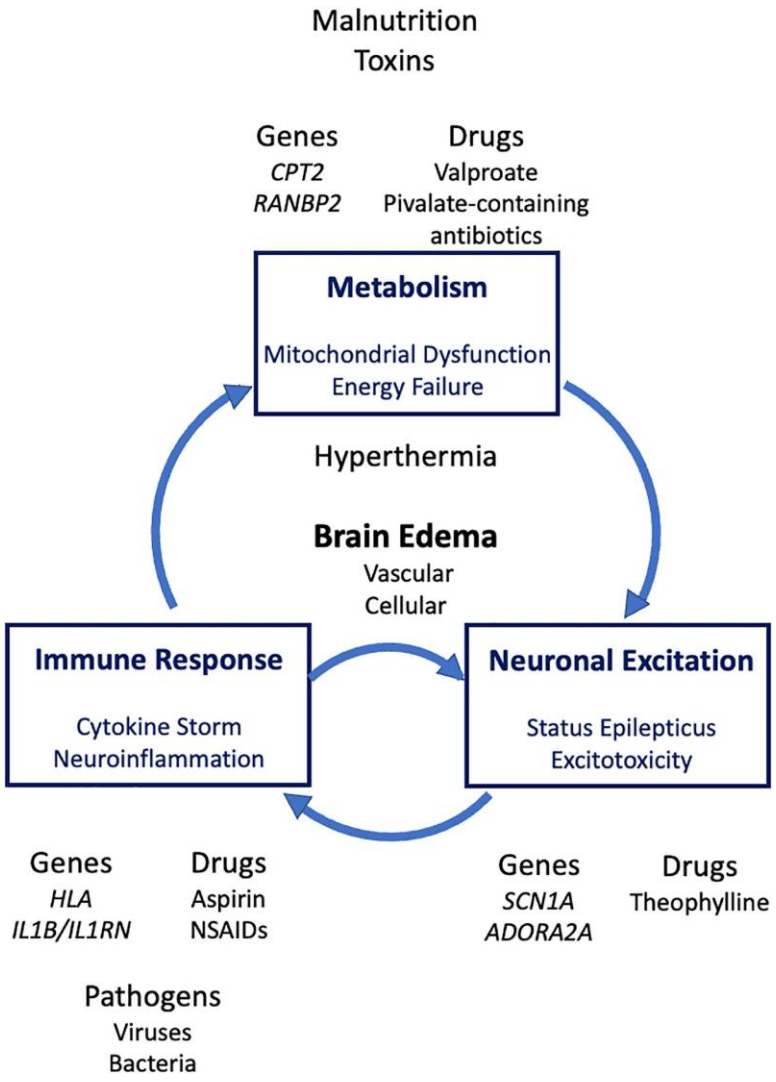


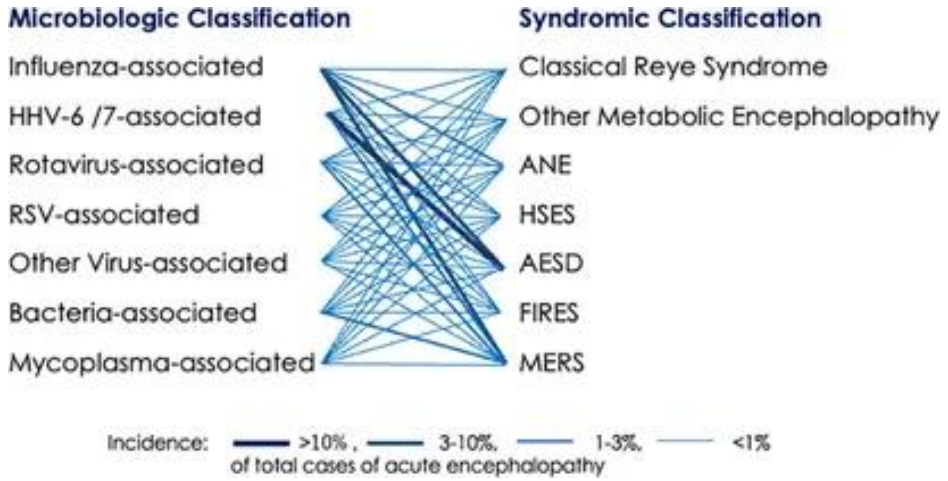
Acute Fulminant Cerebral Oedema

Infection triggered encephalopathy A severity spectrum



Pathophysiology of infection triggered encephalopathy syndrome





Mizuguchi et al., 2023 ***Front Neurosci*** 17:1119708

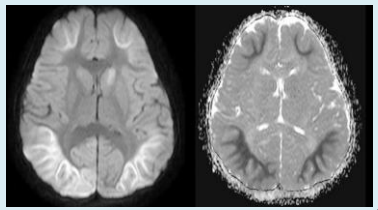
Infection-triggered encephalopathy syndromes (ITES)

Common clinical features

- Febrile illness preceding or concurrent to the onset of neurological manifestations
- Decreased or altered level of consciousness, altered mental status, lethargy, or personality change

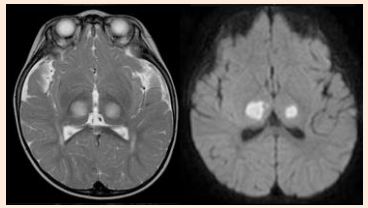
Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)

- Restricted diffusion on MRI in the subcortical white matter (bright tree appearance)



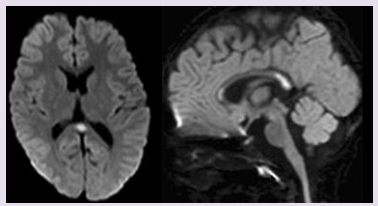
Acute necrotizing encephalopathy (ANE)

- Symmetrical thalamic lesions on head CT and/or MRI



Mild encephalopathy with a reversible splenial lesion (MERS)

- A splenial corpus callosum lesion with homogeneously restricted diffusion on MRI



Acute fulminant cerebral edema (AFCE)
Acute shock with encephalopathy and multiorgan failure (ASEM)

- Diffuse cerebral edema evident on neuroimaging and/or autopsy

ITES-related conditions

- **Febrile infection-related epilepsy syndrome (FIRES)**
- **Hemiconvulsion-hemiplegia-epilepsy(HHE) Syndrome**

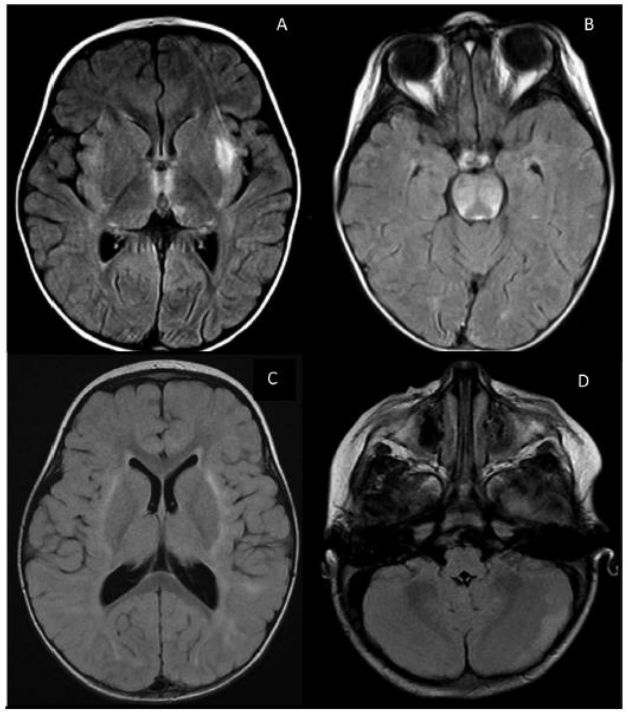
Sakuma et al., ***Dev Med Child Neurol.*** 2024 Aug 14. doi: 10.1111/dmcn.16067

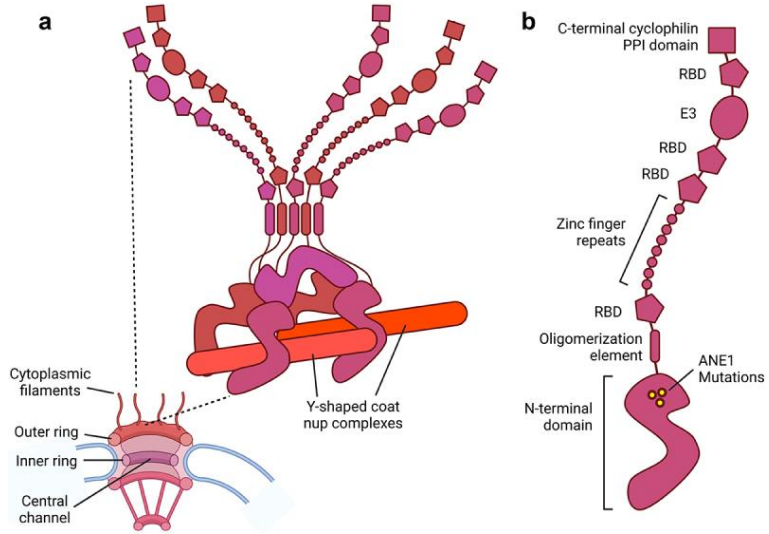
Genetic encephalopathy

RANBP2 mutation (ANE1)

