In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 09-293V

Filed: May 22, 2015

[TO BE PUBLISHED]

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RACHEL MCCULLOCH *as parent and legal guardian of* A.M., Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Ruling on Entitlement; Human Papillomavirus Vaccine; Autoimmune Limbic Encephalitis; Intractable Epilepsy; Aquaporin-4; Developmental Delay; FIRES; Molecular Mimicry
* *		

Christina Ciampolillo, Sylvia Chin-Caplan and Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for petitioner.

Debra A. Filteau Begley, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Gowen, Special Master:

On May 11, 2009, Rachel McCulloch ("petitioner") filed a petition on behalf of her minor daughter ("A.M." or "minor child") for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 – 34 (2006)[2] (the "Vaccine Act" or "the Program"). Petitioner alleged that as a result of receiving a Human Papillomavirus vaccine ("HPV" or "Gardasil") on August 16, 2007, her minor child developed a severe neurological injury. On

[1] Because this published ruling contains a reasoned explanation for the action in this case, I intend to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to delete medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2006).

December 7, 2009, petitioner filed an Amended Petition alleging that the HPV vaccine caused the minor child to develop encephalitis, intractable epilepsy, and subsequent developmental delays. (Amended Petition at Preamble).

The Vaccine Act provides that a special master may not make a finding awarding compensation based on the claims of a petitioner alone, unsubstantiated by medical records or medical opinion. *See* § 13(a)(1). Petitioner has proffered both medical records and expert medical opinions providing a theory of a causal link between A.M.'s HPV vaccination and her injuries. Respondent has countered with an expert medical opinion. Both parties submitted extensive medical literature. [3]

Petitioner contended that A.M.'s diagnosis was seizures caused by autoimmune encephalitis (ALE). Respondent countered that the evidence was only sufficient to establish the more general diagnosis of febrile infection related epilepsy syndrome (FIRES). Petitioner also asserted that cross reactivity caused by molecular mimicry between the viral particles in Gardasil and the aquaporin 4 water channels in the temporal lobe and particularly the hippocampus damaged the aquaporin 4 water channels and thereby disrupted the osmotic homeostasis in this area of the brain causing a hyperexcitable state and severe seizures.

For the reasons stated herein, I find that petitioner has provide sufficient evidence to demonstrate that A.M. had ALE and that the molecular mimicry between the vaccine and the aquaporin 4 water channels caused hyperexcitability in the temporal lobe and severe seizures. Accordingly, I have concluded that petitioner is entitled to compensation.

I. Procedural History

This case was filed on May 11, 2009, and assigned to then-Chief Special Master Golkiewicz. In the ensuing eight months following the filing of the petition, petitioner filed extensive medical records detailing A.M.'s diagnosis and treatment of "encephalitis of unknown origin." See Pet. Ex. 1-20, 23. On December 30, 2009, petitioner filed a status report informing the court that all medical records necessary to substantiate the petition have been filed.

Petitioner filed an Amended Petition on December 7, 2009 alleging that the HPV vaccine caused petitioner to develop encephalitis, intractable epilepsy, and developmental delay. (Amended Petition at Preamble). On March 9, 2010, respondent filed her Rule 4(c) Report against compensation under the Vaccine Act asserting, petitioner had not produced any medical or scientific explanation of her claim sufficient to establish causation. Res. Rep. at 10-11. Respondent further argued that none of A.M.'s treating physicians linked her condition to the HPV vaccination. Id. Accordingly, on April 8, 2010, petitioner was ordered to file an expert report addressing the *Althen*[4] criteria.

[3] I have considered the entire record in arriving at my decision (§ 300aa–13(a)(1)). This includes extensive medical literature submitted by both parties which I have read and considered. I will discuss in the course of this opinion the exhibits that are most relevant to the resolution of this case.

[4] *Althen v. Sec'y of HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Petitioner filed a motion to stay the proceedings on September 7, 2010. In support of her motion, petitioner argued that then-current medical literature and scientific evidence did not adequately address the safety of the HPV vaccine, and that additional time was therefore needed "to allow the science surrounding the [HPV vaccine] to develop." Pet. Mot. To Stay Proceedings at 8. On October 7, 2010, respondent filed a response to petitioner's motion arguing against an indefinite stay of the proceedings—stating that there was no legal basis under the Vaccine Act for such a request. Resp. Response at 4 (citing *Hennessey v. Sec'y of HHS*, 2009 WL 1709053 at *5 n.21 (Fed. Cl. Spec. Mstr. May 29, 2009), *aff'd*, 91 Fed. Cl. 126 (2010), which held that "the Vaccine Act contains no express or implied 'right' to [indefinitely] park a [] claim . . . in which no expert is presently prepared to opine in favor of vaccine causation . . . ."). Respondent further argued that the reports and literature petitioner relied on in support of her motion do not demonstrate that scientific evidence will develop to causally link the HPV vaccine to any of A.M.'s conditions. Id. at 6-10.

After holding a status conference to discuss petitioner's motion to stay, Special Master Golkiewicz denied petitioner's motion on November 23, 2010. Petitioner was granted ninety days to file an expert report. Petitioner subsequently filed an expert report from Dr. Svetlana Blitshteyn along with several exhibits of medical literature in support of the opinion on February 22, 2011. See Pet. Ex. 25-26.

The case was reassigned to Special Master Zane on March 16, 2011. Thereafter, respondent filed a responsive expert report along with medical literature from Dr. John Sladky on April 22, 2011. See Resp. Exs. A-G. A status conference was held on June 1, 2011 and petitioner was ordered to file a supplemental expert report addressing several issues with Dr. Blitshteyn's initial report. Respondent was also ordered to file a responsive supplemental expert report within sixty days from the filing of petitioner's supplemental expert report.

Petitioner filed a supplemental expert report from Dr. Blitshteyn on August 16, 2011. See Pet. Ex. 27. Respondent filed a supplemental amended expert report from Dr. Arun Venkatesan on November 21, 2011. See Resp. Ex. H. Petitioner was then ordered to file another supplemental expert report in response to respondent's expert report, or file a status report if she determined an additional report was not needed.

Petitioner filed a supplemental report from Dr. Lawrence Steinman on October 10, 2012. See Pet. Ex. 34. Respondent filed a responsive supplemental expert report from Dr. Venkatesan on March 25, 2013. See Resp. Exs. Q-R.

After the parties indicated a willingness to engage in settlement discussions, Special Master Zane ordered the filing of periodic status reports on the progress of settlement beginning on July 15, 2013. In addition, a two-day entitlement hearing was scheduled for April 10, and 11, 2014. After several months of settlement discussions, the parties filed a joint status report on December 20, 2013 stating settlement was not feasible.

Chief Special Master Vowell was assigned this case on September 6, 2013. Thereafter the undersigned was assigned to this case on March 4, 2014. The parties filed their respective pre-

hearing briefs on March 14, 2014 and an entitlement hearing was held before the undersigned on April 10, and 11, 2014.

On May 22, 2014, a post-hearing status conference was held. The undersigned ordered the parties to file, in addition to post-hearing briefs on the matter, a joint stipulation of facts not in dispute. The parties filed the joint stipulation on September 2, 2014. On December 16, 2014, the parties filed their respective post-hearing briefs, thus making this case ripe for a decision on entitlement. The Special Master has accepted the stipulation of facts prepared by the parties as follows:

II. Evidentiary Record

Petitioner's minor daughter, A.M., was born on October 8, 1994. Pet. Ex. 1 at 5. At twelve years old, on June 8, 2007, she received the first of three HPV vaccinations, as well as meningococcal and varicella vaccines. Pet. Ex. 10 at 1. On August 16, 2007, A.M. received her second dose of the HPV vaccine. Id.

Approximately five weeks later, on September 22, 2007, A.M. presented to the emergency room with "a one day history of fever . . . a sore throat and right sided neck pain." Pet. Ex. 1 at 125-26. A.M.'s temperature was noted to be 102.1° F. The emergency room physician diagnosed "viral pharyngitis . . . [and] [r]ight cervical adenopathy most likely due to viral etiology." Id. at 126. A throat culture was negative for Group A Streptococcus. Id. A.M. was discharged later that day. Id.

A.M.'s symptoms persisted for several days after the initial emergency room visit. On September 26, 2007, her pediatrician noted a sore throat for the previous four days, as well as a stiff back and shoulders, swollen lymph nodes on both sides of her neck, and a headache. Id. at 14-16. Additionally, A.M. continued to suffer from a fever of 100.9° F. Id. Petitioner reported that her daughter's fever persisted over the previous four days, reaching as high as 102° F. Id. at 14-16. A.M.'s pediatrician, Dr. Ashu, assessed a viral infection and pharyngitis. Id. at 14-16. A throat culture performed during that visit was positive for Group A Streptococcus infection. Id. at 123-24.

On September 27, 2007, petitioner witnessed A.M. having a tonic clonic seizure. Pet. Ex. 11 at 18. When paramedics arrived, petitioner reported that A.M. had been sick over the previous five days with a persistent fever. Id. The paramedics arrived to observe A.M. in a postictal state with drooling and some convulsions. Id. The paramedics noted that A.M. began seizing enroute to the hospital and upon arrival, and that she continued to seize for five minutes once at the hospital. Id.; Pet. Ex. 7 at 22. A.M.'s temperature was recorded as 100.6° F at the emergency room. Pet. Ex. 7 at 17.

A brain CT showed "no acute disease," and a cerebral spinal fluid (CSF) analysis showed no white blood cells, no growth, no organisms, and protein within normal limits. Id. at 18, 37; Pet. Ex. 24 at 109, 283. A blood chemistry test revealed elevated AST and ALT, as well as abnormal glucose, calcium and salicylate levels. Pet. Ex. 7 at 33. A.M. was taken by helicopter to Miami Children's Hospital ("MCH") for continued care.

Upon arrival at MCH, A.M. was "[c]hemically paralyzed and sedated, unarousable to painful stimuli[,]" intubated and ventilated. Pet. Ex. 4 at 478. Her temperature was recorded at 102.2° F. Id. A September 28, 2007 EEG was abnormal—showing "diffusely slow activity for [her] age, [and] diffuse cerebral dysfunction, without focality." Id. at 266. An MRI of her brain showed no intracranial pathology; although, the study was limited due to her dental braces. Id. at 422. A.M. was treated unsuccessfully with medications to control the seizure activity.

On September 29, 2007, after being extubated, A.M. continued to experience seizure activity with facial twitching. Id. at 483-85. The neurology assessment on that day noted a febrile illness, new onset of seizures, and elevated AST and ALT. Pet. Ex. 18 at 62. A.M.'s treating physicians suspected encephalitis. Id. at 62-63. An October 1, 2007 EEG was "very abnormal," showing an awake (but sedated) state, diffusely slow background, and diffuse cerebral dysfunction, without focality. Id. at 189. The EEG findings were consistent with encephalopathy. Id.

Despite several different anti-seizure medications and an increase in her Versed[5] drip dosage, A.M. continued to have seizures with facial twitching and tonic-clonic movements. Pet. Ex. 18 at 75. A.M. began intravenous immunoglobulin (IVIG) treatments on October 2, 2007. Id. at 85. Also on that day, A.M. began multi-day video EEG monitoring. Pet. Ex. 4 at 266. The EEG findings showed persistent clinical and subclinical seizure activity and "diffuse cerebral dysfunction and bilateral epileptogenicity having emphasis in the left fronto-central region." Id. A brain CT was unremarkable. Id. at 267.

On October 3, 2007, A.M. was placed in a chemically induced coma due to continued seizure activity. Id. at 491-92. The next day, A.M. was assessed with "status epilepticus likely from infectious etiologies;" although her treating physicians did not rule out other causes. Pet. Ex. 18 at 7. On October 6, 2007, A.M. was noted to be suffering from "encephalitis of unknown cause[.]" Id. at 97. A brain MRI performed on October 10, 2007, while A.M. remained in the chemically induced coma, revealed "no gross abnormality." Pet. Ex. 4 at 267. A.M. continued to undergo testing while sedated from October 11 to 29, 2007. A.M.'s treating physicians opined over the course of her sedation that A.M. suffered a seizure disorder of unknown etiology with encephalitis of unknown cause—most likely viral encephalitis. See Pet. Ex. 18 at 126, 131, 263, 275. A.M.'s seizures were classified as status epilepticus. Id. at 275.

On October 31, 2007, A.M. was weaned from sedation and continued to experience multiple clinical seizures. Pet. Ex. 4 at 692; Pet. Ex. 18 at 302. A CT scan of the brain on November 2, 2007 showed "stable mild atrophy of the cerebral hemisphere." Pet. Ex. 4 at 267; see also id. at 267 (also noting "mild cerebral atrophy"). An MRI of the brain performed on November 8, 2007 showed areas of (possible) cortical dysplasia – associated with hippocampal sclerosis or seizure edema, central and cortical atrophic changes, and an area of high signal abnormality in the left parietal region – "likely representing an artifact." Id. at 267. These findings were consistent with another brain MRI performed on November 14, 2007. Id. A.M. began receiving IV steroid treatments on November 8, 2007. Pet. Ex. 18 at 380-81.

[5] "Trademark for a preparation of Midazolam." Dorland's Illustrated Medical Dictionary 2050 (32d ed. 2012) [hereinafter, "Dorland's"].

On November 19, 2007, A.M.'s pediatric neurologist, Dr. Sayed Naqvi, noted she was doing better neurologically, as reported by her nurse and mother. Pet. Ex. 18 at 507. Specifically, A.M. had last experienced a seizure on November 15, 2007 at which time she responded to her name, attempted to talk, and was able to speak a few words. Id. A neurological exam noted that A.M. was "alert, move[d] head to voice[s] – track[ed] with eyes . . . move[d] all extremities – minimally . . . [and] respond[ed] to tactile stimulus." Id.

Nonetheless, on November 25, 2007, petitioner reported that A.M. was exhibiting a "change in neurologic status as manifested by regression and abnormal movements [.]" Id. at 585. A CT scan showed "[s]table generalized central and cortical loss of volume but no acute pathology[.]" Pet. Ex. 4 at 470. Petitioner also reported that A.M.'s behavior was child-like and not age-appropriate, as it was prior to her illness. Pet. Ex. 18 at 588.

To aid in her recovery, A.M. received occupational, physical and speech therapies while hospitalized. See generally Pet. Ex. 4 at 608, 613. "Mild to moderate cognitive communication deficits and word finding deficits" were noted on December 6, 2007. Id. at 613. In addition, conversational speech was noted to be low and labored. Id. at 613. A.M. continued to experience clinical seizure activity and was disoriented to place and time. Pet. Ex. 18 at 694.

