In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 07-857V

Filed: March 7, 2011

LAURA CONWAY, as parent of her minor child, CASSIDY CONWAY, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	TO BE PUBLISHED Entitlement; Causation in fact; Significant Aggravation; Tuberous Sclerosis; MMR; Seizures; Epilepsy

Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for Petitioner.
Lisa Watts, United States Department of Justice, Washington, D.C. for Respondent.

DECISION ON ENTITLEMENT[1]

LORD, Chief Special Master.

I. INTRODUCTION

On December 5, 2007, Petitioner Laura Conway filed a petition under the National Childhood Vaccine Injury Act ("Vaccine Act" or "Act") on behalf of her daughter Cassidy.[2] Petitioner alleged that vaccinations administered on March 31, 2006, were a cause in fact of Cassidy's intractable epilepsy. Petitioner's theory was that the Measles-Mumps-Rubella ("MMR") vaccination significantly aggravated Cassidy's underlying tuberous sclerosis ("TS") by causing Cassidy to have a complex partial seizure and develop epilepsy. An entitlement hearing was convened on March 11 and 12, 2010, and the case is now ready for decision.

[1] The undersigned intends to post this decision on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire ruling will be available to the public. Id.

[2] The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 et seq. (2006). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Vaccine Act.

At the time of vaccination, Cassidy Conway was a 20-month-old with tuberous sclerosis, a genetic condition known to cause seizures in many patients.[3] She also had suffered from infantile spasms ("IS"), a condition that frequently signals a poor outcome for children with TS. At the time of the vaccination in question, which occurred on March 31, 2006, Cassidy had had no seizures for 14 months. Petitioner alleged that, within hours of administration of the vaccine, Cassidy suffered a seizure leading to neurological injury and serious developmental delay. Alternatively, Petitioner asserted that Cassidy suffered an adverse reaction to the measles component of the MMR vaccine leading to a condition known as viremia, and that this reaction triggered a seizure not hours but days after her March 2006 vaccination.

Petitioner's main theory claimed that Cassidy's post-vaccination seizure was caused by an immune-mediated response to her vaccinations. Petitioner asserted that, because Cassidy had TS, she had an abnormally low seizure threshold. According to Petitioner's expert, Cassidy's vaccinations caused her immune system to produce proinflammatory cytokines, some of which are associated with seizures.[4] The blood circulated those cytokines to Cassidy's brain, where they agitated abnormal collections of cells caused by TS, known as tubers, and induced a seizure. Although the immune system naturally produces such cytokines when it encounters a foreign substance, Petitioner asserted the reason cytokines caused a seizure on this occasion was most likely that Cassidy's TS had evolved as she matured.

Respondent countered that the temporal relationship between the seizure and the vaccination was coincidental, and the two were not causally related. According to the Secretary, Cassidy's pre-existing medical problems, TS and IS, made it much more likely than not that she would eventually experience seizures and epilepsy resulting in serious brain dysfunction. Respondent maintained that Petitioner's cytokine theory would be plausible only if the reaction were accompanied by a generalized immune response such as high fever and/or other signs of inflammation. Respondent asserted that Cassidy showed no evidence of fever, rash, an acute encephalopathy, or other symptoms at the time of vaccination and onset of seizures. With respect to the alternative viremia theory, the Secretary maintained that the seizure took place too soon to be consistent with such a reaction.

It is undisputed that vaccines, like other foreign substances, cause the body to release various cytokines, and that cytokines may be associated with an inflammatory response. Petitioner's expert believes that cytokines can cause seizures, and that Cassidy has a low seizure threshold because of her TS. Petitioner presented no evidence, however, other than the expert's speculative opinion, of a lower seizure threshold, and no reliable evidence that the production of cytokines caused Cassidy to suffer seizures.[5] Much more persuasive was

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[3] TS is a genetic disease characterized by "hamartomas of the brain (tubers) that can cause seizures and mental retardation . . . and skin lesions." Dorland's Illustrated Medical Dictionary (31st ed. 2007) 1706.