- Familial
- Recurrence
- Associated with influenza infection

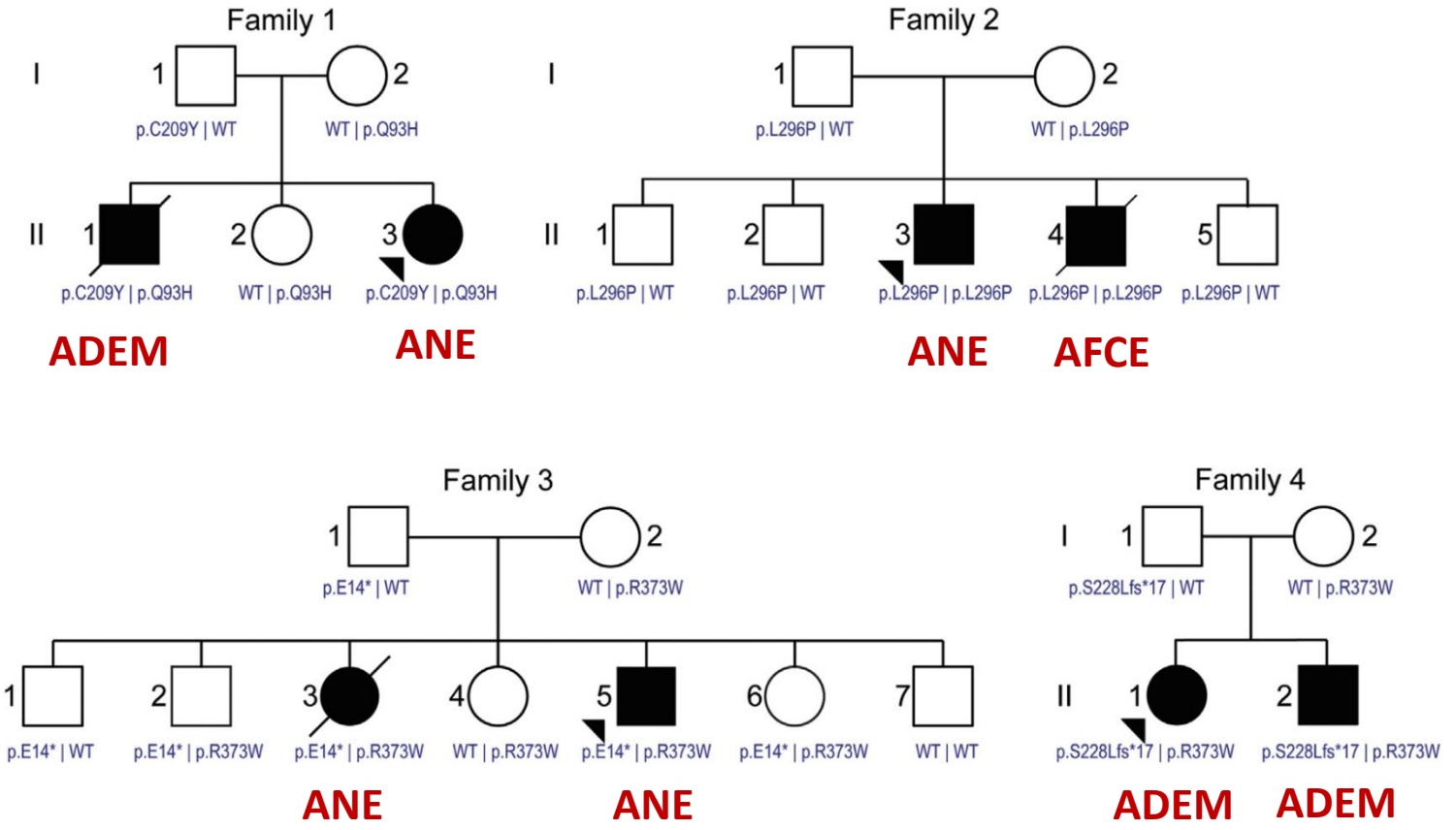
Neilson 2010
Current Opinion in Pediatrics 22: 752-57





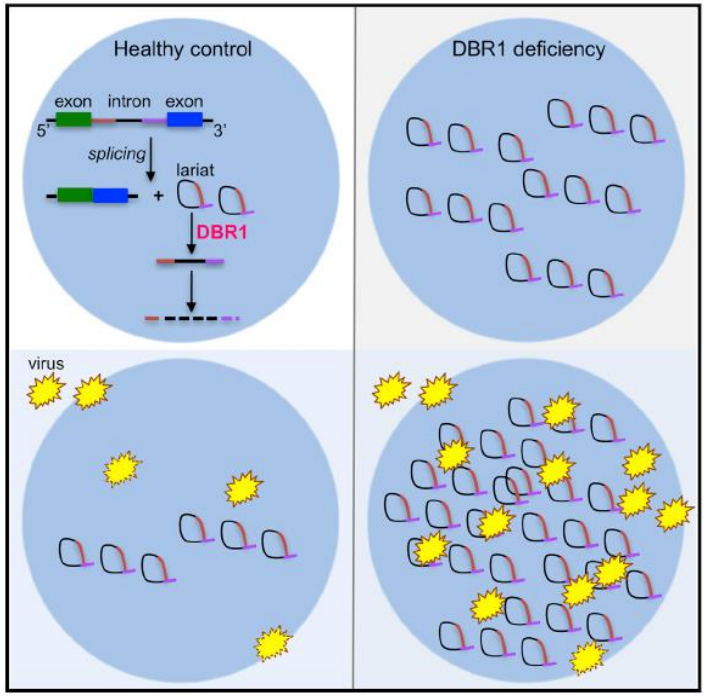
Nucleus 2022 13(1):154-169

Biallelic variants in RNH1 are associated with ANE



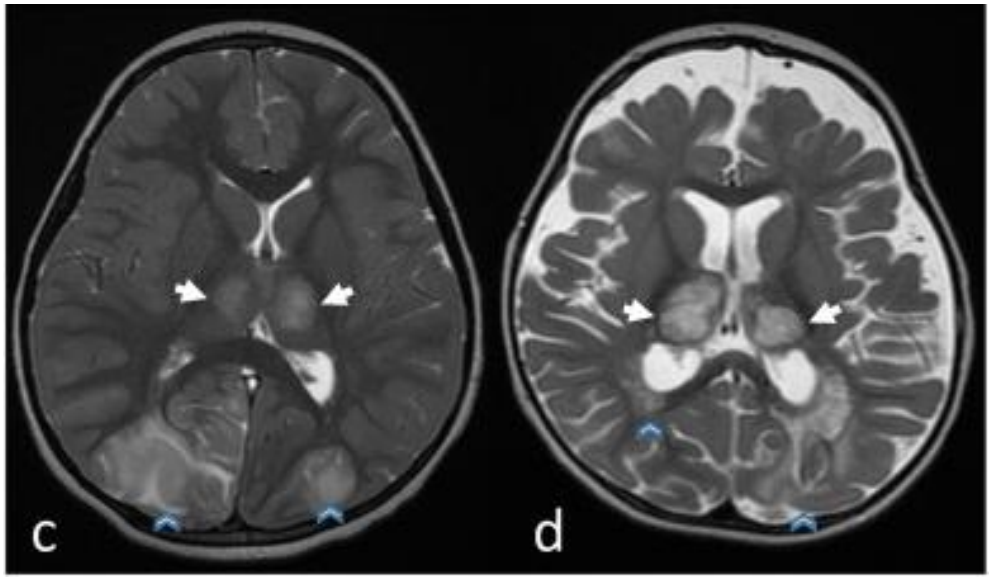
Shasi et al., 2023 ***Genet Med*** 25(9):100897

DBR1 deficiency is associated with brainstem infection



Zhang et al., 2018 ***Cell*** 172(5):952-965.e18

DBR1 mutation in ANE



NM_016216.4:c.359T > C; p. (Ile120 Thr)

Habib et al., 2024 ***Eur J Med Genet***. 68:104918

Outcomes in sporadic and RANBP2 mutation-associated acute necrotizing encephalopathy of childhood