A.M. was discharged from MCH to Jackson Memorial Hospital for rehabilitation on December 14, 2007. Pet. Ex. 4 at 404-07. Her discharge summary stated that her mental status was not fully recovered and that her level of orientation fluctuated from day to day. Id. Her diagnoses upon discharge included status-post status epilepticus, seizure disorder, and status-post encephalitis (suspected). Id.

Because A.M.'s seizure activity increased while at Jackson Memorial Hospital, she was returned to MCH on December 18, 2007. Pet. Ex. 8 at 1, 6-8. Her medical records at MCH noted A.M. was impulsive and had difficulties with recent memory formation. Id. at 6-8. It was also noted that A.M. had three seizures over the previous twenty-four hours. Id. Her treating physicians noted that "[i]t was difficult to assess whether or not [her] cognition was partly due to her encephalopathy [or] her medication dosages." Id. at 8. An EEG performed on December 18, 2007 indicated diffuse cerebral dysfunction along with potentially epileptogenic dysfunction. Id. at 13-14.

A.M. did not experience clinical seizures from December 19 to 24, 2007. Pet. Ex. 4 at 270-72. However, she experienced clinical seizure activity on December 25, 2007. Id. A.M. was discharged from MCH on January 2, 2008 with a diagnosis of "epilepsy secondary to encephalitis," "probably secondary to sudden decrease in medication blood levels." Id. at 77.

A.M. was admitted to Baptist Children's Hospital for daily occupational, physical and speech therapies on January 2, 2008 and stayed until January 18, 2008. Pet. Ex. 5 at 10. She showed "steady slow progress in all areas" during rehabilitation. Id. Upon discharge, it was recommended that A.M. continue outpatient therapy, as her therapy efforts had become stagnant due to her lack of cooperation. Id. at 9-11. It was noted that A.M. continued to experience cognitive difficulties associated with increased processing time, decreased short-term memory, decreased attention, and some mild apathy—suggestive of frontal lobe dysfunction. Id.

The records reflect that as of January 22, 2008, A.M. continued to experience cognitive limitations, behavioral changes, and approximately two to three seizures per day. See Pet. Ex. 1 at 20-23; Pet. Ex. 2 at 43. A.M. was medicated with Keppra, Dilantin, Phenobarbital, Ativan, Prevacid, Diastat, Acudial, and Lovenox. Pet. Ex. 1 at 20-23.

On February 13, 2008, A.M. was transported to the emergency room and later admitted to the hospital for breakthrough seizures. Pet. Ex. 6 at 343-45. The examining physician believed A.M.'s illness was most likely a viral infection that lowered her seizure threshold, resulting in increased seizure frequency. Id. at 344. However, the physician further noted that "given the presentation and the recurrent multiple seizures that are back to back without a return to baseline, [he was] forced to call [her illness] status epilepticus . . . ." Id. A.M. was admitted for observation and discharged with the diagnosis of status epilepticus on February 15, 2008. Pet. Ex. 4 at 343, 367.

A.M. received her third HPV vaccine on February 21, 2008. Pet. Ex. 10 at 1. Later that day, she developed a fever and "brief generalized tonic-clonic seizure." Pet. Ex. 6 at 438-39. Her fever was noted to be 103.5° F on admission to the hospital. Id. at 438. She was discharged home on February 22, 2008. Id. at 449. Thereafter, A.M. was seizure free for six weeks, from February 2008 to early April 2008. Pet. Ex. 2 at 5, 9. Due to A.M.'s poor short-term memory and cognitive impairments, she was deemed medically unable to return to school. Pet. Ex. 9 at 78-79.

A.M. presented to the emergency room on September 14, 2008 after experiencing eight seizures. Pet. Ex. 6 at 117. Her temperature was noted to be 100.5° F. While admitted, A.M. underwent a psychiatric evaluation due to "suicidal ideation as well as verbal and physical aggressiveness towards her mother and grandmother . . . ." Pet. Ex. 3 at 494. A neuropsychological evaluation performed on September 24, 2008 revealed low average range of intellectual functioning and significant behavioral issues. Pet. Ex. 14 at 204-09.

On December 10, 2008, A.M. underwent brain surgery; specifically, a left fronto-temporal craniotomy, intraoperative electrocorticography, tailored left anterior temporal lobectomy and an amygdalohippocampectomy. Pet. Ex. 23 at 130-31. A biopsy of the anterior temporal lobe taken during the procedure showed mild, multifocal, neuronal disorganization "insufficient for Palmini Classification – Chaslin gliosis,[6] mild, multifocal – heterotopic neurons, subcortical white matter," no evidence of inflammatory or neoplastic process, and no definite evidence of cortical dysplasia.[7] Id. at 164. Her discharge summary on December 13, 2008 noted that an MRI of the brain showed bilateral hippocampal atrophy. Id. at 2. It was also noted that a work-up showed that her seizures were predominately left-sided in origin—especially in the medial structures—and that she had persistent post-operative seizures with a different etiology than before, but that her condition improved once prescribed anticonvulsants. Id. After her surgery, A.M. continued to experience three or four seizures weekly, typically occurring over a few days in a row. Pet. Ex. 17 at 18.

[6] Chaslin's gliosis is a type of gliosis (the proliferation or hypertrophy of several different types of supportive cells in the central nervous system) that is associated with status epilepticus. Tr. at 251.

[7] "Abnormality of development." Dorland's at 579.

Despite a vagal nerve stimulator implant on September 11, 2009 to control her seizure activity, A.M. continued to experience three to four seizures per week and exhibited a behavior disorder. Pet. Ex. 12 at 7-8; Pet. Ex. 29 at 78. A.M. was hospitalized intermittently throughout 2009 for continued seizure activity. Pet. Ex. 11 at 9; Pet. Ex. 3 at 16-18, 82, 319-20, 255-57; Pet. Ex. 6 at 58-59.

On August 5, 2011, A.M was hospitalized due to a three-day history of fever, increased seizure activity, altered mental status, and skin lesions on her forehead, thigh, and back. Pet. Ex. 37 at 162. It was suspected that A.M. suffered a herpes simplex infection, but she tested negative for the herpes simplex virus ("HSV"). Id. at 154-57, 161. A CSF test, and blood, urine, and wound cultures showed no growth of organisms and were also negative for HSV. Id. Nevertheless, A.M.'s infectious disease physician recommended a twenty-one day course of acyclovir to treat what appeared to be a clinical course of HSV. Id. at 244. A.M. experienced intermittent episodes of auditory and visual hallucinations and was diagnosed with a second episode of encephalitis. Id. at 161-63. She was discharged on August 26, 2011. Id.

A June 2013 psychological evaluation revealed profoundly impaired intellectual ability, with 99.99% of others her age performing better—a drastic change since her 2008 evaluation. Pet. Ex. 41 at 1-2. A.M.'s intellectual disability is consistent with individuals who have had severe traumatic brain injury. Id.

Testing for possible autoimmune epilepsy was completed in October 2013 and revealed negative results. Pet. Ex. 42 at 285, 475-77. A.M. is currently under the continued care of her physicians. Pet. Ex. 38 at 3-4, 25-31.

III. Discussion

A. Legal Standards to Establish Entitlement to Compensation

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of HHS*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

In order to prevail under the Program, a petitioner must prove either a "Table" injury[8] or that a vaccine listed in the Table was the cause in fact of an injury (an "off-Table" injury). Petitioner alleges A.M. suffered non-Table injuries, autoimmune encephalitis and an intractable seizure disorder. Therefore, petitioner must demonstrate by preponderant evidence that a covered vaccine is responsible for A.M.'s injuries.

[8] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

An "off-Table" injury is initially established when the petitioner demonstrates, by a preponderance of the evidence: (1) that she received a vaccine set forth on the Vaccine Injury Table; (2) that she received the vaccine in the United States; (3) that she sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) that the condition has persisted for more than six months. § 13(a)(1)(A). To satisfy her burden of proving causation in fact, petitioner must establish each of the three *Althen* factors by preponderant evidence: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y of HHS,* 418 F.3d 1274, 1278 (Fed. Cir. 2005); see *de Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y of HHS,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See *Moberly v. Sec'y of HHS,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of HHS*, 931 F.2d 867, 873 (Fed. Cir. 1991).

The Federal Circuit in *Althen* noted that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen*, 418 F.3d at 1280 (quoting *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1325 (Fed. Cir. 2006)) (emphasis added).

Once petitioner establishes each of the *Althen* factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." *Deribeaux v. Sec'y of HHS,* 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280.

In determining whether petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. 'Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act , where such evidence is submitted , the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury….Medical literature and epidemiological evidence must be viewed, however, not through

the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of HHS*, 569 F.3d 1367, 1380 (Fed. Cir. 2009).

B. Parties' Contentions Regarding Entitlement

There is no dispute that petitioner received a covered vaccine administered in the United States. It is also clear from the medical records that approximately five weeks after receiving a second dose of the HPV vaccine on September 22, 2007, A.M. developed a persistent fever over the course of five days and experienced tonic-clonic seizures on September 27, 2007. The medical records further reveal that A.M. developed a severe seizure disorder diagnosed as intractable epilepsy, status epilepticus and encephalitis, and that she has undergone treatment for her condition for longer than six months. Therefore, the issues left to resolve are the diagnostic category of her illness and whether the HPV vaccine was the cause-in-fact of petitioner's encephalitis, intractable epilepsy, and subsequent cognitive impairments.

The hearing testimony was presented by two experts for the petitioner, Dr. Svetlana Blitshteyn and Dr. Lawrence Steinman; and one expert for the respondent, Dr. Arun Venkatesan. All experts came to the court with excellent credentials to address the issues in this case. Dr. Steinman was particularly well qualified in the research on the interactions between the immune system and the central nervous system, while Dr. Venkatesan was exceptionally well qualified in the clinical diagnosis of encephalitis.

i. Petitioner's Experts' Credentials

1. Svetlana Blitshteyn, M.D.

Dr. Blitshteyn, as a clinical neurology expert, opined that A.M. developed autoimmune limbic encephalitis ("ALE") due to the HPV vaccine.

Dr. Blitshteyn is a board certified neurologist and assistant clinical professor of neurology at the State University of New York at Buffalo School of Medicine and Biomedical Sciences. Pet. Ex. 26. In this role, Dr. Blitshteyn educates medical students and residents about basic neurology principles and supervises their research projects. Id. In addition to teaching medical students and residents, Dr. Blitshteyn also has clinical responsibilities as the director and founder of Amherst Neurology Practice, where she treats adolescents and adults with neurological conditions. Id.

Dr. Blitshteyn has been published in numerous peer-reviewed journals and has ongoing editorial responsibilities as an ad hoc reviewer and contributing editor for several medical neurology journals, including the European Journal of Neurology. Id. Additionally, Dr. Blitshteyn has been invited to make numerous presentations to her colleagues in the field of neurology. Id. Dr. Blitshteyn earned her Bachelor of Science in Biochemistry at State University of New York at Buffalo, graduating as the valedictorian of her class. She received her M.D. from the State University of New York School of Medicine and Biomedical Sciences, where she also completed her internship year in Internal Medicine. Id. Subsequently, she completed her Neurology Residency at the Mayo Clinic, School of Graduate Medical Education. Id.; Tr. at 8.

2. Lawrence Steinman, M.D.

Dr. Steinman offered an opinion on three topics: (1) based upon A.M.'s medical records, he believes A.M.'s diagnosis is ALE, (2) a theory by which he proposed the August 16, 2007 HPV vaccine A.M. received could have caused an autoimmune response leading to her ALE, and (3) his explanation as to how the vaccine logically did cause the injury in this case.

Dr. Steinman is a board-certified neurologist and was the former Chair of the Stanford University Medical Center's interdepartmental program in neuro-immunology. Pet. Ex. 35; Tr. at 131. Dr. Steinman currently is the George A. Zimmerman Chair and Professor in Pediatrics, Neurology and Neurologic Sciences at Stanford University School of Medicine, where he has clinical and research responsibilities. Pet. Ex. 35. Dr. Steinman is a renowned researcher within the field of autoimmunity and whose National Institute of Health ("NIH") funded work has led to the grant of over thirty patents and numerous publications in respected medical journals. Id. Specifically, within vaccine research, Dr. Steinman has conducted research and published numerous medical articles on the mechanisms of vaccination triggered autoimmunity. Id. His ongoing research focuses on generating patents related to specific components of certain vaccines. Tr. at 133.

He also serves on editorial boards for prominent medical journals, including the International Immunology and Neurobiology of Disease. Id. For his notable work, he has won the Charcot Prize for lifetime achievement in multiple sclerosis research and was elected to the Institute of Medicine by the National Academy of Sciences in neurology. Id. Dr. Steinman graduated from Dartmouth College with a B.A. in Physics and received his M.D. at Harvard Medical School. Id. Thereafter, he completed an NIH Fellowship at Harvard Medical School. Id. Subsequently, Dr. Steinman completed his internship at Stanford University in surgery, pediatrics and neurology, and thereafter completed his post-doctoral fellowship in neuroimmunology at the Weizmann Institute of Science. Id.; Tr. at 131.

ii. Respondent's Expert's Credentials[9]

1. Arun Venkatesan, M.D.

Dr. Venkatesan offered opinions as to (1) whether or not A.M. suffered autoimmune limbic encephalitis or another illness known as Febrile Infection-Related Epilepsy Syndrome ("FIRES"), and (2) whether there is sufficiently reliable scientific evidence to support the petitioner's proffered molecular mimicry theory linking A.M.'s HPV vaccination to her seizure condition. He testified in favor of a FIRES diagnosis, and opined that there was insufficiently reliable medical evidence to support the petitioner's theory.

Dr. Venkatesan is an assistant professor in the Department of Neurology at Johns Hopkins University School of Medicine. Resp. Ex. S. He also serves as the director of the Johns Hopkins

[9] The respondent also filed an expert report from Dr. John T. Sladky, but did not present his testimony during the hearing and did not otherwise rely on his opinion. In light of Dr. Sladky's ethical issues noted in *Contreras v. Sec'y of HHS*, 116 Fed. Cl. 472 (2014), his opinion has been completely disregarded in the analysis of this case.

Encephalitis Center, and as the program director for the Johns Hopkins Neurology Residency Program. Id. He has been invited to serve on the professional advisory board of the Encephalitis Society, based in the United Kingdom, and on which he is the only non-British member. Tr. at 228.