[4] A cytokine is a chemical released by a cell, and it is used as an intercellular mediator in generating an immune response. Dorland's at 473. Proinflammatory cytokines refers to a class of cytokines that causes inflammation (by recruiting more cells to the area) as part of the immune response to invading organisms. Tr. at 28.

[5] See Hanlon v. Sec'y of Dep't of Health & Human Servs., 191 F.3d 1344, 1349 (Fed. Cir. 1999). In Hanlon, the Federal Circuit upheld the Court of Federal Claims' affirmance of the Special Master's decision, and agreed that "'where a TS child receives DPT vaccine and remains perfectly normal (in temperature, eating, sleeping, affect, and activity) but has a[n] [afebrile] seizure within three days, TS, not

Respondent's presentation concerning the known neurological mechanism, genetic in origin, by which TS causes seizures. That mechanism, according to the Secretary, is not affected by vaccination.

Due to Cassidy's pre-existing TS, Petitioner would prevail only if she proved more likely than not that Cassidy's condition was significantly aggravated by vaccination. Upon review of all the evidence, Petitioner has not proven a prima facie case of significant aggravation. See Loving v. Sec'y of Dep't of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009) (setting forth the elements of a prima facie case of off-Table significant aggravation). Preponderant evidence does not support the contention that vaccination caused significant aggravation of Cassidy's TS. Accordingly, the petition for compensation is dismissed.

II. BACKGROUND

A. Cassidy's Medical History

Cassidy and her twin sister were born on June 25, 2004. Pet'r Ex. 1 at 1. Shortly after birth, Cassidy was observed to have an irregular cardiac rhythm. Pet'r Ex. 3 at 29. On July 8, 2004, Cassidy saw her pediatrician, Brian Stratta, M.D., who noted that Cassidy had a heart arrhythmia. Pet'r Ex. 16 at 25. Dr. Stratta recommended that Cassidy be evaluated for tuberous sclerosis. See id. at 4, 24.

Tuberous sclerosis is a genetic disease that can affect the skin, brain, heart, eyes, and lungs, along with many other organ systems. Nelson's Textbook of Pediatrics (Robert Kliegman, M.D., et al. eds., 18th ed. 2007) at 2485. TS causes growth of hamartomas, which are benign, tumor-like nodules composed of an overgrowth of cells and tissues. Dorland's at 830. Skin lesions, brain and eye lesions, and rhabdomyomas of the heart are major features of TS. Nelson's at 2485.[6] The characteristic brain lesion is a cortical tuber, which is a hamartoma on the surface of the brain. Dorland's at 1706, 2004; see also Nelson's at 2486. "TS is an extremely heterogeneous disease with a wide clinical spectrum varying from severe mental retardation and incapacitating seizures to normal intelligence and a lack of seizures, often within the same family." Nelson's at 2485.

On July 16, 2004, Cassidy was admitted to the hospital for monitoring, for "possible seizures, [and to] [r]ule out tuberous sclerosis." Pet'r Ex. 3 at 231-32. An MRI of her brain and an electroencephalogram ("EEG") were normal. Pet'r Ex. 16 at 4; Pet'r Ex. 3 at 231. She was discharged the next day. On July 21, 2004, Cassidy was re-admitted to the hospital. Pet'r Ex. 3 at 105. A complete pediatric echocardiography showed some abnormalities in Cassidy's heart. Id. at 116-17. The diagnosis was that Cassidy likely had cardiac rhabdomyomas. Id.

Cassidy continued to receive her childhood immunizations. On December 21, 2004, Cassidy saw Dr. Stratta and received her third DT, Hib, and PCV vaccinations. Pet'r Ex. 6 at 1.[7]

DPT, is the cause in fact of that seizure.'" Hanlon, 191 F.3d at 1349 (quoting Barnes v. Sec'y of Dep't of Health & Human Servs., 1997 WL 620115, *33 (Fed. Cl. Spec. Mstr. Sept. 15, 1997)) (Table case).

[6] A rhabdomyoma is a benign tumor of striated muscle such as the heart. Dorland's at 1662.

[7] In Dr. Stratta's notes, the routine vaccinations are typewritten on a standardized form. Dr. Stratta crossed out "DTaP" and wrote "DT" by hand above it. Pet'r Ex. 16 at 10.