7/20 (35%) *RANBP2* mutation positive

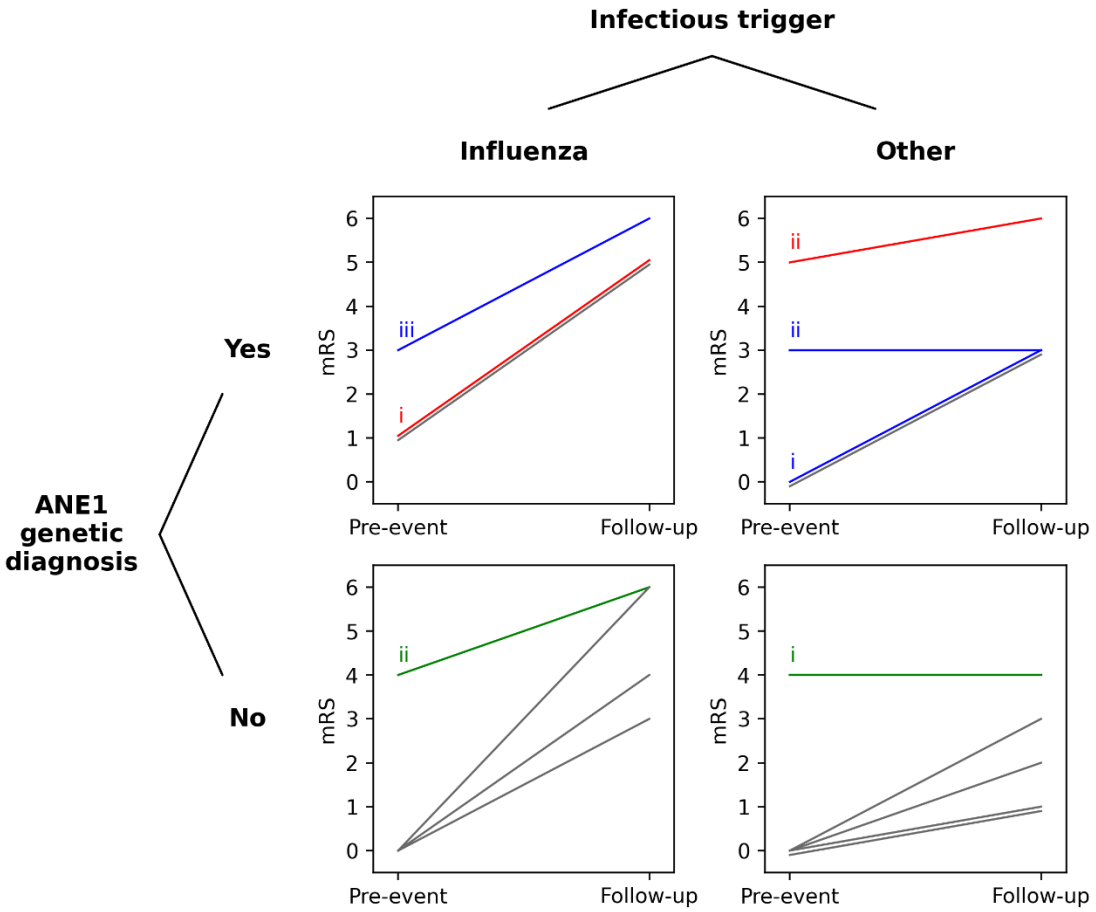
TABLE 3 Outcomes

	All (*n*=20)	*RANBP2* positive (*n*=7)	*RANBP2* negative (*n*=13)	*p*	FDR correction
EDSS by 12mo (baseline or 2 consecutive scores)	1.25 (0–6.5)	2 (0–3.5)	1 (0–6.5)	0.329	0.329
Relapse	3 (15)	3 (43)	0 (0)	0.010	0.030
Death	1 (5)	1[a] (14)	0 (0)	0.299	0.329
Cognitive abnormality, *n*=19	6 (32)	4 (67)	2 (15)	0.034	0.057

High proportion had early immunotherapy (<6 days)

Chatur et al., 2022 ***Dev Med Child Neurol.*** 64(8):1008-1016

Is ANE more severe when associated with influenza?



	Influenza N=7	Others N=9
Mean age years (range)	4.4 (1-9)	1.4 (0.67-3.8)
Mean hospital days (range)	171 (1-850)	16 (3-42)
PICU admission	7/7 (100%)	7/9 (77%)
Mean change mRS (range)	3.75 (3-6)	2.04 (1-6)
Mortality	3/7 (42%)	1/9 (11%)

Khamis et al., 2023 ***Dev Med Child Neurol.*** 65(9):1139-1140

Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study

52 Children

Median age: 9years (range 1 - 17 years; 22 F)
Admitted to ICU: 26 (50%)
3.8% of COVID-19 admisisons

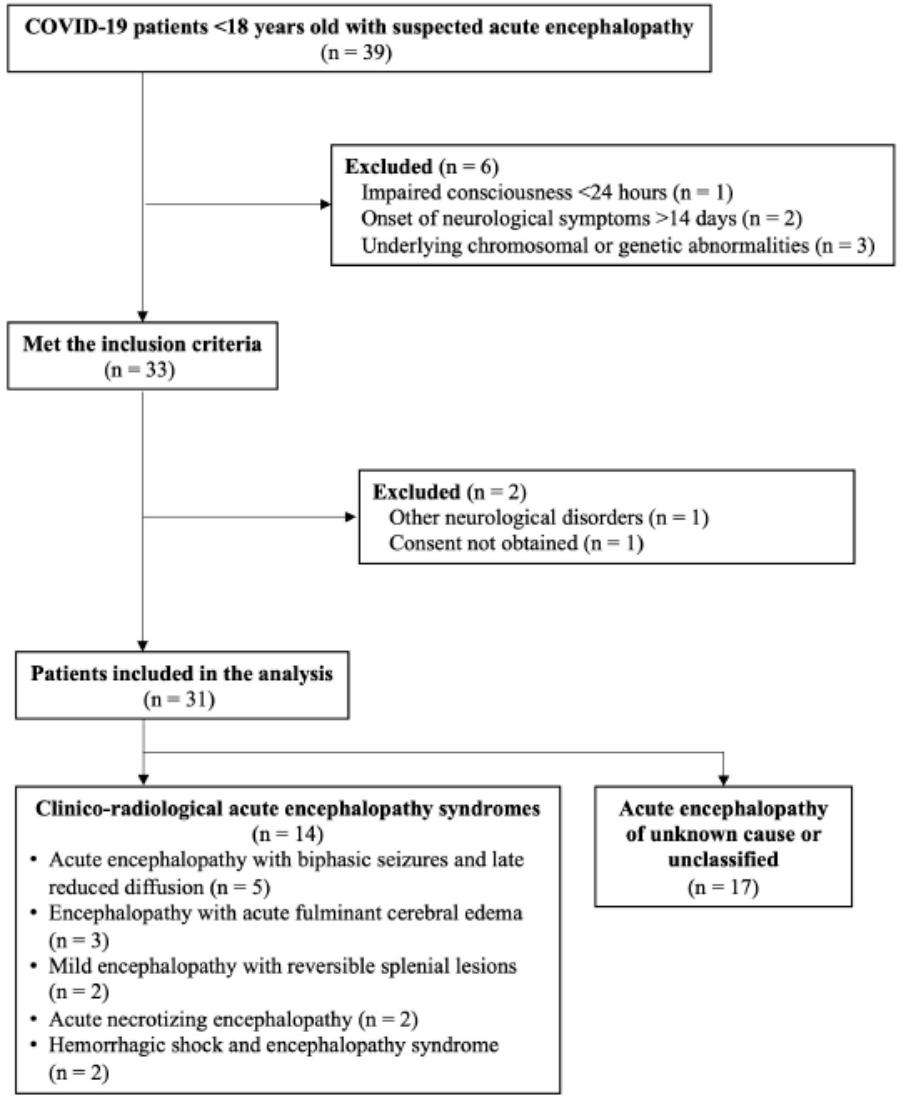
- Encephalopathy: 36 (70%)
- Peripheral nervous system 17 (33%)
- Severe headaches: 14 (27%)
- Seizures: 12 (23%)
- Behavioural change 12 (23%)
- Focal neurology 10 (19%)
- Myositis: 8 (15%)
- Hallucinations 7 (13%)

Worsening of underlying neurological condition (n=8)	**Acute COVID with encephalopathy (n=3)**	**PIMS-TS (n=25)** ***2 CVA***	**Post Infectious (n=16)** 2 Chorea, 2psychosis, 5 GBS, 7 demyelinating syndromes

