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Long-term Neuropsychological Outcomes in Children with Febrile Infection-Related Epilepsy Syndrome (FIRES) Treated with Anakinra

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Background

- Febrile-infection related epilepsy syndrome (FIRES) is a rare epilepsy syndrome in which a previously healthy individual develops refractory status epilepticus with a preceding febrile illness starting 24 hours to 2 weeks before seizure onset.
- Of patients who survive the acute phase, nearly all have ongoing drug-resistant epilepsy without return to prior baseline function.
- Etiology is often unknown, though some cases may be due to an abnormal immune response.
- Anakinra, an IL-1 receptor antagonist, is an emerging treatment that has been shown to reduce seizures in the acute phase.
- There is limited data on long-term neurocognitive outcomes in FIRES patients.
- No prior studies describe long-term cognitive outcomes in FIRES patients treated with anakinra.

Methods

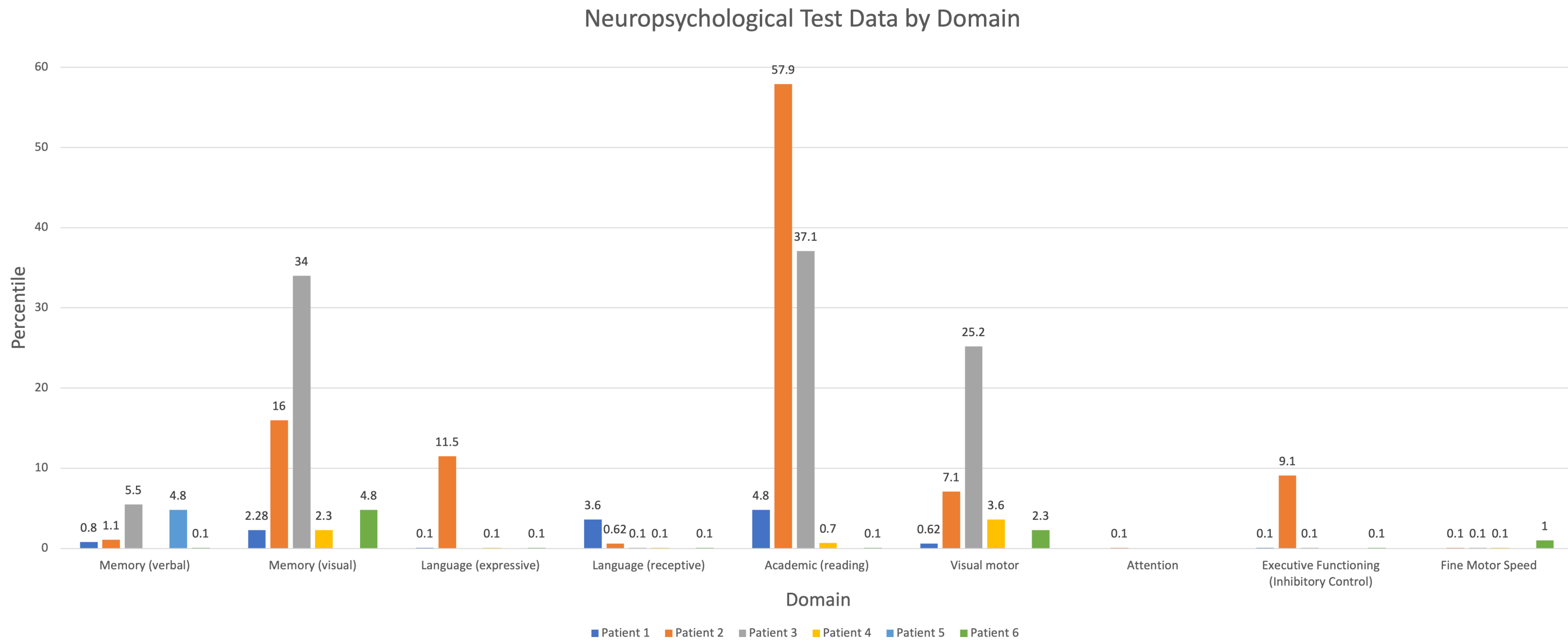
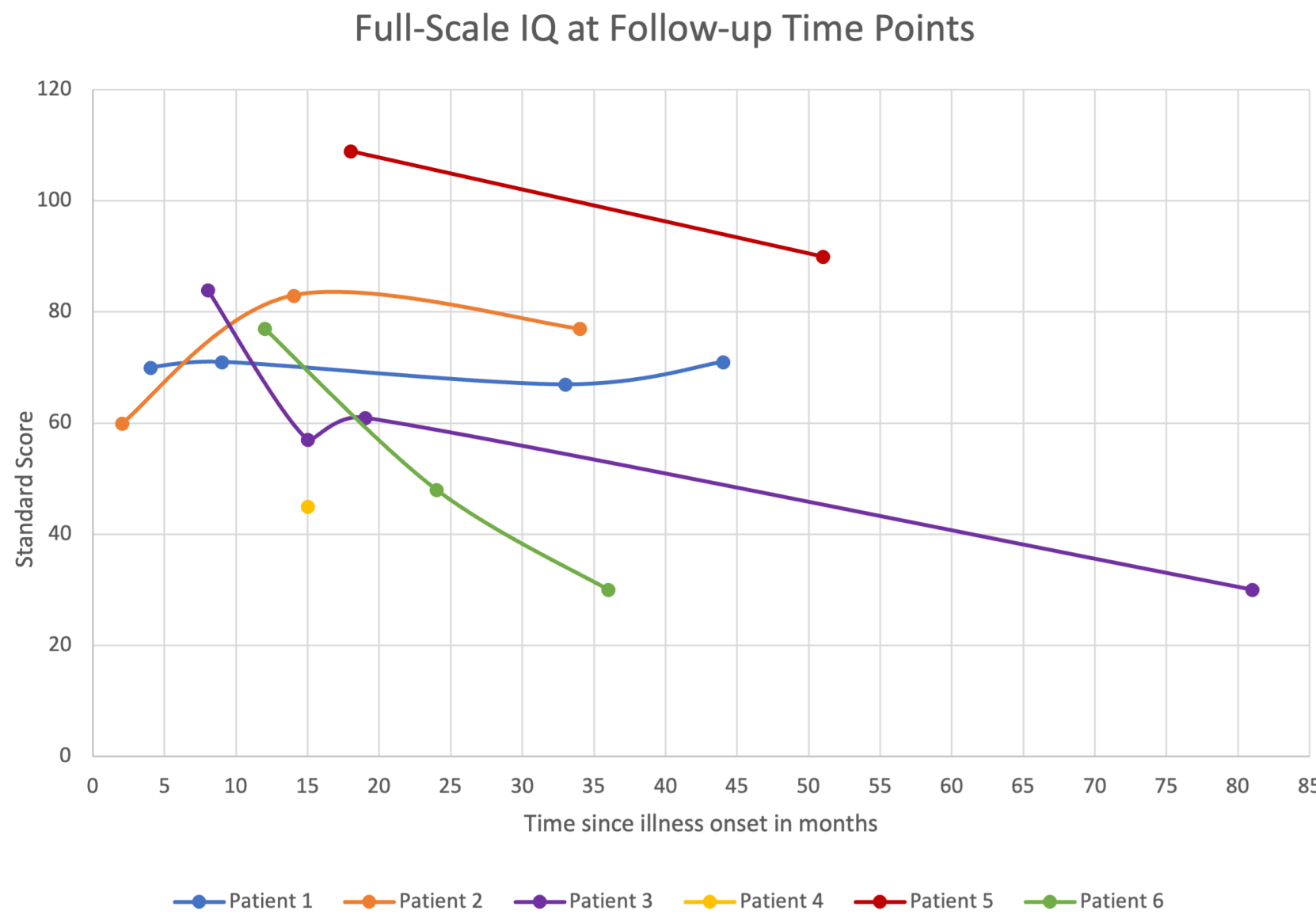
- Multicenter retrospective case series of 6 pediatric FIRES patients treated with anakinra who had neuropsychological testing ≥ 1 year after refractory status epilepticus onset.
- Neuropsychological testing completed as part of routine clinical care across 3 academic medical centers.