At that visit, Dr. Stratta observed that Cassidy might have tuberous sclerosis. Pet'r Ex. 16 at 10. A few days after that visit, Petitioner first noticed that Cassidy "was experiencing some weird eye blinking and eye watering." Aff. of Laura Conway, May 11, 2008, at 2-3 (Pet'r Ex. 22). These episodes eventually were diagnosed as infantile spasms ("IS").[8]

On January 3, 2005, Cassidy saw Dr. Stratta, who recommended that Cassidy see Ammar Katerji, M.D., a pediatric neurologist, for her episodes. Pet'r Ex. 16 at 29. Dr. Katerji saw Cassidy on January 8, 2005, and he opined that Cassidy had infantile spasms and that she "most likely . . . will be fitting the criteria for tuberous sclerosis." Pet'r Ex. 3 at 165.

On January 11, 2005, Dr. Katerji started Cassidy on vigabatrin. Pet'r Ex. 14 at 15. On January 25, 2005, Dr. Katerji noted that, "After one or two days of medication, [Cassidy's] spasms subsided completely. . . . She has had her EEG repeated, which showed improvement." Id. at 12. On February 15, 2005, Dr. Katerji reviewed a follow up EEG, and stated that "this time [Cassidy's EEG] was normal[,] no further hypsarrhythmia, no epileptiform activity." Id. at 10.[9] On March 1, 2005, Dr. Stratta agreed that Cassidy's medication for infantile spasms "has just done a wonderful job of keeping those under control." Pet'r Ex. 16 at 30. Cassidy's infantile spasms did not recur.

In March 2005, Cassidy underwent a variety of developmental evaluations. A developmental therapy evaluation showed that Cassidy's development was within the normal range, but she required intervention in the areas of cognitive and physical development, speech and language development, social-emotional development, and adaptive self-help skills. Pet'r Ex. 7 at 38-40. It was determined that Cassidy was eligible for Early Intervention Services. Id. at 40, 46, 50.

On April 5, 2005, Cassidy had a genetic evaluation for tuberous sclerosis. Pet'r Ex. 14 at 72. According to the geneticist, TS is associated with mutations in two genes: TSC1 and TSC2. Id. at 73. Tests revealed a mutation of Cassidy's TSC2 gene. Id. Due to Cassidy's gene mutation, cardiac rhabdomyoma, and other clinical features, the geneticist confirmed the diagnosis of tuberous sclerosis. Id.[10]

On February 3, 2006, Dr. Katerji found that Cassidy was doing well, and that she should continue her medication. Id. at 4. He also observed that Cassidy had been discharged from therapy. Id.[11] On March 10, 2006, Cassidy's pediatric cardiologist stated that Cassidy's cardiac

[8] Infantile spasms are a type of seizure disorder that only affects infants. IS is characterized by brief episodes of flexion or extension and by specific findings on an EEG. Tr. at 306-07. It is rare to see infantile spasms beyond 12-15 months of age. Tr. at 147. As noted above, Cassidy was 20 months old when she received the vaccines at issue in March 2006.

[9] Hypsarrythmia is a brain wave abnormality, characterized by random high voltage spikes, that is commonly associated with IS. Dorland's at 921, 1713.

[10] The parties agreed that the TSC2 mutation causes "'greater cognitive and overall disease severity'" in patients with TS. See Tr. at 43-44 (quoting Elizabeth Winterkorn et al., Cognitive Prognosis of Patients with Tuberous Sclerosis Complex, 68 Neurology 62-64 (2007) (Pet'r Ex. 24-G)).

[11] It appears that Dr. Katerji may have meant that Cassidy had been discharged from one type of therapy. On March 13, 2006, Cassidy's speech and language therapist recommended continued therapy in four different areas. Pet'r Ex. 7 at 25. On March 30, her physical therapist recommended continued

tumors had regressed. Pet'r Ex. 17 at 377. An echocardiographic study performed that day was unremarkable. Id. The cardiologist recommended arranging a 24-hour Holter monitor study for Cassidy. Id. at 378.[12]

On March 2, 2006, Cassidy was hospitalized for a few days. Id. at 372-75. Her mother reported she had had symptoms of an upper respiratory infection for the past week and she had vomited nine times the night before. Id. at 373. The final diagnosis was croup. Id. at 374. She was discharged on March 3, 2006.