BPNSU

CoroNerve Studies Group

Ray et al., 2021 ***Lancet Child Adolesc Health*** 2021 S2352-4642(21)00193-0



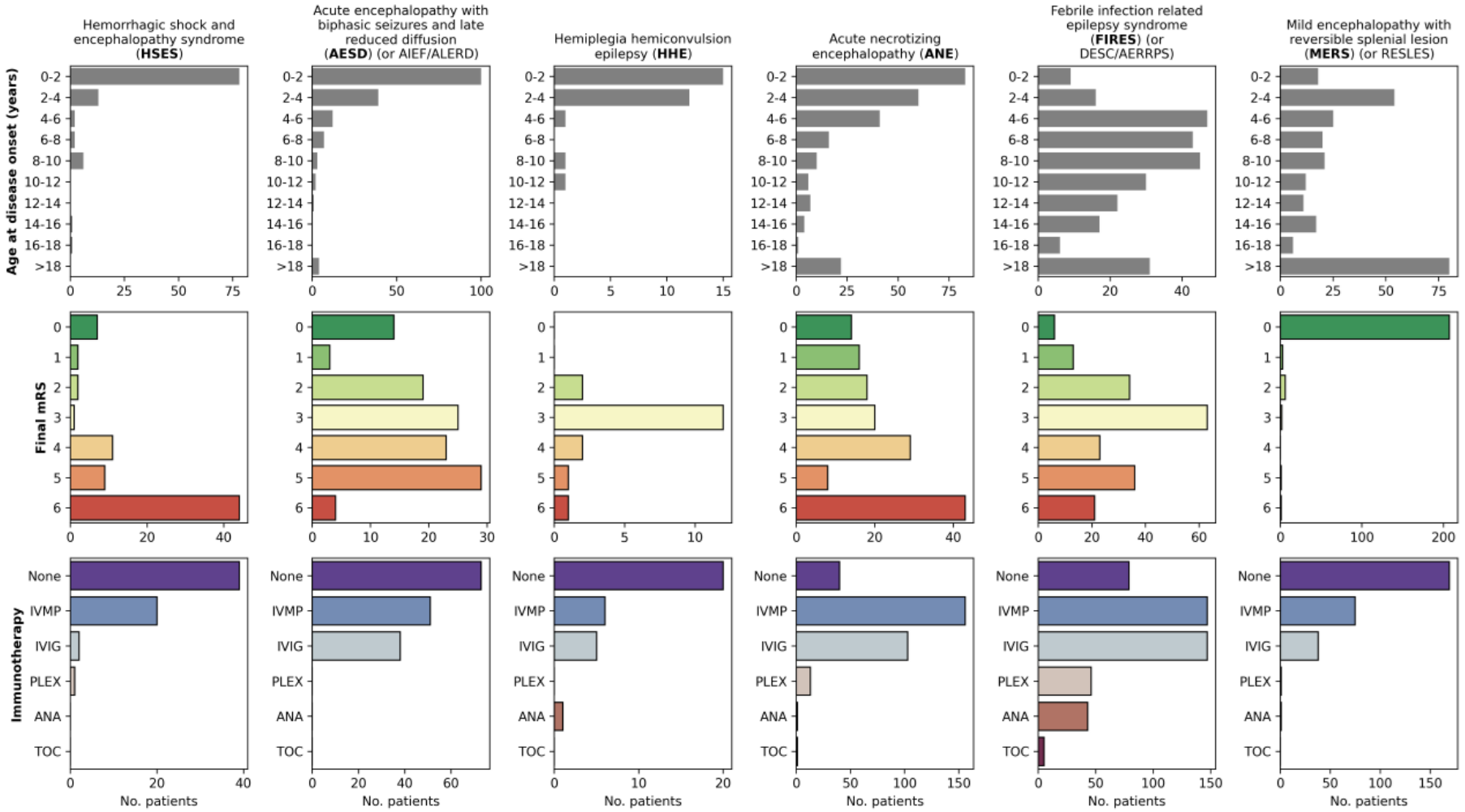
Severe pediatric acute encephalopathy syndromes related to SARS-CoV-2

- Acute fulminant cerebral oedema
- Acute encephalopathy with biphasic seizures and subcortical restricted diffusion (AESD)
- Acute necrotizing encephalopathy

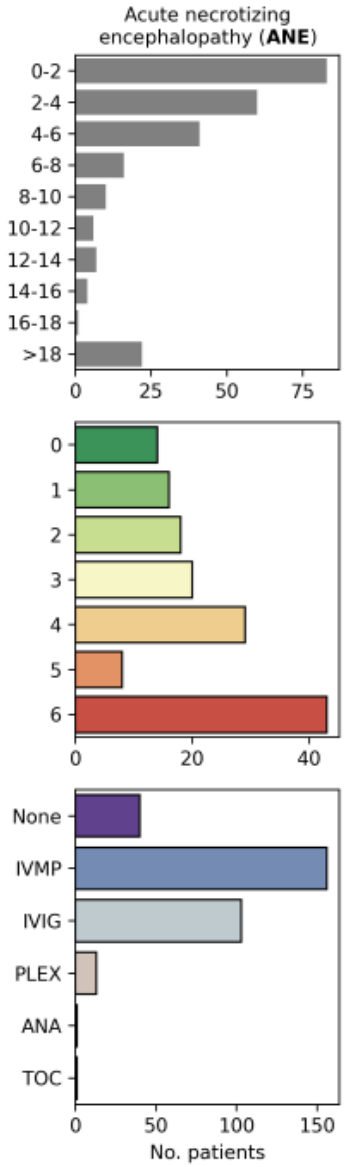
Ninan et al. 2021 ***Child Neurology Open*** *8: 1-6*
Sakuma et al., 2023 ***Front Neurosci*** 17:1085082
Lee et al., ***N2*** 11(1):e200186

Infection triggered encephalopathy syndrome project

Hiroshi Sakuma, Terrence Thomas, Carly Debinski, Velda X Han, Hannah Jones, Go Kawano, Vanessa Lee, Stephen Malone, Toyojiro Matsuishi, Eyre Michael, Shekeeb Mohammad, Takayuki Mori, Hiroya Nishida, Margherita Nosadini, Jun-ichi Takanashi, Masashi Mizuguchi, Ming Lim, Russell Dale.



Meta-analysis 1960 cases from 660 papers



Early analysis from the individualised patient data

77 ANE1 and **240 sporadic** cases were included from 122 publications

ANE1 patients were younger (median age 2.1 vs 3.4; p=0.035)

No difference in:-

- Gender
- Neurological presentation (encephalopathy, seizures, focal deficits)
- Severity and disease course
  - ANE-SS
  - mRS at nadir
  - Length of stay
  - Intensive care admission

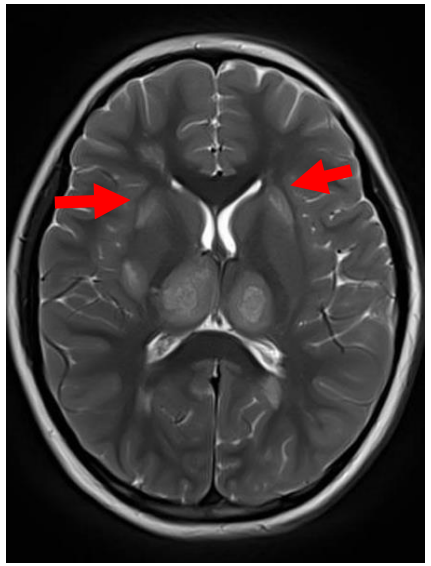
Mortality was higher amongst ANE1 (20/71 (28.2%) vs 17/165 (10.3); p<0.001)

Disability outcomes (mRS grades) in survivors did not differ

Hiroshi Sakuma, Terrence Thomas, Carly Debinski, Velda X Han, Hannah Jones, Go Kawano, **Vanessa Lee,** Stephen Malone, Toyojiro Matsuishi, Eyre Michael, Shekeeb Mohammad, Takayuki Mori, Hiroya Nishida, Margherita Nosadini, Jun-ichi Takanashi, Masashi Mizuguchi, Ming Lim, Russell Dale.