Dr. Venkatesan has published his research in numerous prestigious journals and has been invited to write book chapters on various medical topics, including issues related to encephalitis. Id. Furthermore, he has been an ad hoc reviewer on several prestigious medical journals, including Brain, Journal of Neuroscience, and Journal of Neuroimmunology. Id.

Dr. Venkatesan received his B.S. in Bioengineering from the University of California, Berkeley and completed his Ph.D. in microbiology and immunology. He received a medical degree from the University of California, Los Angeles. Id. Thereafter he completed his internship year at the Santa Clara Valley County Medical Center and finished his neurology residency at Johns Hopkins Hospital. Id. At Johns Hopkins Hospital, he also completed a fellowship in neuroimmunology and neuroinfectious diseases. Id. He is on the faculty at Johns Hopkins in the Division of Neuroimmunology and Neuroinfectious Diseases. Tr. at 222.

iii. Overview of Dr. Blitshteyn's Diagnosis and Opinion on Causation

Dr. Blitshteyn opined, that A.M. suffered from autoimmune limbic encephalitis ("ALE") as a result of receiving the second of a three-shot series of the HPV vaccine. Pet. Ex. 25 at 4. She made that diagnosis based on (1) A.M.'s multiple EEGs, (2) her November 2007 MRI of the brain showing increased signal in the left temporal lobe, (3) the intractable epilepsy A.M. developed in the context of a febrile illness, (4) the December 2008 biopsy demonstrating neuronal disorganization and gliosis without inflammatory, neoplastic or cortical dysplasia, and (4) A.M.'s subsequent behavioral disorder.

According to Dr. Blitshteyn, ALE often presents with a prodromal viral-like illness and an acute amnestic syndrome[10] with seizures evolving over less than one week. Pet. Ex. 25 at 4. Patients with ALE usually have persistent cognitive impairment and seizures. Id. Dr. Blitshteyn cited literature which reported on a series of patients who experienced a prodromal illness before an amnesic syndrome in association with seizures that developed acutely. See Pet. Ex. 24A.[11] All of whom, had persistent cognitive impairment and seizures with normal cerebrospinal fluid ("CSF") counts and highly localized signal change on MRI in the hippocampus, thought to be due to seizure induced edema or gliosis. Id. at 392-93. These signs and symptoms, in the view of the authors, provided circumstantial evidence for an autoimmune process. Id. Dr. Blitshteyn noted the similarity of the presentations to A.M., in which there was a flu like prodrome with rapidly developing seizures, normal CSF, increased signal intensity in the left temporal lobe on the third MRI, gliosis, and persistent cognitive deficits and seizures. Tr. at 30-31.

[10] "Affected with or characterized by amnesia." Dorland's at 64.

[11] Samarasekera, Welch, Jackson, Course and Outcome of Acute Limbic Encephalitis with Negative Voltage-gated Potassium Channel Antibodies, J. of Neurology Neurosurgery Psychiatry, vol. 78, 391-94 (2007).

In this case, Dr. Blitshteyn opined that the temporal association between the onset of encephalitis and the administration of the second HPV vaccine "likely caused an overwhelming autoimmune response [in A.M.], resulting in the development of [ALE]." Pet. Ex. 25 at 5. Based on scientific literature on the occurrence of Acute Disseminated Encephalomyelitis ("ADEM")[12] in persons receiving an HPV vaccine, Dr. Blitshteyn noted that A.M. developed her condition in approximately the same timeframe—five weeks after the second "booster shot" of HPV—as the reported development of ADEM in other persons who have received an HPV vaccine. Id. Dr. Blitshteyn opined that since a booster shot is expected to generate a stronger immune-mediated response than the first injection, "it is not surprising" that A.M. developed encephalitis after receipt of the second HPV vaccine. Id.; Tr. at 26-28. According to Dr. Blitshteyn, this theory is further supported by the fact that A.M. developed a febrile illness and seizures after receipt of the third HPV vaccine on February 21, 2008. Tr. at 95-96.

Dr. Blitshteyn noted that the treating physicians did a very thorough job of ruling out other causes, including viral, fungal, bacterial, other infectious pathogens, genetic, metabolic, toxic, nutritional, congenital, and paraneoplastic (cancer) etiologies of A.M.'s condition—based on the diagnostic workups she received in 2007, documented in the medical records. Tr. at 29. The most likely etiology of A.M.'s encephalitis, according to Dr. Blitshteyn, is an autoimmune response in the limbic portion of her brain. Tr. at 26. More explicitly, Dr. Blitshteyn's opinion was that the HPV vaccine "likely resulted in [a] vaccination-induced autoimmune response and formation of [an] autoantibody cross-reaction with the neuronal components of the limbic system, thereby resulting in a vaccine-induced acute autoimmune limbic encephalitis." Pet. Ex. 25 at 6; see also Pet. Ex. 27 at 1; Tr. at 27. She testified that from what is known from other types of autoimmune limbic encephalitis, such as the voltage gated potassium channel antibody encephalitis, antibodies form against the voltage gated potassium channels in the cellular membranes which cause the normal electrical and water balance to be disturbed. When that occurs, she said, the neurons become hyperexcitable, secondary to this process and thereby result in seizures. Tr. at 26-27. She noted that seizures have been reported to occur in the wake of some vaccinations. Tr. at 27. In this case, she said that it was logical to expect a more pronounced autoimmune response after the second vaccination than the first, that the signs and symptoms were consistent with an autoimmune limbic encephalitis, that the timing was appropriate and that the mechanism of molecular mimicry would explain the syndrome. Tr. at 31.

iv. Respondent argues that a diagnosis must be determined before reaching a causation analysis under the *Althen* prongs.

Respondent argues that a threshold issue in this case is whether A.M. had ALE, as opined by her experts, or whether her diagnosis was more appropriately FIRES. Respondent argues that a determination of what afflicted A.M. is a prerequisite to a causation analysis consistent with *Broekelschen v. Sec'y of HHS,* 618 F.3d 1339, 1346 (Fed. Cir. 2010). Resp. Post hearing br. at 8.

[12] Acute Disseminated Encephalomyelitis is an acute or subacute encephalomyelitis or myelitis characterized by lymphocyte and mononuclear cell infiltration and demyelination. Dorland's at 613.

The undersigned does not agree that this case presents a *Broekelschen* issue because the injury being analyzed by all experts is the same. It is merely the diagnosis that differs, and the criteria for FIRES can readily include a presentation of ALE when the cause is unknown. But nevertheless, I will address the argument raised by the respondent. For the reasons discussed below, the undersigned finds that petitioner presented preponderant evidence to conclude that A.M. has ALE.

1. Overview of Autoimmune Limbic Encephalitis (ALE)

Limbic encephalitis (LE) is inflammation that predominantly occurs within the limbic system of the brain. Tr. at 11, 15, 353-54. The limbic system is the area of the brain that consists of several structures, mainly the hippocampus, limbic cortex, parts of the thalamus and various connections to the prefrontal cortex and parahippocampal gyrus. Tr. at 13-14. It plays a critical role in memory, perception and emotions. One structure of the limbic system, the hippocampus, plays a particularly important role in forming new memories, specifically short-term memories. There is a complex pathway in the hippocampus for formation of short term memories which are also critical for formation of long-term memory. Tr. at 14. Anatomically, the hippocampus lies in the mesial[13] temporal lobe, and damage to this area of the limbic system can result in problems with memory, learning, behavior, and emotions. Tr. at 14-15.

Submitted literature on limbic encephalitis[14] describes changes in the definition of the disease and the continuing progress in its understanding.[15] Limbic encephalitis can result from infectious, genetic, metabolic or autoimmune causes; in those instances in which the limbic encephalitis is due to autoimmune conditions, the diagnosis is labeled as autoimmune limbic encephalitis, or ALE. Tr. at 253.

Traditionally, autoimmune forms of limbic encephalitis were considered extremely rare disorders that were predominantly related to cancer. Resp. Ex. J at 1. Presently, however, many presentations of limbic encephalitis are increasingly understood to occur without any relationship to cancer, and as autoimmune diseases. The literature describes the autoimmune forms of limbic

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[13] Mesial lobe refers to the median aspect of the temporal lobe. Tr. at 14.

[14] The terms limbic encephalitis (LE) and autoimmune limbic encephalitis (ALE) are used throughout the hearing transcript. As a point of clarification, referring to the disease as autoimmune limbic encephalitis, instead of limbic encephalitis, more precisely denotes the autoimmune origin of the disease. Tr. at 35, 239-40, 253.

[15] **"**The last decade has seen many changes in the definition of and our understanding of the cause of limbic encephalitis." Pet. Ex. 25M at 1. [Pet. Ex. 25M is McCoy, Akiyama, Widjaja, et al., Autoimmune Limbic Encephalitis: Case Report and Review of the Literature, J. of Child Neurology, vol. 26, 218-22 (2011)]. "Once considered an extremely rare disorder, almost always related to cancer, and refractory to treatment, limbic encephalitis is now regarded as a relatively frequent disorder, often unrelated to cancer, and with clinical-immunologic variants that respond to treatment." Resp. Ex. J at 1. [Resp. Ex. J is Tuzin, and Dalmau, Limbic Encephalitis and Variants: Classification, Diagnosis, and Treatment, The Neurologist, vol. 13, 261-71 (2007)].

encephalitis as being "a relatively frequent disorder, often unrelated to cancer, and with clinical-immunologic variants that respond to treatment." Resp. Ex. J at 1; Tr. at 15.

The understanding of non-paraneoplastic (not related to cancer) forms of ALE continues to evolve as researchers find additional cell-membrane antigens associated with ALE, which therefore suggests that there is tremendous antigen diversity within the disease.[16] For both forms of ALE, paraneoplastic and non-paraneoplastic, the exact mechanisms of neuronal dysfunction are still unknown. Resp. Ex. J at 8.

2. Classic Presentation of ALE

Clinically, patients with the classic presentation of ALE usually manifest with "rapidly progressive short-term memory deficits, psychiatric symptoms, and seizures." Resp. Ex. J at 1. However, the literature acknowledges that traditional hallmarks of ALE—the short-term memory deficits and behavioral changes—can be overshadowed by other dominant symptoms, such as refractory seizures.[17] In fact, the literature suggests that the first signs to be recognized in childhood cases of ALE are often non-psychiatric symptoms, such as seizures and status epilepticus. "[I]n children, the first symptom to be recognized is often non-psychiatric – e.g. seizures, status epilepticus, dystonia, verbal reduction or mutism." Pet. Ex. 25N at 64. [18] As there has never been a suggestion that A.M. suffered from any type of cancer, the focus of this analysis is on those studies that have examined more recently recognized patterns of limbic encephalitis where the agent appears to be antibodies to neuronal cell surface antigens. See Resp. Ex J at 1. The Tuzin and Dalmau article states "[s]tudies have now shown that many of [ALE patients] do in fact have antibodies to neuronal cell surface antigens. These antigens may be ubiquitously expressed in the nervous system but usually are distinctively enriched in the hippocampus and sometimes the cerebellum. They include voltage-gated potassium channels, N-methyl-D-aspartate receptors and others that remain uncharacterized." Id.

Tuzin and Dalmau further note that "the diagnosis of limbic encephalitis is no longer dependent on the pathologic confirmation of inflammation involving the limbic system. In most studies, the diagnosis relies on the clinical picture combined with the demonstration of [magnetic resonance imaging ("MRI")] and [electroencephalogram ("EEG")] abnormalities in the temporal

[16] "Recent studies show that in addition to anti-VGKC, there are other limbic encephalitis-related antibodies that target novel cell-membrane antigens (nCMAg). These findings have broadened the spectrum of limbic encephalitis and suggest extensive antigen diversity." Pet. Ex. 25B at 381. [Pet. Ex. 25B is Bataller, Kleopa, Fu, et al., Autoimmune Limbic Encephalitis in 39 Patients: Immunophenotypes and Outcomes, J. Neural Neurosurg Psychiatry, vol. 78, 381-85 (2007)].

[17] "In other instances the clinical picture of limbic encephalitis is overshadowed by symptoms of "higher cortical dysfunction," decreased level of consciousness, or refractory seizures." Resp. Ex. J at 2.

[18] Pet. Ex. 25N is Dalmau, Lancaster, Martinez-Hernandez, et al., Clinical Experience and Laboratory Investigations in Patients with anti-NMDAR Encephalitis, Lancet Neurol, vol. 10, 63-74 (2011).

lobes, along with the frequent presence of inflammatory changes in the CSF." Resp. Ex. J at 2. But, "some patients, particularly those with antibodies to voltage-gated potassium channels may have normal CSF or only oligoclonal bands with normal total protein concentration." Resp. Ex J at 2. As noted above, in a 2011 article, Dalmau, Lancaster et al. stated that "[i]n children, the first symptom to be recognized is often non-psychiatric—e.g., *seizures, status epilepticus*, dystonia, verbal reduction or mutism." Pet. Ex 25N at 64 (emphasis added).

Overall, the diagnosis of ALE relies on the clinical picture as a whole, combined with objective test results, which include MRI scans, EEG, and CSF testing.[19] To diagnose all forms of ALE, viral and systemic autoimmune disorders are first excluded prior to examining abnormalities in objective test findings.[20]

EEG testing is described in the literature as being the "most sensitive tool" in making a diagnosis of encephalitis. Resp. Ex. D at 484.[21] Irrespective of the type of presentation, the results of the EEG are "almost always abnormal, revealing foci of epileptic activity in one or both temporal lobes, or focal or generalized slow activity." Resp. Ex. J at 2. Specifically for ALE patients, EEG tests are "abnormal in most patients, usually showing non-specific, slow, and disorganized activity sometimes with electrographic seizures." Pet. Ex. 25N at 64. These abnormalities are generally seen in the temporal lobes of patients with limbic encephalitis. MRI findings are normal in approximately fifty percent of cases and CSF is often negative as well. Id. at 64-65.

3. Petitioner Expert Opinions – A.M.'s case clinically fits ALE.

Dr. Blitshteyn opined that A.M.'s clinical symptoms are consistent with ALE. Tr. at 16-17. She reached this diagnosis after examining A.M.'s complete clinical picture. Clinically, Dr. Blitshteyn noted the following evidence in reaching her diagnosis: (1) A.M.'s localized damage to the limbic structures within the left temporal lobe and hippocampus; (2) A.M.'s severe seizures and post onset memory impairment and behavioral changes; (3) MRI, EEG, and biopsy findings revealing abnormalities in the temporal lobe; and (4) the treating physician's extensive tests ruling out other causes. Tr. at 36-37, 165.