On March 31, 2006, Cassidy received her first MMR vaccine, a varicella vaccine, and a third IPV vaccine. Pet'r Ex. 5 at 1-2. Petitioner has alleged that this MMR vaccination significantly aggravated Cassidy's tuberous sclerosis. Petitioner has claimed that Cassidy's seizures started on the evening of March 31, 2006.

On April 1, 2006, Cassidy underwent a Holter monitor study. Pet'r Ex. 17 at 427. The study was abnormal, indicating sinus tachycardia and several premature arterial contractions. Id.[13] The record from this test does not show whether Cassidy's temperature was taken.

Sometime between March 31 and April 3, 2006, Petitioner contacted Dr. Katerji because Cassidy was experiencing seizures. See Pet'r Ex. 3 at 341; Pet'r Ex. 14 at 2. On April 3, 2006, Dr. Katerji referred Cassidy for a sleep disturbance EEG. On the referral, Dr. Katerji listed the diagnosis as seizures. Pet'r Ex. 3 at 341. On April 5, 2006, Cassidy underwent an EEG, and the EEG, which recorded both awake and sleep brain activity, was normal, with "no lateralization, focal slowing, or epileptiform activity." Pet'r Ex. 17 at 430.

On April 11, 2006, Cassidy had an annual developmental evaluation with a developmental therapist. Pet'r Ex. 7 at 14. The evaluator's notes indicated that Petitioner reported that Cassidy's behavior that day was normal. Id.

On April 12, 2006, Cassidy was admitted to the hospital by Dr. Katerji due to seizure activity. Pet'r Ex. 9 at 3. According to the history given by Petitioner, Cassidy had been experiencing up to four seizures per day for the past 12 days, and they started two hours after Cassidy received her vaccinations. Id. at 6-7. Petitioner reported that the seizures were brief, maybe 15-30 seconds, and she described Cassidy as having a furrowed brow, with staring and blinking. Id. at 3. At the time of admission, Cassidy had a low grade fever and a lacy erythematous rash that was macular on her trunk. Id. at 3-7. Petitioner reported that Cassidy had run a low grade fever over the weekend. Id. at 7.[14] Cassidy had a 48-hour EEG with video, but no seizures were detected. Id. at 2. Cassidy was discharged on April 14, 2006, with a diagnosis of seizures and tuberous sclerosis. Id.

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therapy in two different areas. Id. at 19. On April 11, 2006, her developmental therapist recommended continued therapy in three different areas. Id. at 16.

[12] A Holter monitor is an electrocardiograph monitor that attaches to a person's body, allowing the person to walk around. Dorland's at 1194. Cassidy regularly underwent such studies.

[13] Previous Holter monitor studies showed similar results. See, e.g., Pet'r Ex. 17 at 346A (1/8/2005), 425 (9/15/2005).

[14] Although it is not clear which weekend the note is referring to, the weekend before April 12, 2006, was April 8 and 9, 2006.

Cassidy continued to undergo evaluation of her condition. A July 27, 2006, MRI showed that "[t]iny bilateral subependymal tubers [had] developed" on Cassidy's brain. Pet'r Ex 3, at 364-65. On August 31, 2006, Petitioner received a second opinion that confirmed the diagnosis of tuberous sclerosis, complex partial seizures, and speech delay. Pet'r Ex. 14 at 32.

Over the next year, the medical records show that Cassidy continued to be treated for her seizure disorder. On October 1, 2007, Cassidy underwent a craniotomy with grid placement. Pet'r Ex. 17 at 41.[15] By December 13, 2007, Cassidy's condition was somewhat improved; although she was still having the same number of seizures, they were shorter and less intense. Id. at 9. She underwent brain surgery again on June 3 and 6, 2008. Pet'r Ex. 27 at 11.