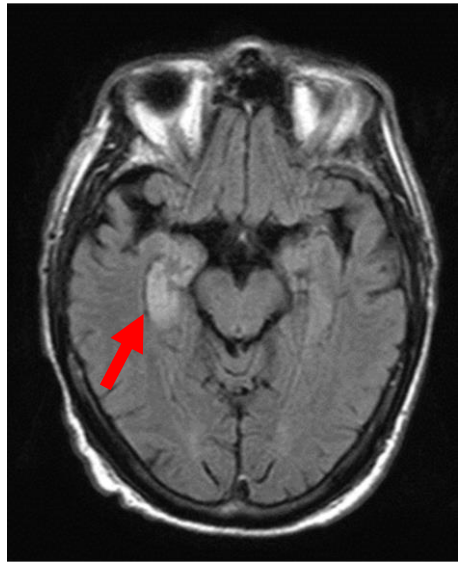
Neuroimaging differences between ANE1 and sporadic cases

ANE1



External capsule/insular

ANE1 39/71(54.9%)
Sporadic 23/150 (15.3%)
p<0.001



Medial temporal

ANE1 26/68 (38.2%)
Sporadic 28/156 (18.0%)
p=0.001

Sporadic

Cerebellum

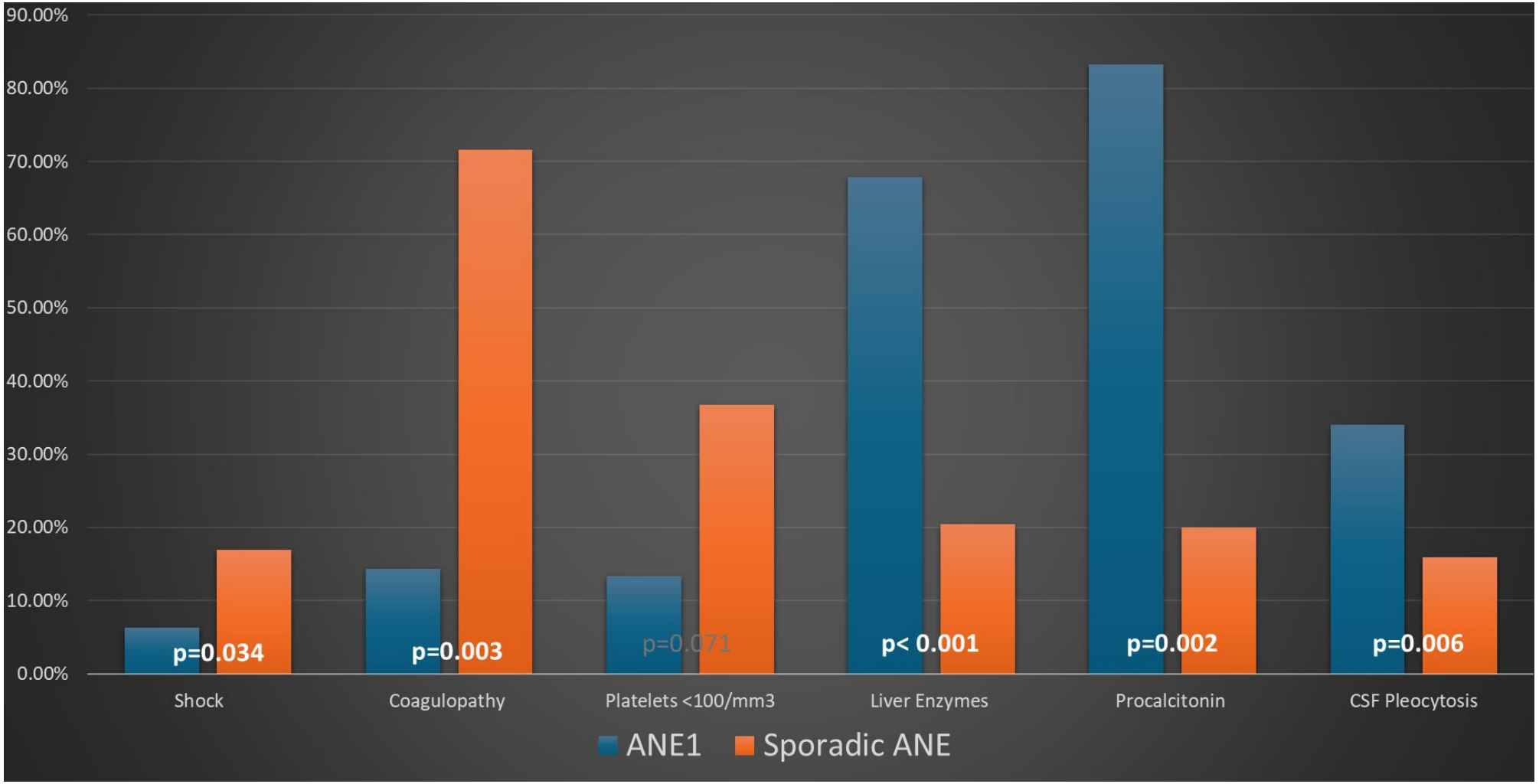
Sporadic 97/179 (54.2%)
ANE1 24/73 (32.3%)
p=0.002

White matter

Sporadic 102/183 (55.7%)
ANE1 26/71 (36.6%)
p=0.006

Hiroshi Sakuma, Terrence Thomas, Carly Debinski, Velda X Han, Hannah Jones, Go Kawano, **Vanessa Lee,** Stephen Malone, Toyojiro Matsuishi, Eyre Michael, Shekeeb Mohammad, Takayuki Mori, Hiroya Nishida, Margherita Nosadini, Jun-ichi Takanashi, Masashi Mizuguchi, Ming Lim, Russell Dale.

Systemic features in ANE1 and sporadic cases



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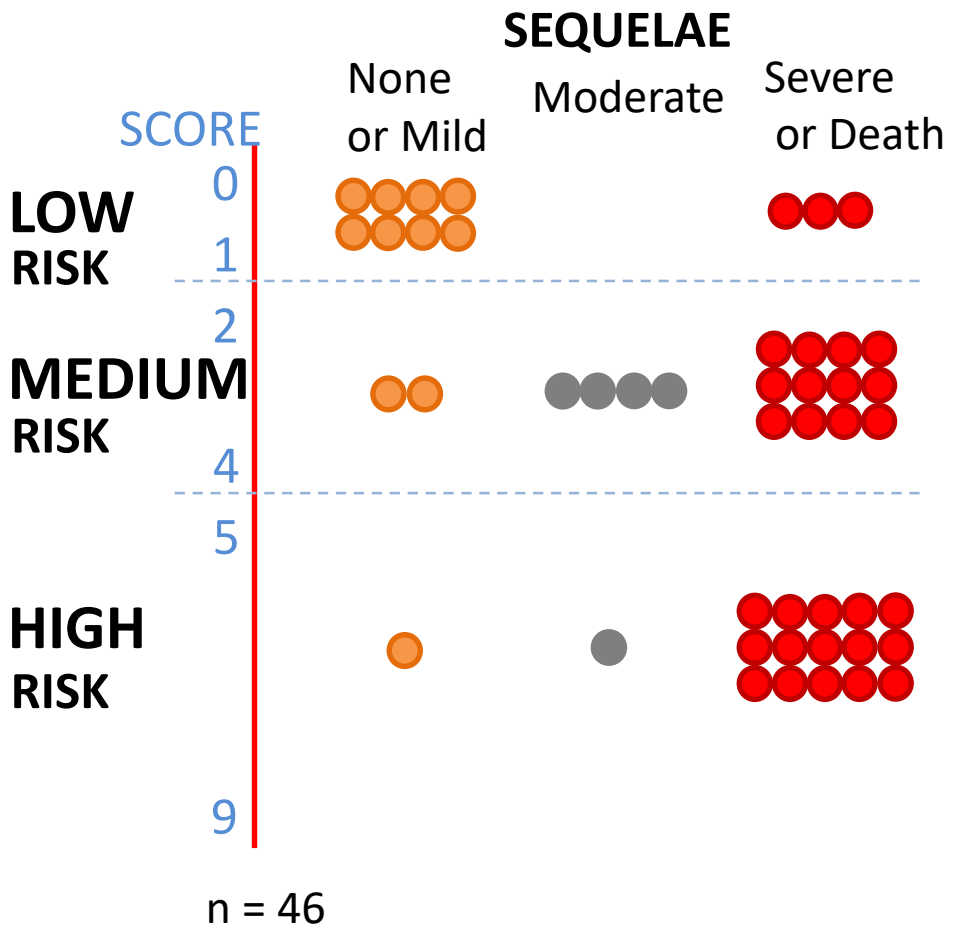
Acute necrotizing encephalopathy outcome

ANE-Severity Score (ANE-ss)

Feature	Score
CLINICAL	
Age > 4 years	2
CSF Protein > 0.6 g/L	1
RADIOLOGICAL	
Brainstem lesion	2
MULTIORGAN FAILURE	
Platelets < 100,000/ml	1
Shock on admission	3
TOTAL	9



Yamamoto et al., 2017 ***Brain Dev***. 37(3):322-7

Courtesy of Dr Terence Thomas, Singapore

STEROIDS/IVIg/PLASMA EXCHANGE +/- HYPOTHERMIA

27 Tertiary Hospitals, Japan

Yamamoto. Brain Dev 2015

All ANE, n = 14

SEQUELAE

	None or Mild	Moderate	Severe or Death
LOW RISK			
ANE ANE-ss 0-2	●		●●●
MEDIUM RISK			
ANE ANE-ss 4	●		●
HIGH RISK			
ANE ANE-ss 5-6		●	●●●
ANE ANE-ss 7-9			●●●●