A.M.'s EEGs were consistently abnormal with initial EEGs revealing diffuse slow activity compatible with cerebral dysfunction. Tr. at 17-18; Pet. Ex. 4 at 266. Thereafter, her EEGs showed epileptiform foci in the left anterior temporal region, with occasional emanations from the

[19] "In most studies, the diagnosis relies on the clinical picture combined with the demonstration of MRI and EEG abnormalities in the temporal lobes, and frequent presence of inflammatory changes in the cerebrospinal fluid (CSF)." Resp. Ex. J at 2.

[20] "After excluding viral and systemic autoimmune disorders, many patients with limbic encephalitis (paraneoplastic or not) have cerebrospinal fluid inflammatory findings, EEG or MRI abnormalities in the temporal lobes, and anti-neuronal antibodies," in particular cell membrane antibodies. Resp. Ex. J at 1.

[21] Resp. Ex. D is Fowler, Stoberg, Eriksson, et al., Childhood Encephalitis in Sweden: Etiology, Clinical Presentation and Outcome, European J. of Pediatric Neurology, vol. 12, 484-90 (2008).

right temporal region, demonstrating localization to the bilateral temporal lobes, left greater than right. Tr. at 18-19. As A.M.'s condition progressed, later EEGs showed multiple foci of her seizures as, by that stage, her seizures had become intractable and difficult to treat. Id. They took on a life of their own and emanated from multiple sources. Id.

A.M.'s initial MRIs performed on September 29, 2007, and October 10, 2007, did not reveal any abnormality. Pet. Ex. 4 at 438. The interpreting radiologist noted that these were limited studies due to the presence of braces on her teeth, which frequently cause artifact obscuring the images. Id. Respondent's expert, Dr. Venkatesan, reviewed the films himself and found them adequate to conclude that they did not show inflammation. Tr. at 367. Her third MRI, after the braces were removed, showed increased signal in the temporal lobe with atrophy in the hippocampus. Pet. Ex. 4 at 457; Tr. at 19-20. A PET scan done in November 2007 demonstrated hypometabolism of glucose in the temporal lobe. Pet. Ex. 4 at 461; Tr. at 20-21. While these two results do not verify an instigating cause of the seizures, they do localize the damage caused by the seizures to her temporal lobes, particularly on the left.

With that clinical underpinning, Dr. Blitshteyn opined that A.M.'s clinical symptoms, including severe seizures, status epilepticus, subsequent memory deficits, severe learning disabilities, and behavioral problems, were consistent with ALE. Tr. At 24. She testified the EEG findings were quite consistent with limbic encephalitis and the MRI and PET scans helped to localize the damage to the temporal lobes. Tr. at 21-23, 17-20. She also noted that the operative biopsy after A.M.'s temporal lobe was removed ruled out cortical dysplasia and cancer, and found gliosis consistent with a reaction to seizures. Tr. at 20-23. Further, a flu-like prodromal illness has been reported in case reports on limbic encephalitis. Tr. at 30 (referencing Pet. Ex 25A at 392).[22]

Dr. Steinman concurred with the ALE diagnosis and agreed that the second HPV vaccination was the etiologic trigger for A.M.'s ALE. Tr. at 134-35. Both experts also agreed that A.M. likely had a susceptibility to an autoimmune disease, in that she suffered from a previous autoimmune disorder, idiopathic thrombocytopenic purpura[23] ("ITP"), when she was eight years old. Tr. at 378-79; Pet. Ex. 25 at 6; Pet. Ex. 34 at 6. All experts, including Dr. Venkatesan, agreed that a prior autoimmune disorder may make a patient more susceptible to a subsequent one. Tr. at 350.

Dr. Blitshteyn acknowledged that some of the more typical presentations of ALE, mainly the short-term memory and behavioral deficits, were not initially noticed in A.M.'s case; rather, she opined that these deficits were overshadowed by her rapidly developing severe seizure

[22] Pet. Ex. 25A is Samarasekera, Vincent, Welch, et al., Course and Outcomes of Acute Limbic Encephalitis with Negative Voltage-gated Potassium Channel Antibodies, J. Neurol Neurosurg Psychiatry, vol. 78, 391-94 (2007).

[23] Idiopathic thrombocytopenic purpura (ITP) is "an acquired autoimmune disorder defined by isolated [deficiency of platelets in the blood (also known as thrombocytopenia)] and the exclusion of other causes of thrombocytopenia." Pet. Ex. 25S at 4. [Pet. Ex. 25S is Stasi, Evangelista, Stipa, et al., Idiopathic Thrombocytopenic Purpura: Current Concepts in Pathophysiology and Management, Thromb Haemost, vol. 99, 4-13 (2008).

disorder. Tr. at 59. In this regard, as A.M. went straight into severe seizures and became unresponsive shortly after being admitted, Dr. Blitshteyn opined that A.M.'s treating physicians did not have an opportunity to notice these memory and behavioral changes. Tr. at 59-60. She does state, however, that shortly after A.M. came out of her coma, her treating physicians did in fact notice significant memory deficits and behavioral changes. Id. Dr. Venkatesan agreed that once the seizures began, it would have been very "difficult to ascertain whether there were any memory changes or personality changes." Tr. at 356.

4. Respondent Expert Opinion – A.M.'s symptoms do not clinically fit ALE.

Dr. Venkatesan contended that there was insufficient evidence in A.M.'s case to make a diagnosis of ALE. Tr. at 252-55. He opined that the lack of history of memory disturbance or personality disorder in the days preceding the onset of seizures, and the lack of documentation of inflammation in the brain or CSF, were missing pieces in what is known as a typical presentation of ALE. Id. In Dr. Venkatesan's view, A.M.'s post-induced coma medical history, which significantly documented behavioral and memory deficits, are not convincing for an ALE diagnosis, as in his view, seizures alone, regardless of the cause, can also cause memory problems and personality changes. Id.

Dr. Venkatesan noted the lack of evidence for inflammation on A.M.'s CSF testing that would support a diagnosis of autoimmune limbic encephalitis. Tr. at 253-54. He did not view the localization of the encephalitic activity in the temporal lobe, or the unquestionable evidence of severe damage in that area of the brain, as being sufficiently specific evidence for ALE in that the temporal lobe is a common area that, for reasons that are not well understood, serves as a focus of seizures, regardless of their etiology. Tr. at 325.

For Dr. Venkatesan, A.M.'s EEG findings are "potentially sensitive, but, unfortunately, not specific for the diagnosis of encephalitis." Tr. at 312. In other words they could suggest a diagnosis of ALE but not rule out alternatives. Similarly, Dr. Venkatesan acknowledged that the documented MRI and PET scan abnormalities could be caused by limbic encephalitis, but were not specific and could have resulted from the prolonged seizures that she suffered in that area of the brain. Tr. at 326-27. Furthermore, Dr. Venkatesan attributed the differences from A.M.'s first MRI to the third as being common changes that occur in the setting of refractory seizures, regardless of etiology. Tr. at 367-68. Overall, Dr. Venkatesan's contention is that by simply examining the MRI, one cannot make an assessment whether the damage in her left temporal lobe caused the seizures, or whether the seizures caused the damage seen on the MRI. Tr. at 249-50.

Notwithstanding the above, Dr. Venkatesan acknowledged that limbic encephalitis is encephalitis that occurs in the limbic system, Tr. at 353, that the fact that she was having seizures is likely indicative of neuronal excitability, Tr. at 353, that a seizure disorder like this may begin without an initiating inflammatory response, Tr. at 362, that it would have been very difficult to evaluate A.M.'s mental status before the onset of seizures when she presented with severe seizures, Tr. at 356, and that he could imagine a case of ALE presenting with the seizures dominating the clinical picture. Tr. at 357.

5. Alternative Diagnosis of FIRES

Respondent, through Dr. Venkatesan, offered an alternative diagnosis for A.M.'s symptoms, suggesting that A.M. has febrile infection-related epilepsy syndrome, or FIRES. FIRES is defined as "a catastrophic epileptic encephalopathy with a yet undefined etiology." Resp. Ex. L at 1.[24] This rare syndrome comprises a small minority of all patients with status epilepticus (SE). Resp. Ex. L at 1.

There is extensive debate in the medical community as to how to name and characterize FIRES. Resp. Ex. L at 1. The Japanese medical community prefers to highlight the presumed pathogenesis of the syndrome, and has used the term "acute encephalitis with refractory, repetitive partial seizures" or (AERPS) to refer to the syndrome. Id. Others within the medical community prefer the term FIRES, as it emphasizes the characteristics of acute refractory partial epilepsy.[25]

Dr. Venkatesan explained his diagnosis of FIRES as one that has been applied to a clinical subgroup of patients who clinically presented with "expected encephalitis, who did not have an identifiable cause of the encephalitis, but had very distinct signs and symptoms"Tr. at 230-31.

Dr. Venkatesan stated that the distinguishing factors of FIRES are: (1) no known etiology for the syndrome, and (2) a characteristic time course. Tr. at 357-58. "The necessary symptoms include a febrile illness followed shortly thereafter by refractory seizures or status epilepticus." Tr. at 234-35; Res. Ex. H at 2; Resp. Ex. M at 6.[26] The median age at onset of the syndrome is eight years of age, with seizures developing into status epilepticus within a few days. Tr. at 234. Furthermore, FIRES patients have very poor outcomes, as they continue to suffer refractory seizures as well as cognitive and intellectual impairments. Tr. at 237.

The exact mechanism of FIRES is unidentified, but some authors suspect genetic predisposition, an immunologic source, or inflammation-mediated causes, as potential factors.[27]

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[24] Resp. Ex. L is Kramer, Chi, Lin, et al., Febrile Infection-related Epilepsy Syndrome ("FIRES): Pathogenesis, Treatment, and Outcome. A Multicenter Study on 77 Children, Epilepsia, vol. 52, 1956-65 (2011).

[25] "The syndrome described as FIRES has been known by many names that emphasize either the characteristics of acute refractory partial epilepsy or the presumed pathogenesis, among them: "acute encephalitis with refractory, repetitive partial seizures (AERPS), "severe refractory status epilepticus due to presumed encephalitis," "idiopathic catastrophic epileptic encephalopathy," "new-onset refractory status epilepticus (NORSE)," "devastating epileptic encephalopathy in school-aged children (DESC)," and FIRES. Japanese authors prefer the term AERPS and European authors prefer FIRES." Resp. Ex. L at 1.

[26] Resp. Ex. M is van Baalen, Hausler, Boor, et al., Febrile Infection-related Epilepsy Syndrome (FIRES): A Nonencephalitic Encephalopathy in Childhood, Epilepsia, vol. 51, 1323-28 (2010).

[27] "The mechanism underlying this prolonged state is not clear, and an immunologic source, a genetic predisposition, and an inflammation-mediated process have been hypothesized." Resp. Ex. L at 2; see also Resp. Ex. M at 6 (stating, "[t]here is increasing evidence for involvement of the

Typical MRI findings for FIRES show no abnormalities at the onset of seizures, but MRI abnormalities do develop over the course of the disease, primarily due to refractory seizures. Tr. at 236. These abnormalities tend to involve the temporal lobes and the hippocampal areas of the brain, with either one or both lobes potentially affected. Id.

Given the rarity of the syndrome, there is a limited sample size[28] of brain biopsies conducted on FIRES patients; however, in the ones that have been conducted, typical findings include the presence of gliosis,[29] and an absence of inflammation. Resp. Ex. L at 2; Resp. Ex. M at 6; Tr. at 236-37. On EEG testing, FIRES patients show evidence of focality, multifocality, or generalization. Resp. Ex. H at 2. Upon CSF testing, approximately forty percent of FIRES patients demonstrate normal results, and extensive CSF studies do not identify infectious pathogens. Resp. Ex. H at 2; Resp. Ex. L at 322.

At the outset, the undersigned notes that FIRES is a very rare syndrome, but that Dr. Venkatesan has significant clinical expertise in the syndrome having treated between five to ten FIRES patients per year in his clinical practice. Tr. at 226. Dr. Venkatesan opined that his clinical experience led him to conclude that A.M. has FIRES. Tr. at 283-84. He posits that A.M.'s clinical picture, along with her EEGs, brain MRI results, CSF findings, and biopsies are consistent with the diagnosis of FIRES. Tr. at 244-46, 249-50. Furthermore, he also contends that no portion of A.M.'s medical records is inconsistent with this diagnosis. Tr. at 240.

Specifically, Dr. Venkatesan notes that the febrile illness experienced by A.M. five days prior to the onset of seizures initiated her FIRES syndrome. Resp. Ex. H at 3. He contends that this timing between the onset of the febrile illness and her seizures is consistent with the appropriate time frame established in the literature for FIRES patients. Tr. at 241-42; Resp. Ex. H at 2-3. Furthermore, A.M. was twelve years old at the onset of her seizures, which Dr. Venkatesan indicates is within the appropriate age range for a FIRES diagnosis. Tr. at 234.

Dr. Venkatesan was asked to explain the difference between limbic encephalitis and FIRES. He responded that the clinical syndromes are very different:

> "In FIRES, what one has is this kind of acute febrile illness followed very rapidly by this refractory seizure condition. In limbic encephalitis, one typically has a

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immune system in the pathogenesis of some forms of severe epilepsy syndrome. Our clinical findings suggest an immune mechanism as well, but prospective studies are needed to clarify the relation between banal febrile infections and this evidently nonencephalitic encephalopathy. These studies should address both immune and nonimmune mechanisms (e.g. channelopathies, antibodies against ion channels and receptors, and infection-triggered alterations of receptor expression)").

[28] In one particular study, only seven out of the total twenty-two patients studied had brain biopsies performed. Resp. Ex. M at 6.

[29] Gliosis is the reactive change in the glial (supportive) cells within the brain due to an injury. Tr. at 236-37.

subacute development of short-term memory loss, behavioral changes, and one can develop seizures, but *typically* not so acutely and *typically* not without the other symptoms that I mentioned." Tr. at 238 (emphasis added).

Dr. Venkatesan testified that A.M.'s condition is consistent with FIRES and indeed she did demonstrate the general, non- specific characteristics of FIRES. However, these symptoms could also describe a presentation of ALE. She had a fever that began several days before the onset of seizures, the seizures from the outset were catastrophic and her condition remained refractory to treatment. She also developed over time severe deficits of memory and IQ, and personality problems consistent with injury to the limbic area of the brain.