B. Procedural History Regarding Possible Viremia

On July 17, 2008, Petitioner filed an expert report by pediatric neurologist Marcel Kinsbourne, M.D. In his report, Dr. Kinsbourne asserted that proinflammatory cytokines aggravated tubers on Cassidy's brain, which led to a seizure and epilepsy. Pet'r Ex. 24. The report did not set forth any other theory of causation. At the expert hearing on March 11 and 12, 2010, however, Petitioner's counsel propounded a second, alternative theory of causation, that Cassidy suffered viremia, which is an immune response to viral particles in the blood stream.

After reviewing the transcript of the hearing, it appeared that the parties had not fully addressed Petitioner's alternative theory of causation. Respondent's expert, pediatric neurologist Mary Anne Guggenheim, M.D., had agreed at hearing that, eight days after vaccination, Cassidy showed symptoms consistent with an MMR vaccine viremia. Dr. Guggenheim conceded that the MMR vaccination is known to cause viremia in some cases. Symptoms of viremia include fever and rash, and such a reaction typically occurs 6 to 12 days following vaccination. This possible theory of causation was not fully developed because the parties had assumed at hearing that Cassidy's seizures started on the same day as her vaccination, as reported by Petitioner.

Based upon my review of the medical records, however, it appeared that the only medical record documenting the onset of Cassidy's seizures was created on April 12, 2006, twelve days after vaccination; the contemporaneous medical records did not corroborate this onset date. Between March 31 and April 12, 2006, Petitioner had three visits with health care providers. None of the records of those visits documented the onset of seizures. The silence of the medical records about seizures was noted by Dr. Guggenheim in her expert report. See Resp't Ex. A at 2.

To discuss this possible discrepancy, I held a status conference with the parties on October 20, 2010. I informed the parties that, in light of Respondent's admission that Cassidy's condition was consistent with an MMR vaccine reaction and on the absence of corroboration of

[15] According to the National Institutes of Health's website, a craniotomy is a surgical procedure in which part of the brain is removed. National Library of Medicine, Brain Surgery, Medline Plus (last updated: January 22, 2009), http://www.nlm.nih.gov/medlineplus/ency/article/003018.htm. Many young TS patients are considered for surgery, especially if seizure activity seems to predominantly focus on one tuber or area of the brain. Gregory Holmes et al., Tuberous Sclerosis Complex and Epilepsy: Recent Developments and Future Challenges, 48(4) Epilepsia 617-30 (2007) (Resp't Ex. C).

the onset date in the contemporaneous medical records, I was considering making a fact finding that Cassidy's seizures did not start until April 8, 2006. Under that scenario, Petitioner might have been able to show entitlement under a viremia theory of causation. I noted that other special masters have concluded that the MMR vaccine is capable of causing fever-mediated seizures. See Cusati v. Sec'y of Dep't of Health & Human Servs., No. 99-492V, 2005 WL 4983872 (Fed. Cl. Spec. Mstr. Sept. 22, 2005). Because the parties had not addressed these issues at hearing, I allowed them to submit evidence regarding the onset of Cassidy's seizures and whether Cassidy's seizure could have been caused by viremia.

On December 15, 2010, Respondent filed a supplemental expert report from Dr. Guggenheim. Resp't Ex. N. In her report, Dr. Guggenheim identified a referral from Dr. Katerji, dated April 3, 2006, for Cassidy to have an EEG and listing Cassidy's diagnosis as seizures. Because Cassidy's next regular appointment with Dr. Katerji had not been scheduled until the following summer, this referral most likely was provided at the request of Cassidy's mother. That would indicate the seizure occurred before April 3, 2006 – too soon for a viremic reaction. Dr. Guggenheim opined that viremia did not cause Cassidy's seizures because the seizures, if they commenced before April 3, 2006, started one week before the viremic symptoms noted in the medical record. See Resp't Ex. N.

On January 13, 2011, Petitioner filed a response to Dr. Guggenheim's report. Petitioner stated that, on April 3, 2006, Dr. Katerji did not include a note that set forth his thinking in referring Cassidy to have an EEG. Petitioner argued that the April 5, 2006, EEG was interpreted as "normal" and not consistent with the occurrence of daily seizure activity. On this basis, Petitioner asserted that no evidence could corroborate the March 31, 2006 onset date, and a finding of a later onset date would be warranted.