EARLY STEROIDS + **IL-6R ANTAGONIST** +/- HYPOTHERMIA **(HT)**

KK Hospital, Singapore

& Penang Hospital, Malaysia

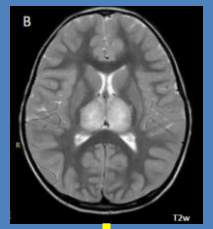
Mixed VAE, n = 12

SEQUELAE

	None or Mild	Moderate	Severe or Death
ANE ANE-ss 4	●		
ANE ANE-ss 5-6	●●●	●	
AESD	●●		
HSE (ANE-ss 7-9)	+HT		●●●

SEVERE ACUTE NECROTIZING ENCEPHALOPATHY OUTCOMES: A MULTICENTRE EXPERIENCE IN MALAYSIA

Acute necrotizing encephalopathy in childhood (ANEC)



viral associated encephalopathy with seizures & rapid drop of GCS

No CSF pleocytosis

Elevated serum aminotransferases

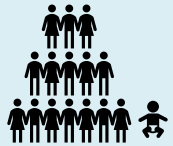
Symmetric multifocal brain lesion with bi-thalamic involvement

And exclusion of other resembling diseases

ANE- Severity score (ANE-SS): predicts risk of mortality
High – 5 to 9 (Max score 9)
Medium – 3 to 4
Low – 0 to 2

STUDY OBJECTIVE

To compare clinical variables, treatment and outcomes for children with severe ANEC



27 children with ANEC
Age 7mths- 14 years
Females 15

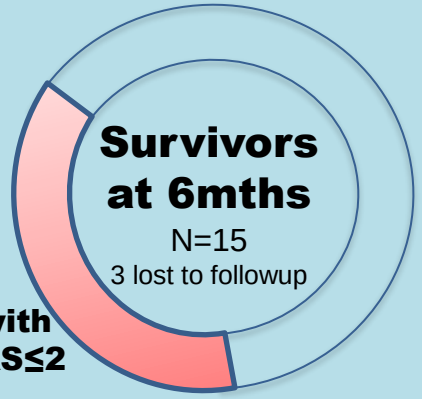
Retrospective review

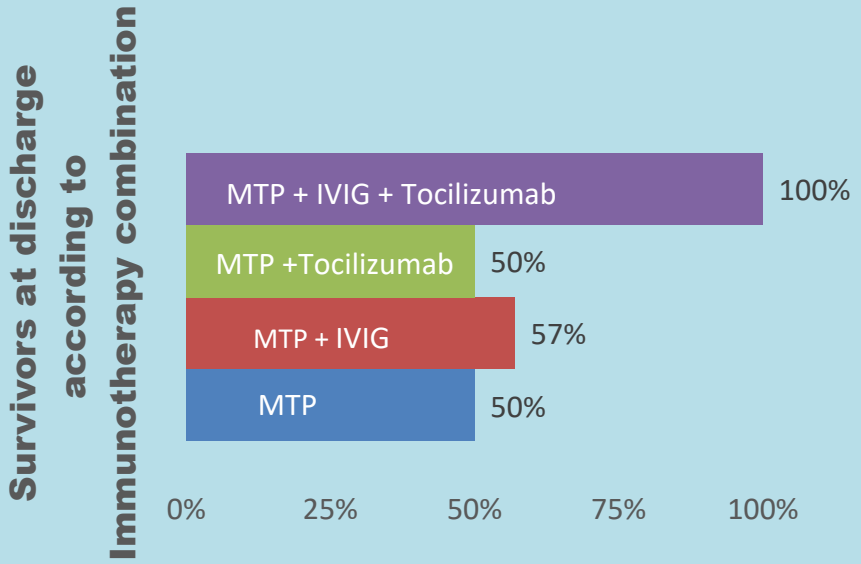
Clinical, paraclinical, treatment and outcome

23 with high risk ANE-SS
22 with brainstem lesion

All received immunotherapy (20 within 48hrs of admission)
MTP only 2; MTP+IVIG 14;
MTP+Tocilizumab 4; MTP+IVIG+Tocilizumab 7