Dr. Venkatesan also opined that the "typical" presentation of limbic encephalitis was different than what occurred in this case, in that "typically" the patient has subacute symptoms of memory loss or personality problems. However, as Dr. Venkatesan himself acknowledged, it would have been difficult to assess A.M.'s higher cognitive functions or whether she was behaving normally when she presented with severe seizures that rapidly went into status epilepticus. Tr. at. 326. Dr. Venkatesan also acknowledged that while he may expect other neurologic signs and symptoms in limbic encephalitis, he "could imagine a case where the seizures dominated the picture." Tr. at 357. Indeed some of the literature submitted by the parties discusses the evolving knowledge of limbic encephalitis, which was previously thought to be primarily related to the presence of a tumor, but is now recognized to be a much more common disorder with non-neoplastic origins. See Resp. Exhibit J at 2 (stating "[i]n other instances the clinical picture of limbic encephalitis is overshadowed by symptoms of higher cortical dysfunction, decreased level of consciousness or *refractory seizures*"); see also Pet. Ex 25N at 63 (discussing the rapid change in the management of many conditions including seizures and limbic encephalitis since the 2007 discovery of the anti-NMDAR antibodies). "In children, the first symptom to be recognized is often non-psychiatric—e.g., *seizures, status epilepticus,* dystonia, verbal reduction or mutism." Pet. Ex. 25N at 64 (emphasis added). Thus while A.M.'s presentation did not match that of "classic" limbic encephalitis, it certainly appeared to be within the realm of less typical presentations that are described in the literature as commonly occurring.

Dr. Venkatesan also correctly notes that there was no specific test done for an anti-AQP-4 antibody[30] in A.M. However, he and Dr. Steinman both agree that this test would not have been generally available at the time A.M. had seizures. Tr. at 358. Dr. Venkatesan notes that there was no finding of inflammation in her brain at the time various tests, such as CSF tests, MRI, and biopsy, were done. Tr. at 254. Yet, he also acknowledges that this could be a function of when these tests were done. Tr. at 365-66; Tr. at 361-62. CSF tests are usually followed a couple of days later with another, when there is a negative result—as was the case here—but a follow-up was not done in this case until six weeks later. Tr. at 306-07. The evidence of inflammation could have readily come and gone in that time period. The biopsy done at the time of surgery, more than a year later, found no evidence of active inflammation but that did not rule out prior inflammation.

[30] Petitioner's theory is that the Gardasil vaccine caused an autoimmune response to the aquaporin-4 ("AQP-4") water channels in the brain thus triggering her seizures. Dr. Venkatesan explained that the test for anti-AQP-4 antibodies was just coming out in 2007 and it was not widely available. Tr. at 358.

There was significant scarring in the hippocampus, noted by A.M.'s surgeon, which could have been caused by inflammation or by the seizures themselves. Pet. Ex. 23 at 131

Dr. Venkatesan acknowledges that there is great potential for science to understand more about both autoimmune and infectious causes of limbic encephalitis. Tr. at 239. Consequently, he did not rule out the explanation provided by petitioner, but questioned whether there was sufficient evidence to establish the diagnosis and the causal mechanism.

6. Petitioner Expert Opinion - Symptoms of FIRES can fit ALE

Dr. Blitshteyn viewed FIRES as being a relatively new diagnosis. The diagnosis can be applied to "just about anything that has no known cause." Tr. at 46. It is a syndrome or collection of symptoms, not a disease. Id. In this regard, she observed that FIRES includes encephalitis of unknown causes, and remarked that the FIRES label was not used as a diagnosis during her residency at the Mayo Clinic. Tr. at 46-47. Dr. Blitshteyn further stated that if she retrospectively reviewed the patients she treated during her training at the Mayo Clinic, the FIRES label could be attached to all groups of patients that presented with encephalitis of various origins. Tr. at 46. Indeed the criteria for FIRES are themselves quite non-specific and could be suggestive of multiple etiologies. The undersigned observes that, for example, respondent's exhibit H notes that EEG findings in FIRES can be focal, multifocal or general, and thus are so non-specific as to be of limited value in distinguishing the condition from other diagnostic entities. Resp. Ex. H at 2.

Dr. Steinman concurred with Dr. Blitshteyn's opinion and testified about the vague criteria associated with FIRES. Dr. Steinman also remarked that he does not diagnose patients with FIRES because he believes that the diagnosis does not constitute a "bona fide syndrome." Tr. at 166-67. In this regard, he referred to FIRES as a "holding tank of unknown diagnoses" because "as soon as we make a diagnosis then we remove it from the holding tank and call it something else." Tr. at 374. Dr. Steinman further observes that the literature on FIRES supports his view that this condition can also be a manifestation of limbic encephalitis. In fact, limbic encephalitis can be a subcategory of FIRES. Tr. at 211; Tr. at 166-67.

C. Pre-*Althen* FIRES or ALE Analysis

The undersigned acknowledges that ascribing a diagnosis in this case is a close call. The presenting symptoms, EEGs, imaging studies, operative observation of severe scarring in the hippocampus, and post initial seizure symptoms could reasonably place the diagnosis in either category. However, I am inclined to find that the criteria for FIRES are very non-specific and can readily describe a presentation of ALE. In fact, Dr. Venkatesan testified that if a particular antibody were identified in the context of these symptoms, he would remove the diagnosis from the category of FIRES, the hallmark of which is an unknown cause. Tr. at 357-58.

I am persuaded that petitioner has proven by a preponderance of the evidence that A.M. has ALE. The Vaccine Act requires that a Special Master consider the treatment record as a whole in evaluating the evidence offered to establish petitioner's illness. § 13(a)(1). Here, the record supports the conclusion that A.M.'s proffered diagnosis, ALE, is made out by the evidence, taking into account the following facts: (1) the differential diagnoses of petitioner's experts of ALE, (2) the multiple references in the literature noting the clinical variation in manifestations of ALE

which include A.M.s clinical course, (3) the non-specific, general and idiopathic nature of the criteria for FIRES, and (4) the localization of the epileptogenic activity and damage to the brain in the limbic area of her brain by EEG, MRI, PET, electrocorticography, operative observation, and biopsy.

Respondent argues that a determination of what afflicted petitioner is a prerequisite to a causation analysis, consistent with *Broekelschen*, 618 F.3d at 1346. Resp. Post Hearing Br. at 8. In *Broekelschen*, the "injury" itself was in dispute and the question of causation turned on the nature of the injury. In that case, the pathology of the injuries in question differed markedly. A diagnosis of transverse myelitis was compared to a diagnosis of spinal artery syndrome caused by an occlusion of the spinal artery. These conditions were completely different in nature and would give rise to potentially different conclusions about the relatedness of the vaccine to the injury. See 618 F.3d at 1346.

In this case, the injury being described by the experts is the same injury—a severe seizure disorder and status epilepticus—it is the name given to the disorder that differs. There is no disagreement that A.M. suffered severe seizures five days after the onset of a fever, and that the seizures rapidly progressed to status epilepticus and were extremely difficult to treat. She was placed in a medically induced burst suppression coma for weeks and has suffered severe cognitive impairments. Her EEGs showed generalized slowing with epileptiform discharges from the temporal lobe when seizures were recorded. Her PET scan showed hypometabolism in the temporal lobe and the third MRI showed hyperintense signal in the temporal lobe. The operative findings when her mesial temporal lobe was removed showed evidence of significant scarring in the hippocampus and evidence of Chaslin's Gliosis. Dr. Venkatesan testified that the fact that A.M. was having seizures is likely indicative of neuronal excitability, which is consistent with Dr. Steinman's theory of AQP-4 autoimmunity. Tr. at 354. Accordingly, while these physical findings may be consistent with FIRES, they are also consistent with autoimmune limbic encephalitis, which itself may be a sub-category of the more general FIRES syndrome.

Thus, what is fundamentally debated is whether a diagnosis of ALE can be made if all of the "classical" symptoms are not present. Dr. Venkatesan, not unreasonably, testified that he would be more comfortable with more evidence to support the diagnosis that Drs. Blitshteyn and Steinman have made, and in the absence of that level of evidence, believes that the more general idiopathic diagnosis of FIRES is the most definitive diagnosis that can be made. The submitted literature on ALE, however, strongly suggests that seizures may be the dominant presenting symptom in ALE in children, and that the non-classical presentations of ALE are more common than previously recognized. Res. Ex. J at 262.

Dr. Venkatesan disputes the ALE diagnosis on three grounds. First, the lack of common presenting neuro-psychiatric symptoms; second, the lack of evidence of inflammation; and third, his dissatisfaction with the level of certainty of the evidence for the proposed autoimmune mechanism. It is interesting to note that he describes the first two requirements as being those of the "typical" presentation of limbic encephalitis. Tr. at 364. I think it is clear, however, that the literature submitted, as described above indicates that less typical presentations are more common than previously recognized, multiple autoimmune causes of limbic encephalitis are now thought to exist, and that these patients often "do in fact have antibodies to neuronal cell surface antigens.

These antigens may be ubiquitously expressed in the nervous system but usually are distinctively enriched in the hippocampus receptors (NMDAR), and [that there are] others that remain uncharacterized." Resp. Ex. J. at 1. At the time of the writing of the Tuzin, Dalmau article, AQP-4 could certainly have been among the neuronal cell surface antigens that had yet to be characterized. See Res. Ex. J. More recent literature, as will be discussed below, suggests a likely role for these antigens in the generation of seizures.

The second criticism of the ALE diagnosis is the lack of specific evidence of inflammation that Dr. Venkatesan would like to see to make a diagnosis of encephalitis—as he stated the "itis" in the term refers to inflammation. Tr. at 238. Aside from the notations in the literature that specific evidence of inflammation is not necessary to diagnose ALE, Dr. Venkatesan testified that he has seen cases of autoimmune encephalitis that presented with no signs of inflammation in the CSF or on MRI. Tr. at 364. The criteria of inflammation goes to the condition of encephalitis in general and not just to autoimmune limbic encephalitis, and it is here that the opinions of the numerous treating physicians managing A.M.'s care, as delineated in the lengthy footnote provided by petitioner's counsel as set forth below, must be given weight.[31] There are numerous references in

[31] See, e.g., Pet. Ex. 18 at 63 ("suspected encephalitis"); id. at 76 ("suspect encephalitis-onset 9/29/2007"); id. at 88 ("suspect encephalitis-onset 9/29/2007"); id. at 97 ("encephalitis of unknown cause"); id. at 131 ("viral encephalitis"); Pet. Ex. 1 at 621 ("suspected encephalitis"); Pet. Ex. 18 at 703 ("encephalitis of unknown cause"); Pet. Ex. 4 at 404 ("encephalitis of unknown cause"); id. at 407 ("[status post] encephalitis (suspected)"); Pet. Ex. 24 at 6 ("encephalitis of unknown cause"); id. at 9 ("[status post] encephalitis (suspected)"); id. at 251 ("encephalitis of unknown cause"); id. at 254 ("[status post] encephalitis (suspected)"); Pet. Ex. 2 at 41 ("[diagnosed] with encephalitis of unknown etiology"); Pet. Ex. 4 at 76 ("[diagnosed] with encephalitis of unknown etiology"); Pet. Ex. 24 at 47 ("suspected encephalitis on 9/21/07"); id. at 48 ("suspected encephalitis"); id. at 49 ("new onset [seizures] and encephalitis"); id. at 50 ("[patient] [with] encephalitis"); Pet. Ex. 4 at 257 ("viral encephalitis"); id. at 338 ("encephalitis"); id. at 339 ("[patient] [with] encephalitis"); Pet. Ex. 24 at 33 ("suspected encephalitis on 9/21/07"); id. at 34 ("suspected encephalitis"); Pet. Ex. 4 at 369 ("[status post] encephalitis"); Pet. Ex. 24 at 3 ("encephalitis of unknown etiology"); id. at 4 ("epilepsy secondary to encephalitis"); Pet. Ex. 5 at 13 ("encephalitis and motor delay. . . .encephalitis"); id. at 12 ("Encephalitis . . . [Seizures] secondary to encephalitis"); Pet. Ex. 1 at 20 ("[Diagnosed] with encephalitis"); id. at 22 ("[Diagnosis] of Encephalitis"); id. at 117 ("[Patient] had the onset of encephalitis"); Pet. Ex. 6 at 513 ("Patient had the onset of encephalitis"); Pet. Ex. 2 at 45 ("suffered encephalitis of unclear etiology"); Pet. Ex. 4 at 17 ("suffered encephalitis of unclear etiology"); Pet. Ex. 6 at 436 ("bout of viral encephalitis"); Pet. Ex. 1 at 75 ("Encephalitis of unknown cause 9/27/07"); Pet. Ex. 2 at 9 ("Encephalitis of unknown cause 9/27/07"); Pet. Ex. 1 at 51 ("encephalitis in October of 2007"); Pet. Ex. 3 at 625 ("encephalitis in October of 2007"); Pet. Ex. 1 at 66 ("Encephalitis of unknown cause 9/27/07"); Pet. Ex. 2 at 5 ("Encephalitis of unknown cause 9/27/07"); Pet. Ex. 1 at 50 ("Encephalitis of unknown origin 9/27/07"); Pet. Ex. 2 at 2 ("Encephalitis of unknown origin 9/27/07"); Pet. Ex. 17 at 91 ("Encephalitis of unknown origin 9/27/07"); Pet. Ex. 2 at 25 ("encephalitis of unknown origin"); Pet. Ex. 3 at 515 ("status post encephalitis"); id. at 494 ("status post encephalitis"); Pet. Ex. 4 at 2 ("[status post] encephalitis of unknown origin"); Pet. Ex. 17 at 81 ("Encephalitis of unknown origin 9/07"); Pet. Ex. 12 at 1 ("after an encephalitis of undetermined etiology"); Pet. Ex. 3 at 255 ("secondary to encephalitis"); Pet. Ex. 15 at 5 ("episode of encephalitis"); Pet. Ex. 37 at 199 ("encephalitis of undetermined etiology").

the medical records to "encephalitis," "possible encephalitis," "encephalitis of unknown cause" and so forth. The treating physicians certainly considered that they were managing a case of encephalitis regardless of whether there was specific molecular evidence of inflammation. "[M]edical records and medical opinion testimony are favored in vaccine cases." *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). At least as to the diagnosis of encephalitis, the opinions of the treating physicians expressed in the medical records are important and support a diagnosis of limbic encephalitis.

Finally, Dr. Venkatesan's opinion regarding the consistency of A.M.'s symptoms with FIRES, which are non-specific in that they could also be the product of other causes and thus could also be consistent with autoimmune limbic encephalopathy, is significantly grounded in his opinion that the cause is unknown. He opined essentially that there is no reliable evidence that: (1) associates the HPV vaccine with FIRES, (2) the HPV vaccine can cause an autoimmune response directed to AQP-4, or that (3) AQP-4 antibodies can induce a seizure condition. Tr. at 230. If, on the other hand, it is determined that the petitioner through her experts have put forth a reasonable and persuasive explanation of an autoimmune cause for how the HPV vaccine can trigger a seizure disorder, then the cause is no longer unknown and by Dr. Venkatesan's own definition, A.M.'s condition would no longer fit within the rubric of FIRES.