On January 21, 2010, I held another status conference with the parties. The parties had no further evidence to submit, and they agreed that this case was ripe for decision.

C. Findings of Fact and Conclusions of Law Regarding Viremia

The preponderance of the evidence indicates Cassidy's seizures started on March 31, 2006. Dr. Katerji's referral confirmed Petitioner's April 12, 2006, statements that Cassidy's seizures started soon after her vaccination. In addition, further investigation of the medical records revealed that Cassidy had a session with her developmental therapist on April 3, 2006. During the evaluation, the therapist noted that Cassidy's right eye began to twitch and "mom reported it may be a sign of absent [sic] siezures [sic]." Pet'r Ex. 10 at 39. These records confirm that Cassidy's seizures more likely than not started shortly after vaccination. Petitioner's arguments to the contrary are unpersuasive. According to the evidence in the therapist's notes, Dr. Katerji's referral, and the medical history given by Petitioner on April 12, 2006, Cassidy's seizures started on March 31, 2006. The onset of Cassidy's seizures therefore is too soon for their cause to be viremia.

III. DISCUSSION

A. Petitioner's Burden of Proof

The Vaccine Act created the National Vaccine Injury Compensation Program ("Vaccine Program") under which compensation may be paid for vaccine-related injury or death. § 10(a);

Walther v. Sec'y of Dep't of Health & Human Servs., 485 F.3d 1146, 1149 (Fed. Cir. 2007).[16] Among the injuries for which compensation is available is significant aggravation of a vaccinee's pre-existing medical condition. Significant aggravation is defined as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 33(4).

The burden of showing a prima facie case of significant aggravation is on the petitioner, and Respondent "is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief." Doe 11 v. Sec'y of Dep't of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) (quoting de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008)). Only if the petitioner satisfies the prima facie burden is the Secretary required to prove "'that the pre-existing condition was, in fact, the cause of the individual's post-vaccination significant aggravation.'" Loving, 86 Fed. Cl. at 144 (quoting Whitecotton v. Sec'y of Dep't of Health & Human Servs., 81 F.3d 1099, 1106 (Fed. Cir. 1996)). If the petitioner fails to establish a prima facie case of causation, the burden does not shift. Doe 11, 601 F.3d at 1357-58.

The elements comprising the prima facie case consist of three factors relating to significant aggravation plus three factors relating to causation. The petitioner must prove (1) the vaccinee's condition before administration of the vaccine; (2) the vaccinee's current condition; (3) "significant aggravation" of the vaccinee's condition after vaccination; (4) a medical theory causally connecting the significant aggravation to vaccination; (5) a logical sequence of cause and effect showing that vaccination was the reason for the significant aggravation; and (6) a proximate temporal relationship between vaccination and the significant aggravation. Loving, 86 Fed. Cl. at 144; see generally Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Actual causation must be supported by a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly v. Sec'y of Dep't of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting Knudsen v. Sec'y of Dep't of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)); see also Grant v. Sec'y of Dep't of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) (medical theory must support actual cause). A petitioner must show that but for his vaccination he would not have been injured, and that the vaccination was a substantial factor in bringing about his injury. Shyface v. Sec'y of Dep't of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). The vaccination must be only a substantial factor, however. It does not need to be the sole factor. Id. Mere temporal association is not sufficient to prove causation in fact. Grant, 956 F.2d at 1148.