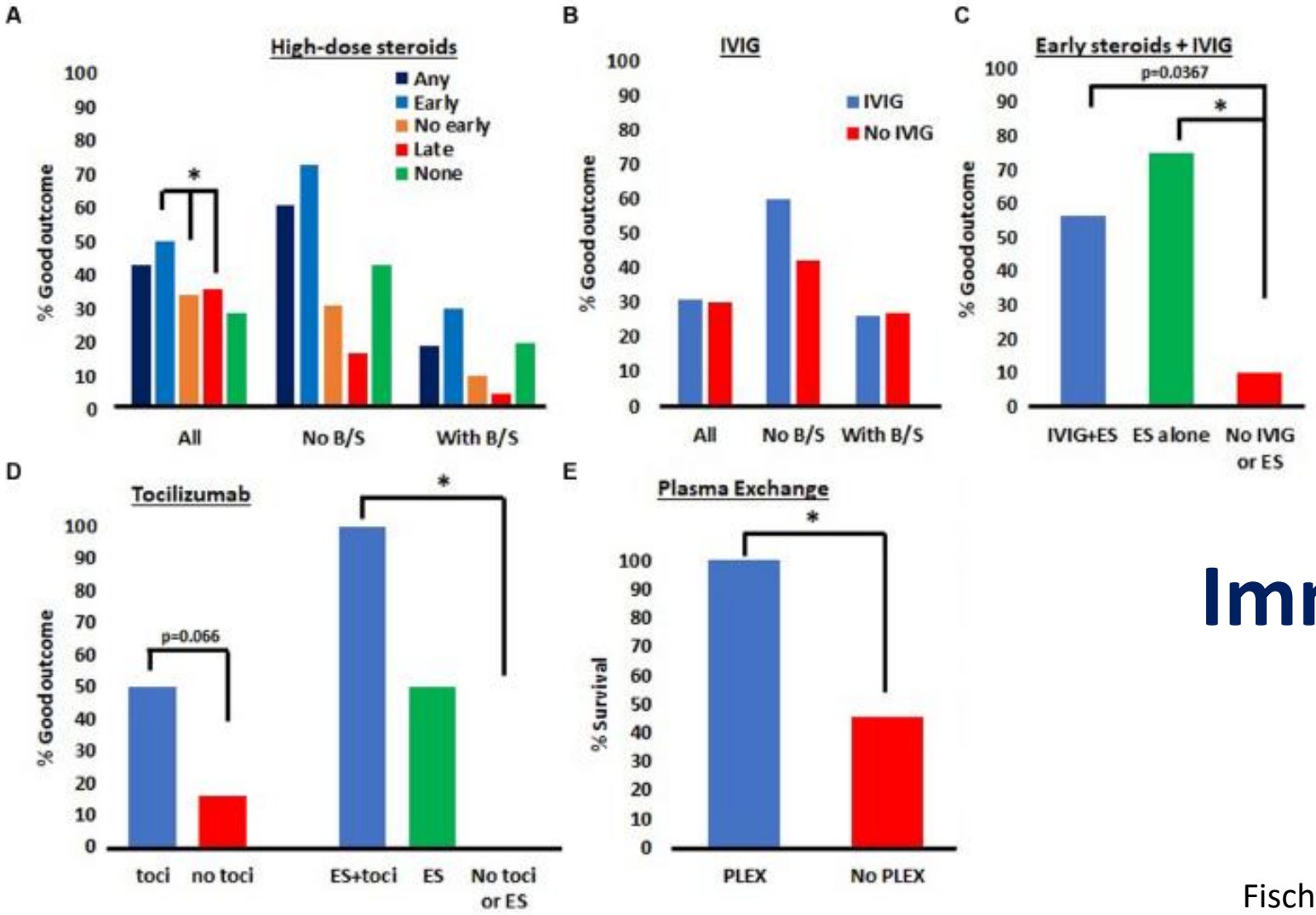
At discharge:
9 died
1 with mRS ≤ 2





CONCLUSION

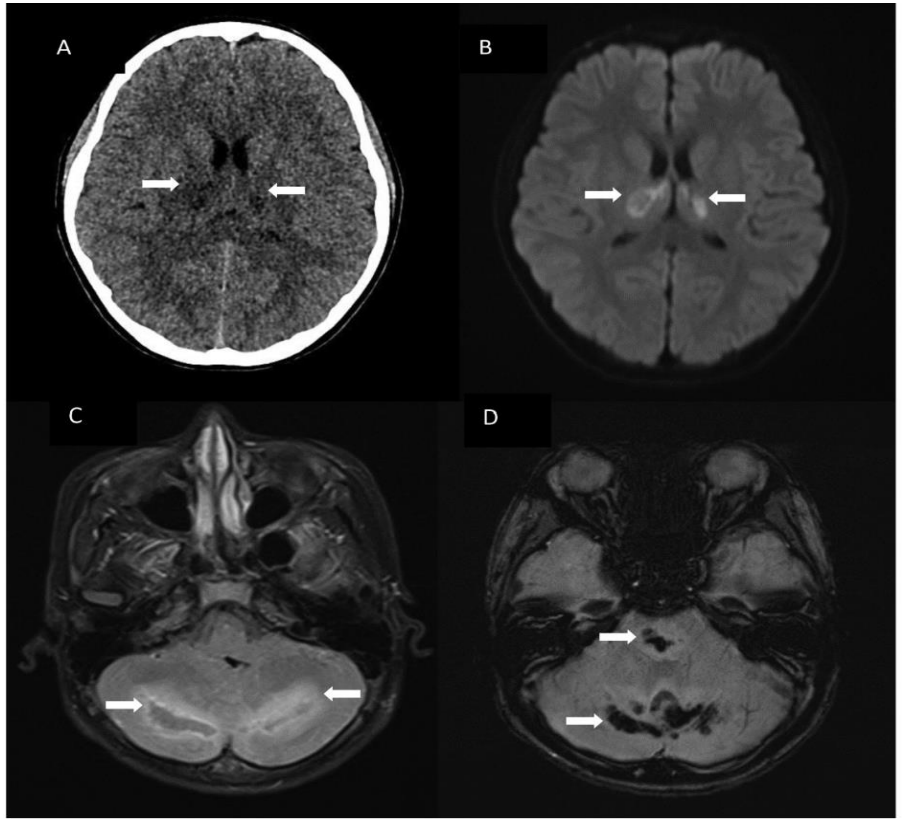
Children who received tocilizumab in combination with methylprednisolone and IVIG showed a trend towards better survival



Immunotherapy in ANEC

Fischell et al., 2023 ***Front. Neurol***. 14:1239746

Early administration of tocilizumab and methylprednisolon is associated with improved neurological outcomes in Acute Necrotizing Encephalopathy of childhood: an international observational study of 63 children



Courtesy of Velda Han and Terrence Thomas

Under review

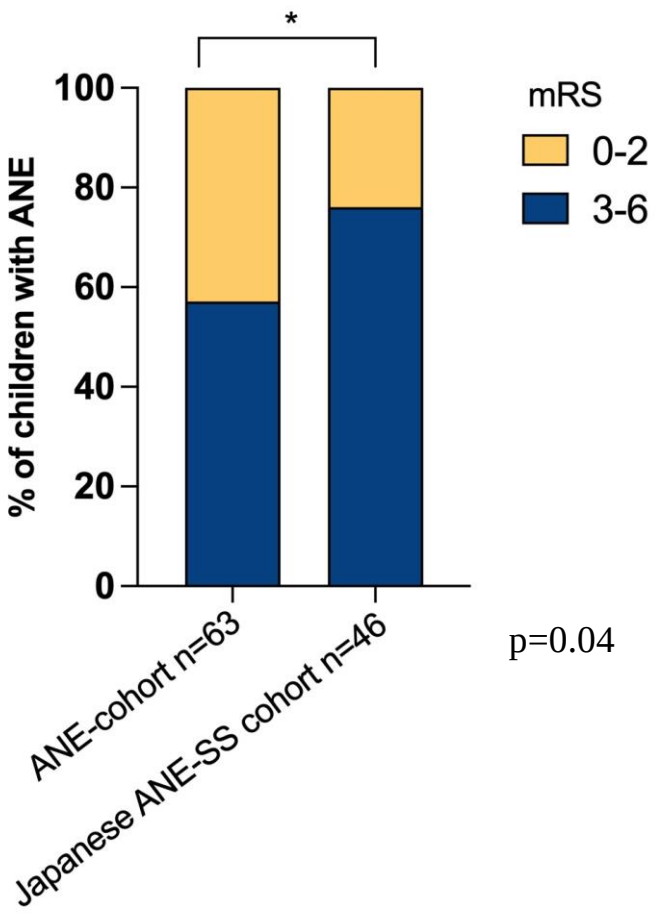
Does the *addition of tocilizumab* improve neurological outcomes in children with ANE compared to conventional treatments ?

	ANE cohort n=63 (%)	Japanese ANE-SS cohort n=46 (%)
Median Age (IQR)	6 (IQR 3.45, 8)	2.2 (IQR 1.3, 3.4)
Immunotherapy	63 (100)	33 (71.7)
Tocilizumab	63 (100)	0
Steroids	63 (100)	31 (67.4)
IVIg	32 (50.8)	17 (37.0)
Plasma exchange	0	5 (10.9)
ANE-SS score ≥ 5	47 (74.6%)	17 (37%)

ANE-severity score (ANE-SS)
3 - shock
2 - brain stem lesions
2 - age > 48 months
1 - platelet <100,000/ul
1 - CSF protein > 60mg/ml

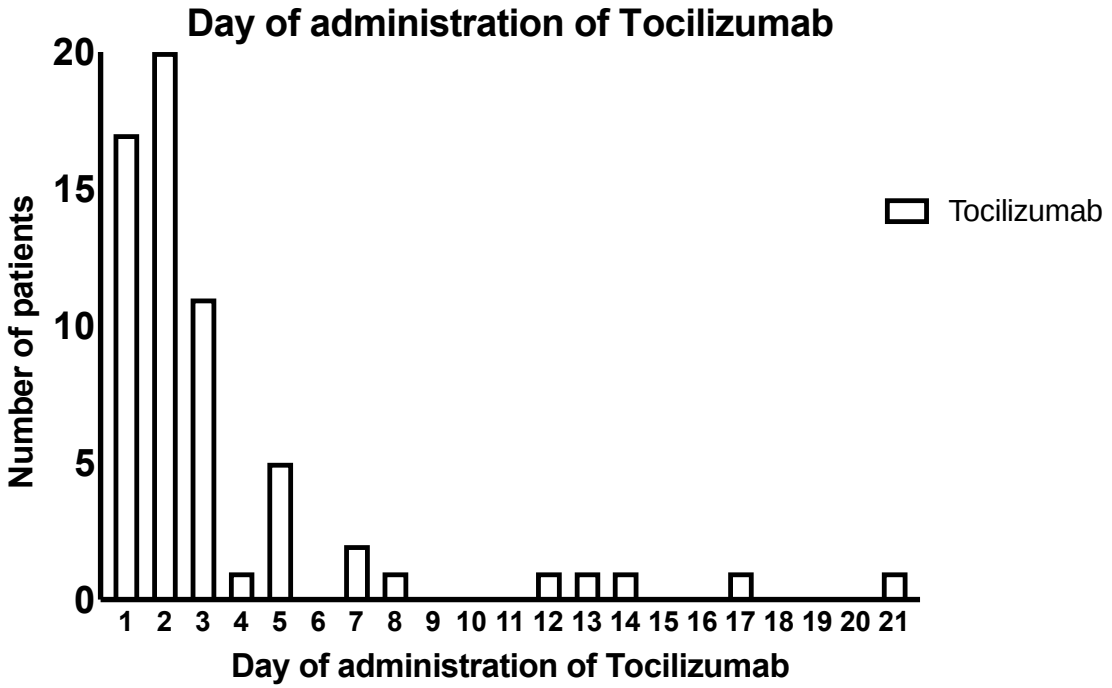
0-1 low risk
2-4 medium risk
≥ 5 high risk

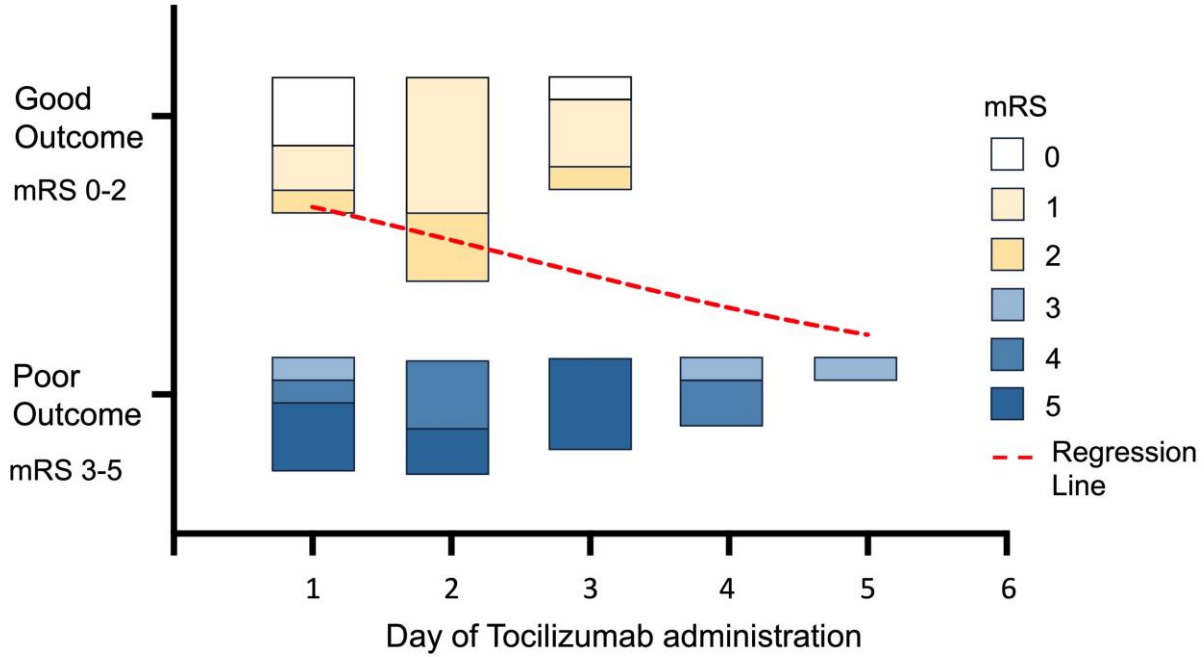
Comparing additional tocilizumab treatment versus conventional treatment in children with ANE



Courtesy of Velda Han and Terrence Thomas

Does *timing of tocilizumab* influence neurological outcomes in ANE?