As I have concluded, for reasons set forth below in the *Althen* analysis, Drs. Steinman and Blitshteyn have presented sufficiently reliable evidence to satisfy prongs one and two of *Althen*, and given that the parties do not dispute that prong three has been satisfied, there is enough evidence to define the cause of A.M.'s illness. It is therefore also reasonable to conclude, by the preponderant standard required in this Program, that the cause not being unknown, A.M. suffered from autoimmune limbic encephalitis as diagnosed by Dr. Blitshteyn and not FIRES. Moreover, in the end it does not appear that it makes a difference whether the diagnosis is called ALE or FIRES. All experts agree that, given the severe seizure condition that A.M. has suffered, she has experienced hyperexcitation in the brain causing seizures; and Drs. Blitshteyn and Steinman have proposed a logical mechanism by which cross reactivity to the AQP-4 water channels caused by molecular mimicry with two parts of the Gardasil vaccine causes loss of neuronal, osmotic homeostasis giving rise to neuronal excitability and seizures. The known physical findings, including epileptogenic activity, MRI hyperintense signal in the temporal lobe, PET scan hypometabolism in the left temporal lobe and severe scarring in the hippocampus, localize the disease to the limbic area of the brain. For all of the above reasons, I have concluded that the diagnosis of ALE made by Drs. Blitshteyn and Steinman is reasonable and provides a sufficient predicate to undertake the *Althen* analysis.

D. *Althen* Analysis

Initially it is important to note that the parties have agreed on several elements key to the issue of causation in this case. First, Drs. Steinman, Blitshteyn and Venkatesan agree that the timing of the onset of A.M.'s seizure disorder is appropriate relative to the second dose of Gardasil, assuming a causal mechanism of molecular mimicry. Tr. at 28, 165, 256, 272, 356. Second, Dr. Blitshteyn, Dr. Steinman and Dr. Venkatesan agreed that the Miami Children's Hospital did a very thorough job of ruling out known alternative causes. Tr. at 29, 381. They acknowledged that there could be a virus that is not yet known at the root of her condition, but agreed that she underwent

comprehensive testing to rule out known disease entities and genetic defects and all were negative. Tr. at 164-65. Third, Dr. Steinman and Dr. Venkatesan agreed that strep was unlikely to be the cause of the seizures. Tr. at 211, 292. Dr. Steinman explained that strep causes a unique set of conditions if it affects the nervous system such as St. Vitus Dance, rheumatic fever or chorea. Id. Fourth, the doctors agreed that a child who had exhibited a prior autoimmune condition such as idiopathic thrombocytopenic purpura, which A.M. had suffered several years before, could be more susceptible to an autoimmune attack, as petitioner contends occurred in this case. Tr. at 350, 380. Additionally, all agreed that molecular mimicry is a generally accepted theory of autoimmunity, but disagreed as to whether there was sufficient evidence to conclude that it had occurred this case. Tr. at 135, 254.

With the above factors agreed upon, the analysis turns to the questions presented by *Althen* prongs one and two. First, could the Gardasil vaccine stimulate an autoimmune response by molecular mimicry that could give rise to a severe seizure disorder? Second, has the petitioner presented a logical cause and effect explanation for how it did?

In addressing these questions, definitions of several of the key terms are helpful. First Gardasil is a quadrivalent vaccine, administered in three doses, and is designed to provide immunity to four human papillomaviruses. Tr. at 25. Gardasil contains virus like particles developed from the L1 protein of HPV 6, 11, 16, 18 along with amorphous aluminum hydroxyphosphate sulfate as the adjuvant.[32] A.M. received the first dose earlier in the summer of 2007. Pet. Ex. 10 at 1. She received the second dose on August 16, 2007. Id.

Molecular mimicry is a mechanism for the instigation of autoimmune disease where there occurs sufficient homology or structural similarity between a foreign antigen, such as that presented in a wild virus or a vaccine, and a self-structure, such as some part of the central nervous system. Tr. at 142-46. When such biological overlap occurs, the immune system may mistakenly recognize a body structure such as the hippocampus as being the foreign antigen and attack the body structure rather than the foreign antigen. Id. Both parties agree that molecular mimicry is an accepted theory of autoimmunity in the medical profession that is taught in medical school, and has been discussed in peer reviewed journals and textbooks. Tr. at 138, 254.

The aquaporin-4 ("AQP-4") water channels are pore like structures that occur in abundance in the surface of cells in different parts of the brain. Pet. Ex. 340 at 1204. They are particularly prevalent in the hippocampus. Tr. at 213. The AQP-4 channels facilitate the movement of water back and forth between the interior and exterior of the cells. Pet. Ex. 34O at 1204; Tr. at 148. Together with the inwardly rectifying potassium channels, they also appear to play a critical role in managing the amount of extracellular fluid, and thus influence the movement of potassium in the brain as Dr. Venkatesan testified. Tr. at 360-61.

i. *Althen* Prong One

Dr. Steinman has done considerable research and publication in the field of molecular mimicry, with particular reference to the mimicry between the HPV virus and myelin basic protein.

[32] IOM (Institute of Medicine), ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY 506 (The National Academies Press 2012).

See Pet. Ex. 35. Myelin basic protein is a major constituent of the myelin which wraps and insulates the axons in the brain. See generally Pet. Exs. 34A, 34B. Axons carry the signals sent from neuron to neuron. Id. The insulation provided by the myelin facilitates the rapid transit of the messages being sent from nerve to nerve and protects the underlying axon. Id. When the myelin is damaged, the function of the brain in that area becomes impaired by slowing the transit of signals and ultimately, in some situations, the axons can become completely disrupted. Id. Dr. Steinman's research has demonstrated molecular mimicry between the HPV virus and myelin basic protein at the FFK motif of the amino acid chain in the T cell epitopes. Pet. Ex. 34A at 7.

In this case, his focus was not on the molecular mimicry between Gardasil and myelin basic protein, but rather between Gardasil and the aquaporin-4 water channels in the mesial temporal lobe and particularly in the hippocampus. Tr. at 147-53; see also Pet. Ex. 34O at 13-14. Knowledge of the AQP-4 water channels in the brain is of fairly recent vintage. See Pet. Ex. 34O.[33] Petitioner's exhibit 34O, the Binder article, provides a review of the literature on the potential roles of the glial water channel AQP-4, and explains that:

> The aquaporins [("AQPs")] are a family of membrane proteins that function as water channels in many cell types and tissues in which fluid transport is crucial. (*internal citation removed*). The AQPs are small hydrophobic integral membrane proteins that facilitate bidirectional water transport in response to osmotic gradients . . . . AQP-4 is of particular interest in neuroscience as it is expressed in brain and spinal cord by glial cells, especially at specialized membrane domains including astroglial end feet in contact with blood vessels and astrocyte membranes that ensheath glutamatergic synapses. Pet. Ex. 34O at 1204.

The article also explains that "alteration of water and potassium ("K+") homeostasis could dramatically affect seizure susceptibility. The authors state, "brain tissue excitability is exquisitely sensitive to osmolarity and the size of the extracellular space ("ECS"). Decreasing ECS volume with hypoosmolar treatment produces hyperexcitability and enhanced epileptiform activity." Id. (*internal citation removed*).

The Binder article reviewed multiple articles discussing research done with AQP-4 "knockout" mice in which the AQP-4 water channels were deleted in laboratory mice and in which stimulation evoked frequent and prolonged seizures. Id. at 1207. Binder went on to explain that the most common pathology in patients with medically intractable Temporal Lobe Epilepsy ("TLE") is a mesial temporal sclerosis[34], characterized by marked neuronal cell loss in specific hippocampal areas, gliosis, and microvascular proliferation. Id. Emerging work also demonstrates dysregulation of water and K+ homeostasis in patients with mesial TLE. Both Binder and Dr.

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[33] Pet. Ex. 34O is Binder, Nagelhus, and Ottersen, Aquaporin-4 and Epilepsy, Glia, vol. 60.8, 1204-14 (2012).

[34] Mesial temporal sclerosis is scarring in the temporal area of the brain. Tr. 214. The operating surgeon in A.M.'s case observed during surgery that her hippocampus was quite obviously scarred. Pet. Ex. 23 at 131.

Steinman, in his testimony, made reference to the article by Lee, Pet. Ex. 34G.[35] In this study, Lee and colleagues injected kainic acid, an excitatory amino acid, into both AQP-4 positive and AQP-4 negative, or knockout mice, to induce status epilepticus. Pet. Ex. 34G at 248. During post status epilepticus, both positive and negative mice experienced seizures, but AQP-4 negative mice experienced significantly more seizures per day, and in addition, there was a trend toward greater total seizure duration per day in the knockout mice. Id.

Binder, concluded:

> Compelling evidence indicates that the glial water channel AQP-4 plays a fundamental role in water transport in the brain. AQP-4 is expressed in astrocytes, and along with the inwardly rectifying K+ channel Kir4.1 is thought to be responsible for water and K+ homeostasis during neural activity . . . . Dysfunctional K+ homeostasis and upregulation and altered subcellular distribution of AQP-4 have been observed in human epileptic tissue. Pet. Ex. 34O at 1211.

Consistent with Binder's explanation of the effect of damage to the AQP-4 water channels, Dr. Steinman's theory is that there is molecular mimicry between the HPV virus like particles 16 and 18, which are found in the Gardasil vaccine, and the AQP-4 water channels in the brain. Tr. at 148. He proposed that there are segments on these HPV types in the vaccine which have homology at five or six different amino acids, as shown in Petioner's Exhibit 34F at 286.[36] Tr. at 150. Dr. Steinman testified that based on his research and knowledge of the field, homology between four or five amino acids is enough to instigate molecular mimicry and that there are suitable substitutions for some molecules that extend the level of potential mimicry. Tr. at 151-52.

His theory essentially proposes two questions. First, can damage to the aquaporin-4 water channels in the brain cause seizures? Second, can molecular mimicry between components of the Gardasil vaccine and aquaporin-4 proteins in the brain cause damage to the water channels thus producing seizures? In answering in the affirmative, Dr. Steinman examined the function of the aquaporin-4 water channels—the discovery of which, about fifteen years ago, led to a Nobel Prize for a member of the Johns Hopkins faculty, according to Dr. Steinman. Tr. at 162. Since their relatively recent discovery in molecular biology, Dr. Steinman indicated that there has been growing scientific interest in their function in the brain and their potential role in epileptogenesis or the cause of seizures. Tr. at 149. He explained that experiments have been done whereby the AQP-4 channels were eliminated or knocked out in mice exposed to kainic acid. Pet. Ex. 34G at 248; Tr. at 197-98. The experiment caused a condition known as experimental autoimmune encephalitis. Tr. at 369-71. In this condition, the mice experienced more frequent and more prolonged seizures. Tr. at 153. The likely explanation was that when the AQP-4 water channels in the brain were knocked out, the facilitation of water movement through the cell membranes and in the extracellular space was impaired, which then influenced the movement of potassium, and

[35] Pet. Ex. 34G is Lee, Hsu, Seldin, et al., Decreased Expression of the Glial Water Channel Aquaporin-4 in the Intrahippocampal Kainic Acid Model of Epileptogeneis, Experimental Neurology, vol. 235 (2012).

[36] Pet. Ex. 34F is Menge, Cree, Saleh, et al., Neuromyelitis Optica Following Human Papillomavirus Vaccination, Neurology, vol. 79, 285 (2012).

together resulted in the increase in neuronal hyperexcitability and seizures secondary to the loss of osmotic homeostasis. Pet. Ex. 34G at 253.

Dr. Blitshteyn noted that the research linking the AQP-4 water channels to epilepsy started to be produced in about 2012. Tr. at 106. Dr. Steinman testified that "the water channels are a very important component of our ability to either be susceptible or resistant to seizures." Tr. at 153. In summary, he explained that the AQP-4 water channels are likely to play an important role in facilitating the transport of water and potassium back and forth across the cellular membranes. Tr. at 148. This process is critical to the maintenance of homeostasis or balance in the cellular environment. Tr. at 383. Sodium, water, and potassium are constantly moving back and forth across cellular membranes in the normal brain and in the extracellular space. Id. Disturbance of the balance of water and ion movement can result in unopposed excitatory impulses in the brain giving rise to seizures. Id. In reviewing studies done to date, the Lee article notes that experimental data parallel extensive clinical experience indicating that hypoosmolar states lower seizure thresholds while hyperosmolar states elevate seizure threshold and that millimolar increases in extracellular potassium concentration powerfully enhance epileptiform activity in the hippocampus. Pet. Ex. 34G at 246. This small increase in extracellular potassium can be produced by interference with water transport secondary to damage to the AQP-4 water channels. Id. As Binder observed, "brain tissue excitability is exquisitely sensitive to tissue osmolarity and the size of the extracellular space." Pet. Ex. 34O at 1204.

Given that the aquaporin-4 water channels in the brain are a relatively recent discovery and the investigation of their role in epileptogenesis even more so, the considerable amount of scientific interest and consistent opinion as to the role of dysfunctional aquaporin-4 water channels in the causation of epilepsy, particularly in the temporal lobe and hippocampus, gives significant support to the foundational basis of Dr. Steinman's theory. He makes reference to submitted articles and work by Lee, Binder, Menge, and Verkman, among others, proposing the same theory. Dr. Steinman's theory is persuasively supported in the literature as to the role of AQP-4 in the brain and as to the effect of damage to these water channels in the generation of frequent and prolonged epileptic seizures.

The second part of the theoretical basis for epileptic causation is its foundation in molecular mimicry between the Gardasil vaccine and the AQP-4 water channels in the mesial temporal lobe. Dr. Steinman explained that the homology between a foreign antigen and a self-structure is based upon the structural homology or identity between amino acids in the foreign antigen and the self. Tr. at 135-36, 143. Homology is usually discussed in terms of alphabetical or sequence homology. But the alphabetical homology is used essentially for ease of description. Tr. at 144. Drs. Steinman and Venkatesan agree that the actual chemical structure is determinative of the potential for molecular mimicry. Tr. at 145-56; 342. Dr. Steinman explained structural homology as analogous to a child building a castle with a Lego set. Tr. at 135-36. He explained that nature builds molecules that have similar molecular features. Id. What may be part of the major capsid protein in human papillomavirus can mimic a myelin protein or an aquaporin-4. Tr. at 135. When this occurs, cross reactivity may occur when the immune system, believing that it is attacking the foreign antigen, mistakenly attacks a self-antigen causing some people to develop autoimmune disease as a result. Tr. at 138. Dr. Steinman explained that an autoimmune response to the AQP-4 water channels can either kill the cell or block the channel. Tr. at 154. According to Dr. Steinman, both arms of

adaptive immunity can be at play, with the T-cells actually killing the underlying cells, and the antibodies, produced by B-cells, blocking the channel. Tr. at 154-55. He added that the B-cells can actually kill the cells if they stimulate complement. Id.