Results

- No patients returned to baseline after onset of FIRES, with PCPC scores ranging from moderate to severe disability.
- Patient 5 demonstrated average IQ scores; all others demonstrated low average to extremely low IQs.
- Patients demonstrated a diffuse pattern of deficits across domains at last follow-up.

Patient #	PCPC at admission	PCPC at discharge	PCPC at last follow-up	Return to neurocognitive baseline	Ambulation	Return of speech	Return to school	Additional academic supports
1	1	3	3	No	Independent	Yes	Yes	Medical day program followed by IEP, special education classes
2	1	4	3	No	Independent	Yes	Yes	Medical day treatment program
3	1	4	4	No	Independent	Yes	Yes	Homebound tutor
4	1	4	4	No	Independent	Yes	Yes	Special education classes, IEP
5	1	3	3	No	Independent	Yes	No	Special education classes
6	1	3	3	No	Independent	Yes	Yes	1:1 paraprofessional or tutor

PCPC, Pediatric Cerebral Performance Category; IEP, individualized education plan.



Conclusions

- Neuropsychological testing suggests global decline in functioning.
- Youngest patients at FIRES onset had 2nd and 3rd largest declines in IQ, consistent with studies showing poorer cognitive outcomes associated with younger age at onset.
- One patient had improvement in IQ over time, suggesting that recovery of neurocognitive function can occur.
- Cognitive impairments may have multifactorial causes, including seizure location (temporal and frontal lobes), use of multiple high-dose antiseizure medications in the acute and chronic phase of FIRES, and underlying etiology when identified.

Implications

- Recommend standardized long-term serial neuropsychological assessments for all FIRES patients.
- Multidisciplinary teams including neurologists, rehabilitation, neuropsychology, and mental health providers can support maximal neurocognitive recovery.

References

Bourgeois BFD. Determining the effects of antiepileptic drugs on cognitive function in pediatric patients with epilepsy. *J Child Neurol.* (2004) 19:S15–24. doi: 10.1177/088307380401900103
Brandt C, Lahr D, May TW. Cognitive adverse events of topiramate in patients with epilepsy and intellectual disability. *Epilepsy and Behavior.* (2015) 45:261–4. doi: 10.1016/j.yebeh.2014.12.043
Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures—Effects on intelligence and seizure recurrence. *N Engl J Med.* (1990) 322:364–9. doi: 10.1056/NEJM199002083220604
Nabbout R, Vezzani A, Dulac O, Chiron C. Personal view acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol.* (2011) 10:99–108. doi: 10.1016/S1474-4422(10)70214-3
Vasquez A, Farias-Moeller R, Sánchez-Fernández I, Abend NS, Amengual-Gual M, Anderson A, et al. Super-refractory status epilepticus in children: a retrospective cohort study. *Pediatric Critical Care Medicine.* (2021) 22:E613–25. doi: 10.1097/PCCM.00000000000002786