Logistic regression model (n=38)

cut-off time of ***2.4 days*** for tocilizumab administration to achieve a good outcome (mRS 0-2).

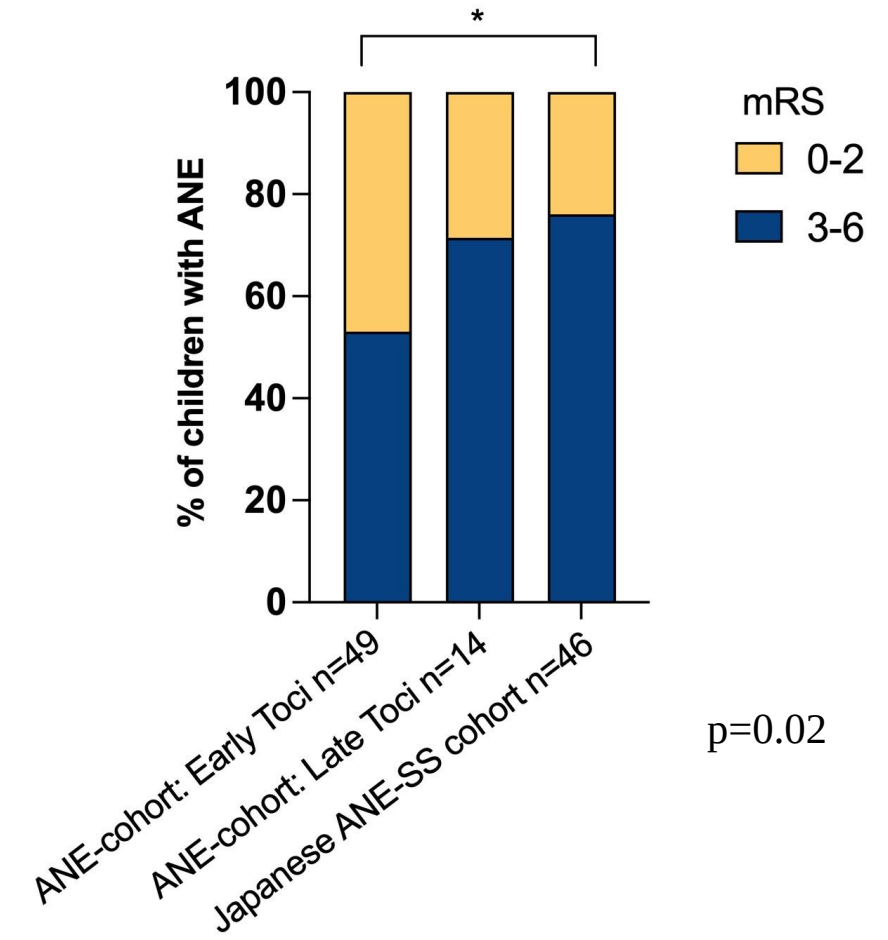
Courtesy of Velda Han and Terrence Thomas

Does *timing of tocilizumab* influence neurological outcomes in ANE?

ANE cohort
n=63 received tocilizumab

Early tocilizumab **< 72 hours** from onset of encephalopathy	Late tocilizumab **> 72 hours** from onset of encephalopathy
n = 49	n = 14

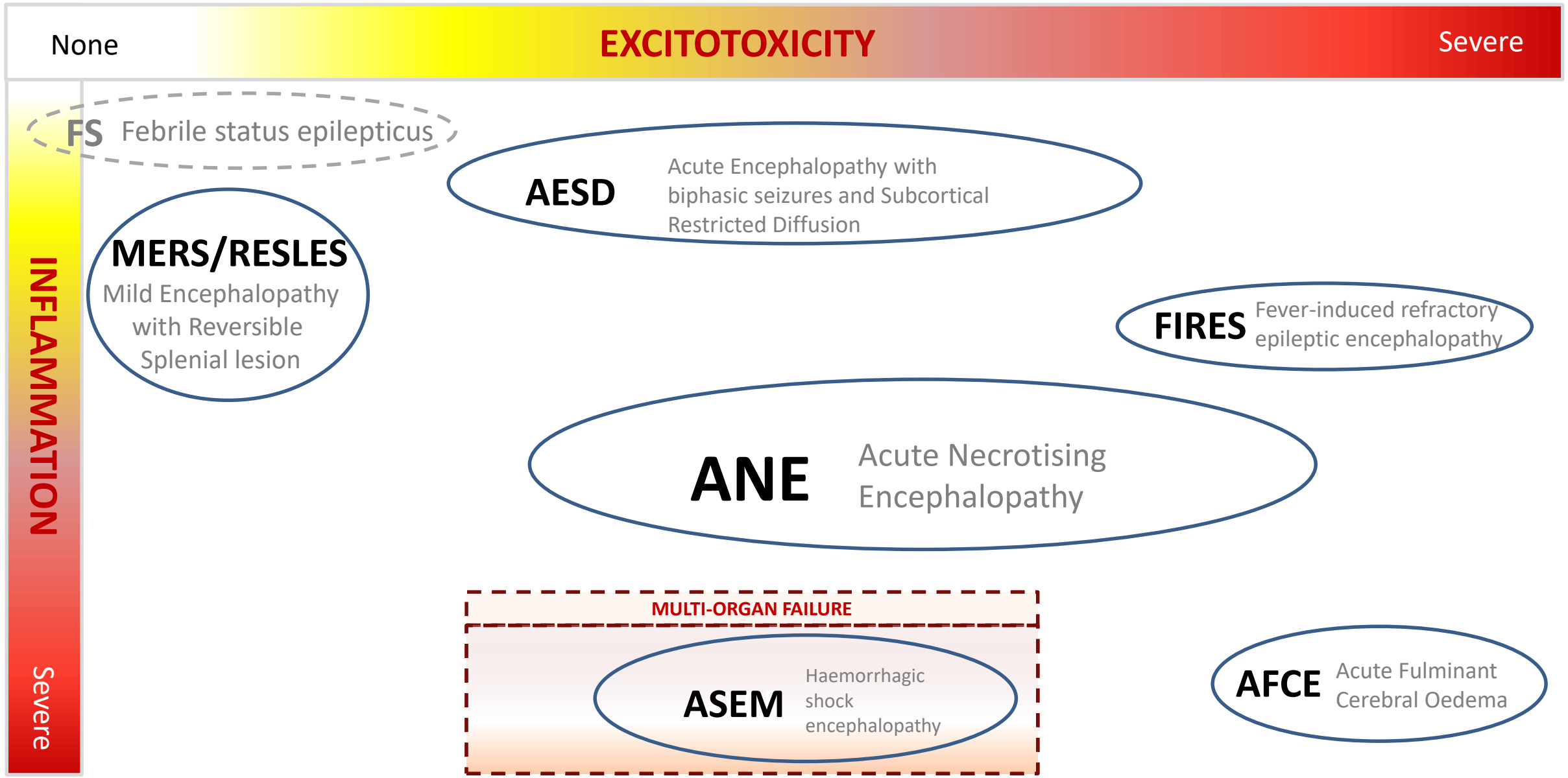
Comparison of additional early vs late tocilizumab treatment compared to conventional treatment in ANE



p=0.02

Courtesy of Velda Han and Terrence Thomas

Infection triggered encephalopathy A severity spectrum



Conclusion

- Infection (predominantly virus but not exclusively) can trigger a range of neurological syndromes
- Establishing international management consensus would be next step forward
- Treating inflammation quickly and optimally is only one determinant of improved outcome
- Excitotoxicity and systemic (with secondary CNS) inflammation appears to be key mechanisms driving pathobiology and we really need to evaluate this

Brain and Spine Inflammation

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