In this case, he focused upon the homology between AQP-4 and two strains of the Gardasil vaccine. As previously noted, Gardasil contains the capsid L1 protein of HPV types 6, 11, 16 and 18. In the Menge study, the authors found, using Blastp (Basic Local Alignment Search Tool for proteins-National Center for Biotechnology Information) that three sequence homologies between the L1 capsid protein of HPV 16 and 18, and AQP-4 were identified. Tr. at 25, 147. The authors stated that "three sequence homologies between AQP-4 and the L1 capsid proteins of HPV were identified, one being a shared epitope of HPV 16 and 18, and one unique to HPV 16 . . . . None of the three alignment pairs required gap insertions or substitutions for improved alignment." Pet. Ex. 34F at 286. Dr. Steinman testified that the five of nine amino acid homologies at two segments of HPV 16 and 18 with AQP-4, and six of thirteen amino acid identities at another segment of HPV 16, as shown in the Menge article, were sufficient to cause molecular mimicry. Tr. at 146. Dr. Steinman referenced the chart reported by researchers in the Menge article, showing the homology between Gardasil 16 and 18 and AQP-4. See Pet. Ex. 34F at 286.

Through cross examination, respondent emphasized that the four subjects on whom the Menge article reported as having experienced autoimmune disease after receiving the Gardasil vaccine did so at about the four-to-five month time period after the most recent vaccination. Tr. at 181-90; see generally Pet. Ex. 34F. Dr. Steinman acknowledged that it would be unlikely that an adaptive immune response would be the cause of the autoimmune disease in these young women that far out from the vaccination, at least by the frequently agreed upon period of eight weeks as the outside time period for an adaptive immune response, and so their conditions would not provide significant support for autoimmunity in themselves. Tr. at 185. However, the undersigned notes that this does not negate the value of the article. First, the basic research to which Dr. Steinman refers, in which homology between Gardasil viruses 16 and 18 and AQP-4 is shown through the computer database of the National Center for Biotechnology Information, detailing the amino acid sequences in the respective peptides, is of significant importance. Dr. Steinman testified that he selected the article because of the molecular mimicry table. Tr. at 192. Second, even if there were unquestioned homology between a vaccine and a self-structure such as AQP-4 or myelin basic protein, the disease causing autoimmune response would still be the atypical outcome. If it was not, then one would expect a very large number of autoimmune responses when there is homology between a body structure and a vaccine. Thus, even if the autoimmune diseases of the four study subjects in the Menge article are discounted based on timing, and they are, that does not discount the value of the research on homology showing the overlap in the requisite number of amino acids to serve as a foundation for molecular mimicry in a patient such as A.M.

The Menge authors did not find humoral cross reactivity, but also did not report on T-cell reactivity, which Dr. Steinman indicated was the important factor in experimental autoimmune encephalitis. Tr. at 193. Dr. Steinman referenced his work with colleagues on experimental autoimmune encephalomyelitis, in which he explained that experimental autoimmune encephalitis ("EAE") is "the quintessential autoimmune model for encephalitis." Tr. at 369-70; see Pet. Ex.

34D.[37] He stated that autoimmune encephalitis is mediated by T-cells because you cannot initially get antibodies across the blood brain barrier as they are too big. Tr. at 373. He testified that T-cells do cross the barrier, and once the barrier is broken, antibodies (B-cell produced) may become present. Id. Dr. Steinman referenced petitioner's exhibit 34D, which discussed the fact that he and his colleagues had demonstrated that homology at just five amino acids could induce EAE in mice, but noted that in the actual sequence shown, there were only three contiguous amino acids and EAE was still induced. Pet. Ex. 34D at 1280; Tr. 370. He explained that initially in the work on molecular mimicry, they had discussed the need for four or five amino acids in sequence, but that was in 1998 and "science is a work in progress," and we are now fifteen years past that initial study. Tr. at 370-71. He testified that it is now known that "dense sequence homology" is not needed. Tr. at 371. He made particular reference to petitioner's exhibit 34A which discussed that the FFK sequence in myelin basic protein had to be conserved for autoantibody binding, but that in T-cell autoimmunity, which is what is involved with encephalitis, the second F or phenylalanine in the FFK sequence may be substituted in the T-cell epitope by other hydrophobic acids. Tr. at 371; see Pet. Ex. 34A at 1119.[38]

Dr. Steinman also discussed the McKeon article. This article reported on a study of fifty-seven NMO serum IgG positive patients. See Pet. Ex. 34N at 94.[39] In the McKeon study ninety-eight percent (98%) of the patients had either optic neuritis or transverse myelitis consistent with neuromyelitis optica ("NMO")[40]. Pet. Ex. 34N at 95; Tr. at 204. But eleven percent (11%) also had seizures and/or encephalopathy in the temporal lobe. Tr. at 158. Given that NMO IgG was the selection criterion for the study, it is not surprising that ninety-eight percent (98%) of the patients had symptoms of NMO. The study found that sixty percent of the subjects had antibodies to AQP-4. Pet. Ex. 34N at 96. Although, A.M. does not have NMO, Dr. Steinman noted that eleven percent (11%) of the patients did present with seizures and that given the support in the other literature for the role of AQP-4 damage in epilepsy, the spectrum of non-NMO disorders shown in this study, including seizures, suggests a much broader role for AQP-4 in autoimmune encephalitis. Tr. at 158; Pet. Ex. 35N at 95. Dr. Steinman further referenced some of the papers that he submitted which talk about AQP4 water channels in the brain, and in particular in the hippocampus and temporal lobe. He explained that they are part of the fundamental homeostatic mechanism which allows water to move in and out of cells by travelling through these channels. Because of their integral role in maintaining osmotic homeostasis, he expressed the view that an immune response

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[37] Pet. Ex. 34D is Ruiz, Garren, Hirschberg, Steinman, et al., Microbial Epitopes Act as Altered Peptide Ligands to Prevent Experimental Autoimmune Encephalomyelitis, J. of Experimental Medicine, vol. 189, 1275-84 (1999).

[38] Pet. Ex. 34A is Wucherpfennig, Catz, Hausmann, Steinman, et al., Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2-restricted T Cell Clones from Multiple Sclerosis Patients, J. of Clinical Investigation, vol. 100, 1114-22 (1997).

[39] Pet. Ex. 34N is McKeon, Lennon, Lotze, et al., CNS Aquaporin-4 Autoimmunity in Children, Neurology, vol. 71, 93 (2008).

[40] Neuromyelitis optica or NMO is combined, but not usually clinically simultaneous, inflammation and demyelination of the optic nerve and the spinal cord. Dorland's at 1267.

against the AQP-4 channels can have an effect well beyond neuromyelitis optica particularly in the production of seizures. Tr. At 158, 383-84.

1. Dr. Venkatesan's Testimony

Dr. Venkatesan testified in response to the testimony of Drs. Blitshteyn and Steinman. He testified as a specialist in the field of encephalitis and as the director of a national encephalitis clinic at Johns Hopkins. He disagreed with the diagnosis of limbic encephalitis, questioned the degree of homology that would be necessary to cause an autoimmune attack, and stated that Dr. Steinman's theory was possible but that he would like to see more evidence for binding to support the diagnosis before he would be able to agree with it. He advocated a diagnosis of FIRES which has been addressed above.

The theory of molecular mimicry was also questioned by the respondent through Dr. Venkatesan's testimony. He questioned whether there was sufficient proof of homology to cause the response that Dr. Steinman described. Tr. at 267-68, 273. He also questioned whether enough proof existed of the excitatory and seizure producing effect of the absence of AQP-4 water channels in the knockout mice, and whether it equated to the same effect in humans. Tr. at 328. He questioned whether the effect would be the same if the AQP-4 channels were just reduced and not knocked out in the experimental mice. Tr. at 269. He testified that he did not think there was sufficiently reliable evidence developed to date to prove those points convincingly so that he could agree with this analysis of causation. Tr. at 328. Dr. Venkatesan said that it was difficult to come to a more specific diagnosis than FIRES based upon the available evidence in this case. Tr. at 292.

His questioning of homology largely focused on a 1997 article by Dr. Steinman and colleagues in which molecular mimicry with myelin basic protein was first described. See Pet. Ex. 34A; Tr. at 258-65. He questioned, based on this article whether sequence identity with at least four or five amino acids would be required to produce mimicry. Tr. at 273. Dr. Steinman however, in response, testified that science has moved on and that fifteen years later it is understood that the required structural homology does not require five sequential amino acids, but rather a three dimensional chemical structure that sufficiently fits together through the presence of both identical amino acids and similar substitutions. Tr. at 370-71. Dr. Venkatesan agreed that the potential for molecular mimicry is actually based upon structural homology rather than sequence homology, and that it is possible that there could be an entirely different set of amino acids that would sufficiently fit structurally that they could cause molecular mimicry. Tr. at 340.

In short, Dr. Venkatesan would have liked to have seen more definitive scientific studies of molecular mimicry, such as specific studies of cross reactive binding, and cause-and-affect between disruption of the aquaporin-4 water channels and the production of seizures. Tr. at 276; 328. However, he admitted that the type of studies he seeks to definitely establish evidence on the level of homology necessary for molecular mimicry are hard to undertake and hard to model. He candidly opined that the evidence that Dr. Steinman presents "is really the best evidence that we have at this point." Tr. at 267-68.

The type of evidence which Dr. Venkatesan would have preferred is more than is required to carry the burden of proof in the Vaccine Program. "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or

medical rules. The determination of causation in fact under the Vaccine Act involves ascertaining whether a sequence of cause and effect is 'logical' and legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548-49 (Fed. Cir. 1994).

While Dr. Venkatesan's view of the level of proof that he would like to see before attributing an autoimmune cause can be respected from a scientific point of view, it is requiring more than the law of the cases in this Program require. As the Federal Circuit observed in *Knudsen*, "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen*, 35 F.3d at 551 (quoting House Report 99-908 at 3, 1986 U.S. Code Cong. & Admin. News at 6344). The Program is "not to be seen as a vehicle for ascertaining precisely how and why vaccines sometimes destroy the health and lives of certain individuals while safely immunizing others." Id. at 549. To the extent that the fever played a role in pushing the adaptive response into full blown seizures, it is clear that the petitioner's experts testified that the adaptive reaction to the vaccine was a substantial factor in producing the severe seizure disorder, even if it was aided by the prodromal fever. Under *Shyface v Sec'y of Health & Human Servs.*, 165 F.3d 1344 (Fed. Cir. 1999), when two forces act in concert, as long as the vaccine was a "but for cause" and a substantial factor in producing the harm, causation may be found. I have concluded that the vaccine was the "but for cause" and substantial factor in the development of A.M.'s seizures, status epilepticus, and ongoing seizure disorder, as well as the severe cognitive deficits that she has suffered secondary to this illness.

As the Federal Circuit noted in *Althen,* "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen v. Sec'y of HHS*, 418 F.3d 1274, 1280 (Fed. Cir. 2005). "The assessment of whether a proffered theory of causation is reputable can involve assessment of the relevant scientific data. Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard . . . ." *Andreu v. Sec'y of HHS*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules. The determination of causation in fact under the Vaccine Act involves ascertaining whether a sequence of cause and effect is 'logical' and legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548-49 (Fed. Cir. 1994).

The Federal Circuit held in *Knudsen* that to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the Vaccine Compensation Program. Id. at 549. Dr. Steinman presented a physiologically reasonable and persuasive explanation of the role of the AQP-4 water channels in maintaining water and potassium homeostasis by managing the water flow into and out of cells and in the extracellular space. He testified persuasively to the role of impaired AQP-4 in generating seizures, a theory supported in multiple peer reviewed articles. He also testified as to the mechanism of molecular mimicry and presented evidence of sufficient homology between the HPV virus particles 16 and 18 in Gardasil and the aquaporin-4 water channels in the brain. As such, Dr. Steinman has reasonably and persuasively explained how molecular mimicry between the Gardasil 16 and 18 virus like particles and the aquaporin-4 water channels could cause the severe seizure disorders that befell A.M. In fact, petitioner has presented more specific evidence than that which would be

necessary to carry her burden, and I find that Dr. Steinman's and Dr. Blitshteyn's testimony and supporting literature have satisfied prong one of *Althen*.

Accordingly, I conclude that petitioner has shown by a preponderance of the evidence that autoimmune damage to the aquaporin-4 water channels can disrupt the critical water and potassium homeostasis in structures, including the hippocampus, giving rise to unopposed excitatory impulses and more frequent and prolonged seizures as demonstrated in the Lee study, consistent with Dr. Steinman's opinion. See Tr. at 153. Further, I have concluded that Dr. Steinman has presented evidence to support the mechanism of molecular mimicry between Gardasil and the AQP4 water channels sufficient to demonstrate that an adaptive immune response to these channels can occur secondary to the administration of the vaccine.

ii. *Althen* Prong Two

Proof of *Althen* prong two requires a logical explanation as to how the vaccine did cause the injury in the petitioner. "A logical sequence of cause and effect' means what it sounds like—the claimant's theory of cause and effect must be logical." *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). The proof need not rise to the level of scientific certainty but rather to the Vaccine Act's preponderance standard under the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.'" *Andreu*, 569 F.3d at 1378. A treating physician may rely on the close temporal proximity between a vaccine and an injury in concluding that there is a logical sequence of cause and effect between the vaccine and the injury. *Capizzano*, 440 F. 3d at 1326. "Requiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." Id. at 1325-26. A claimant was entitled to recover in *Althen* even "where her theory linking the tetanus vaccine to a central nervous system injury involved 'a sequence hitherto unproven in medicine.'" *Andreu*, 569 F.3d at 1378 (quoting *Althen*, 418 F.3d at 1280).

Dr. Steinman explained that the hippocampus is richly supplied with aquaporin-4 water channels. Tr. at 213. When A.M. presented with her severe seizure disorder and status epilepticus, she showed generalized slowing in the brain and epileptogenic activity in the mesial temporal lobe including the hippocampus. Her initial scans, not surprisingly, were negative, but eventually a PET scan, done on November 14, 2007, demonstrated hypometabolism in the left temporal lobe extending into the left occipital, temporal and parietal junction area. Pet. Ex. 4 at 461. These findings in the mesial temporal area are indicative of damage to that area of the brain. Tr. at 250. An MRI, done on November 8, 2007, identified a subtle increase in signal intensity of the cortex in the left temporal lobe and haziness of the gray-white matter interface, better seen on the FLAIR images consistent with seizure edema in the limbic area of the brain. Pet. Ex. 4 at 457. There was also a decrease in size of the hippocampal formation especially on the left side. Pet. Ex. 4 at 457. The findings in the left temporal lobe were interpreted as possibly representing areas of cortical dysplasia[41] associated with hippocampal sclerosis (scarring) or seizure edema with central and cortical atrophic changes (atrophy). Pet. Ex. 4 at 457-58. Dr. Venkatesan testified that these findings are suggestive of injury to the brain and very typical of someone who has been in status

[41] Cortical dysplasia is a genetic abnormality that can result in severe seizures. It was subsequently ruled out in the post lobectomy pathology report. Tr. at 22, 23; Pet. Ex. 23 at 164.

epilepticus. Tr. at 249. I have concluded that the imaging studies do not shed significant light on the triggering mechanism of the seizures, but they do localize the injury to the limbic area and in particular to the temporal lobe and hippocampus consistent with the diagnosis of limbic encephalitis.

When her doctors eventually decided to do a mesial temporal lobectomy (surgical removal of the mesial temporal lobe) before proceeding and after opening of the craniotomy, intraoperative electrocorticography (placing of electrodes directly on the exposed surface of the brain) was performed with a thirty-two channel EEG recording, which revealed a severely abnormal discontinuous background over the anterior and medial temporal lobe and temporal gyrus with diffuse irregular spikes in the bursting activity, which were seen most prominently over the anterior temporal pole. Pet. Ex. 23 at 168. These EEG readings from the open brain convincingly localized the seizure activity to the temporal lobe and the left hippocampus such that based on the finding of frequent discharges (descriptive of epileptic or seizure activity) arising from the anterior two centimeters of the temporal lobe and the medial structures, the surgeons decided to remove the anterior two centimeters of the temporal lobe and proceeded with dissection of the mesial structures including the amygdala and the left hippocampus. The operating surgeon observed that "the hippocampus was quite obviously scarred." Pet. Ex. 23 at 131.

The electrocorticography readings, as well as the surgeon's observation of the open brain, were sufficiently convincing of the locale of the seizure generation to justify the decision to remove the left mesial temporal lobe of the brain. They are also sufficiently convincing to localize the source of the seizures in the limbic area of the brain for the purposes of this case.

The pathology report indicated the presence of Chaslin's gliosis, heterotopic neurons in the subcortical white matter, no evidence of cortical dysplasia, and scattered foci of macrophage proliferation and gliosis. Pet. Ex. 23 at 164. Dr. Venkatesan explained that Chaslin's gliosis is a type of gliosis that is associated with status epilepticus. Tr. at 251. He noted that there were no findings of active inflammation at the time that the surgery was done, but he acknowledged that the operative procedure performed more than fourteen months after the onset of seizures did not rule out inflammation at the outset. Tr. at 251. He stated that the pathology findings indicated damage and that scarring is a reaction to damage that was likely the result of refractory seizures and status epilepticus. Tr. at 365.

All of the above findings are consistent with Dr. Steinman's theory that A.M. suffered damage as a result of molecular mimicry to the aquaporin-4 water channels causing severe generalized seizures in the temporal lobe and status epilepticus. These findings are consistent with an autoimmune limbic encephalitis triggered by cross reactivity to strands 16 and 18 of the Gardasil vaccine. They could also be consistent with a less specific diagnosis such as FIRES, but they are not inconsistent with limbic encephalitis and do strongly localize the source of the seizures to the limbic area of the brain.

Dr. Steinman also addressed the issue of the prodromal fever that A.M. experienced in the days before the onset of her seizures. The fever may have been secondary to "strep throat." A.M. initially tested negative for strep, but on September 26, 2007, the day before her seizures began, she had a positive strep test. Dr. Steinman said, and Dr. Venkatesan agreed, that it was unlikely

that the strep directly caused the seizures as strep would likely cause much different conditions which A.M. did not have. It would be unlikely to cause encephalitis. Tr. at 211, Tr. 287. However, according to Dr. Steinman, if she had the underlying adaptive immune response to the vaccine building at the time of the fever, the fever may have been enough to push her off the edge into this intractable seizure disorder but the adaptive immune response remained the dominant force at work. Tr. 211, 175. Interestingly, support for this proposition is found in respondent's exhibit M, a study of patients diagnosed with FIRES by van Baalen and colleagues. After reviewing all of the data in their study, the authors noted that many patients suffered a biphasic course in which the fever preceded the seizures and may have played a role in triggering them, but that the seizures and not the fever became the main clinical course, as was the case with A.M. van Baalen noted that frequently there was no specific evidence of inflammation, and concluded:

> "Altogether, this points to neuronal hyperexcitation rather than to inflammatory cerebral damage as the leading process. Accordingly, the main clinical course was dominated by intractable recurrent or prolonged seizures but not by fever. In our cohort, fever was considerably more characteristic before than at seizure onset . . . There is increasing evidence for involvement of the immune system in the pathogenesis of some forms of severe epilepsy syndrome." Res. Ex. M at 1328.

Dr. Steinman's theory of an autoimmune attack on the aquaporin-4 water channels in the temporal lobe, and especially the hippocampus, is consistent with van Baalen's observation. The prodromal fever may have played a role in triggering the seizures but the adaptive immune process was likely the dominant factor in their production. The autoimmune disruption of osmotic homeostasis, giving rise to hyperexcitation and seizures in the temporal lobe, is exactly the theory proposed by Dr. Steinman, which is supported by the aquaporin-4 literature such as the articles by Binder and Lee.

Dr. Steinman explained the process of a differential diagnosis that he applied in reaching his conclusion as to causation in this case. He explained that molecular mimicry between Gardasil and AQP-4 were at the top of his differential:

> It was at the top of my differential diagnosis and way higher than all the rest, and it's there because there's a plausible scientific mechanism for relating aquaporin-4 to a neurologic problem that could be seizures, in which case, it was with [A.M.]. There are segments in the Gardasil vaccine that are similar to aquaporin-4. We know that aquaporin-4 immunity can lead to seizures. So we have a scientific basis for making that claim. The time frame is right.
>
> And then I said I made a differential diagnosis. So the list–on the list was—and still is—viral encephalitis. But I can't find the virus. And they looked very, very hard. So, that goes to a much lower position, far beyond 50 percent probability, somewhere around closer to zero percent because I don't know what it is. And they also ruled out other metabolic and genetic possibilities.
>
> Now tomorrow, they might find out it's some other virus that we never heard of, but until that comes, for my purposes, I think that beyond reasonable

doubt, it was the Gardasil vaccine that triggered her horrendous seizure situation. Tr. at 164-65.

At a later point in the testimony, when asked by the undersigned whether there was anything else from an evidentiary standpoint that helped him to put the autoimmune response to Gardasil at the top of his differential diagnosis, Dr. Steinman responded that the fact that A.M. had a prior autoimmune disease, idiopathic thrombocytopenic purpura at age eight makes him think that she has more propensity to break down self-tolerance. Tr. at 380. He noted that strep could also cause a breakdown in normal tolerance, but that strep could not have done this directly because it causes other autoimmune diseases not consistent with what happened here. "So given her propensity to autoimmune disease, the Gardasil rises ahead of the strep." Tr. at 380.

Dr. Venkatesan also agreed that a child who had a previous autoimmune disorder such as idiopathic thrombocytopenic purpura, as A.M. had at the age of eight may make a patient more susceptible to a subsequent autoimmune disorder. Tr. at 349-50. Dr. Steinman stated that the prior ITP reinforced his differential diagnosis of causation in this case. Tr. at 380.

Differential diagnosis is a well-accepted medical methodology for determining diagnoses and causation. It has been accepted by multiple courts under a *Daubert* analysis. The Third Circuit addressed the reliability of differential diagnosis as a method for assessing causation. The court held:

> We have recognized that differential diagnosis is a technique that involves assessing causation with respect to a particular individual, *In Re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 758 (3d Cir. 1994). Differential diagnosis is defined for physicians as "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings." STEDMAN'S MEDICAL DICTIONARY 428 (25th Ed. 1990). The elements of a differential diagnosis may consist of the performance of physical examinations, the taking of medical histories, and the review of clinical tests, including laboratory tests. A doctor does not have to employ all of these techniques in order for the doctor's diagnosis to be reliable. See *Paoli,* 35 F.3d at 759. A differential diagnosis may be reliable with less than all the types of information set out above. See id. Indeed as we held in *Paoli* to the extent that the district court concluded otherwise [i.e. that a differential diagnosis made on less than all types of information cannot be reliable] we hold that it abused its discretion . . . . As noted by this court in *Paoli*, evaluation of the patient's medical records is a reliable method of concluding that a patient is ill even in the absence of a physical exam. *Kannankeril v. Terminix*, 126 F.3d 802, 807-08 (3d Cir. 1997).

I conclude that Dr. Steinman applied reliable methodology in making his differential diagnosis, which is supported by his own extensive scientific research regarding molecular mimicry and is consistent with medical literature regarding AQP-4 and epilepsy, as well as his review of A.M.'s extensive medical records.

Respondent argues that the treating physicians did not suspect a connection of Gardasil to the seizures. It is not clear from the records that they even considered the vaccine before 2013, when two of her physicians raised the issue. However, given the extensive expert analysis in this case, A.M. can still satisfy this prong of the *Althen* test. Further, the fact that the treating physician's ruled out all other known potential causes significantly reinforces this conclusion. In order to establish that petitioner's vaccination did cause her injury, she is "permitted to use evidence eliminating other potential causes to help carry the burden on causation." *Walther v. Sec'y of HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007). In fact, "the exclusion of alternative etiologies is usually quite probative with respect to prong two of the *Althen* analysis – i.e., whether the vaccine caused the injury in a particular case." *Caves v. Sec'y of HHS*, 100 Fed. Cl. 119, 144 (Fed. Cl. 2011), *aff'd,* 463 F. App'x 932 (Fed. Cir. 2012).

In this case, Dr. Steinman testified that the physicians at Miami Children's Hospital tried very hard to identify a viral, genetic or metabolic cause of A.M.'s seizures and essentially ruled out all known alternative causes. Tr. at 381. Dr. Venkatesan also agreed that they had been quite comprehensive in ruling out known causes. Tr. at 381. Both doctors agreed that there may be an unknown virus or as yet unidentified autoimmune, genetic or molecular cause that could have been at work in this case. Tr. at 164-65. But in 2007 and 2008, when A.M. was hospitalized with this severe seizure disorder, extensive testing did not identify an alternative cause. The Federal Circuit has held, "[a]ny idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition' may not be considered a 'factor [] unrelated to the administration of the vaccine' and therefore cannot defeat a petitioner's recovery." *Knudsen*, 35 F.3d at 547-48 (quoting 42 U.S.C. § 300aa-13(a)(2)).

For all of the above reasons, I have concluded that Dr. Steinman and Dr. Blitshteyn have presented a logical cause and effect explanation of the way molecular mimicry caused the severe seizure disorder and status epilepticus in A.M. by damaging the AQP-4 water channels, and further find that Dr. Steinman's explanation of molecular mimicry between Gardasil 16 and 18 and the AQP-4 water channels to be logical, persuasive and preponderant.

E. Alternative Cause

The Vaccine Act permits the respondent to present evidence of an alternative, unrelated cause once the petitioner has made out a case sufficient to satisfy the *Althen* prongs. In this case, the respondent did not propose FIRES as an alternative, unrelated cause but rather as a question of the appropriate diagnostic entity at issue. But even if the respondent had presented FIRES as an alternative cause, the result would have been the same. FIRES is at its essence a collection of idiopathic symptoms. Dr. Venkatesan testified that if a specific autoantibody was identified that could cause the symptoms, he would take the diagnosis out of FIRES. That testimony is much like that which was offered by the respondent in *Koston v. Sec'y of HHS ,* 974 F.2d at 157 (Fed. Cir. 1992), where the respondent's experts described the symptoms of Rett Syndrome as an alternative explanation for a seizure disorder which fit the petitioner's symptoms but acknowledged that medicine had not identified a cause for the condition. The Federal Circuit held, that "[s]ection 300aa-13(a)(2)(A) defines unrelated factors as not including 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness, or condition.' Since the word 'or' is used with both the adjectives (idiopathic, unexplained, unknown,

or hypothetical) and the nouns (cause, factor, injury, illness, or condition), it is apparent that an unrelated factor is not an idiopathic illness, an unexplained illness, or an unknown cause. As [petitioner] says, '[t]he statute is plain enough. An 'idiopathic' condition, or a condition with an 'unknown cause', is not a 'factor unrelated to the administration of the vaccine.'" Id. at 160.

The Federal Circuit further stated that it did not suggest that Rett Syndrome could never be an unrelated factor if someday the medical community identified a specific cause for it. Id. at 161. But under the state of knowledge about the condition at the time, it held that an idiopathic diagnosis such as Rett Syndrome could not be an unrelated factor used to defeat compensation under the language of the statute. Id. The undersigned finds this case persuasive in applying the same logic here.

IV. Conclusion

I find that petitioner has presented a persuasive medical theory and a logical explanation of cause and effect in this case consistent with the theory of causation. Further, the parties agreed that despite extensive testing there was no identified alternative cause such as a virus or bacteria. They have further stipulated, and I agree, that the timing of the onset of A.M.'s seizure disorder relative to the second dose of Gardasil was medically appropriate for the theory of molecular mimicry. I therefore conclude that petitioner has satisfied her burden under *Althen*.

Ultimately, there can be no doubt that A.M. suffered a devastating seizure disorder and early status epilepticus resulting in severe damage to her mesial temporal lobe which would be consistent with limbic encephalitis or FIRES. She has also suffered severe neuropsychological or cognitive damage as documented after she came out of her coma and subsequently, which is consistent both with ALE and a post status epilepticus condition. Drs. Blitshteyn and Steinman have presented theories of causation that are sufficiently probable to satisfy the preponderant evidentiary requirements of *Althen* in this Program. As such, I have concluded that petitioner has presented sufficient evidence to establish causation in this Program and she is entitled to compensation.

A separate damages order will issue.

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master