The preponderance of evidence standard under the Vaccine Act requires proof that a vaccine more likely than not caused the vaccinee's injury. Althen, 418 F.3d at 1279. Causation

[16] To receive compensation, a petitioner must prove that either: 1) he suffered a "Table Injury" – that is, an injury falling within the Vaccine Injury Table – corresponding to one of his vaccinations, or 2) he suffered an "off-Table" injury that was actually caused by or "caused-in-fact" by a vaccine. See §§ 13(a)(1)(A), 11(c)(1); Shalala v. Whitecotton, 514 U.S. 268, 270 (1995). In this case, Petitioner alleged that Cassidy suffered an off-Table injury.

is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." Knudsen, 35 F.3d at 548. A petitioner may use circumstantial evidence to prove her case, and "close calls" regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

B. Significant Aggravation Analysis

To establish the significant aggravation elements, Petitioner must show 1) Cassidy's pre-vaccination condition, 2) Cassidy's post-vaccination condition, and 3) significant aggravation of Cassidy's condition after vaccination. Loving, 86 Fed. Cl. at 144. The parties agreed that, before vaccination, Cassidy had TS. Cassidy also had infantile spasms prior to vaccination, and TS patients who develop IS frequently progress to epilepsy. See Goh et al., Infantile Spasms and Intellectual Outcomes in Children with Tuberous Sclerosis Complex, 65 Neurology 235-38 (2005) (Pet'r Ex. 24-B). The parties disagreed whether the change in Cassidy's condition demonstrated significant aggravation or just the natural evolution of her TS.

Dr. Kinsbourne testified that in children with TS prevention of a first seizure (following remission of infantile spasms), is critical to preventing serious seizure disorders and brain damage. Tr. at104-05. If infantile spasms are promptly controlled and "if no further epileptic activity occurs subsequently[,] the prognosis for mental development is far better than if there is seizure relapse," he stated, citing studies by Jambaque and Winterkorn. See Pet'r Ex. 24 at 4-5; see also Winterkorn et al., supra Pet'r Ex. 24-G; I. Jambaque et al., Mental and Behavioural Outcome of Infantile Epilepsy Treated by Vigabatrin in Tuberous Sclerosis Patients, 38 Epilepsy Research 151-60 (2008) (Pet'r Ex. 24-D). In his view, Cassidy's vaccinations on March 31, 2006, triggered a seizure that would not otherwise have occurred. Tr. at 40-41. This seizure, Dr. Kinsbourne testified, led to the additional seizures and brain damage in Cassidy's case. Tr. at 31-32, 102-04.

In support of his opinion, Dr. Kinsbourne stated that before vaccination Cassidy's condition was improving and she had been meeting developmental milestones. See Tr. at 91-102. Her IS had been treated early and "responded to treatment right away." See Pet'r Ex. 24 at 4. He conceded that Cassidy had a variety of underlying problems, see Tr. at 91-102, but he emphasized that Cassidy had responded well to vigabatrin, her IS medication, and had been seizure free for 14 months before vaccination, Tr. at 120; see Pet'r Ex. 24 at 5. Relying on optimistic statements made by Cassidy's treaters, Dr. Kinsbourne concluded that Cassidy had been doing well at the time of vaccination. Tr. at 72-73, 88. Post-vaccination, Cassidy developed intractable epilepsy; her condition clearly was much worse. It was Dr. Kinsbourne's opinion that, even though Cassidy had problems before the vaccination, "the problems she had subsequently were of a totally different level of severity," Tr. at 96-97, but he recognized that, "It is also typical that, once epilepsy has recurred, [] it is refractory to antiepileptic drug treatment." Pet'r Ex. 24 at 5.

Respondent's expert, Dr. Guggenheim, claimed that Cassidy most likely would have developed epilepsy due to her pre-existing medical condition and that the March 31, 2006, vaccinations did not cause her seizure. Conceding that Cassidy's post-vaccination condition was worse than her pre-vaccination condition, Dr. Guggenheim maintained that her post-vaccination condition was not worse than would be expected, given her TS-IS. See Resp't. Ex. A at 3 (citing two reports consistent with "most published follow-up studies of children with TSC who present with infantile spasms," which show the majority of TS-IS children "have long term problems with ongoing, often intractable, epilepsy and associated developmental impairments").

Dr. Guggenheim did not interpret the cessation of infantile spasms in Cassidy's case as a sign that she would be seizure-free in the future, because infantile spasms naturally cease as the child matures. Tr. at 147. In her opinion, the epileptic process causing the deterioration in Cassidy's condition was attributable to her TS and was not affected by the vaccination. Tr. at 330-32; see Resp't Ex. A at 4 ("[T]he seizure disorder and developmental impairments that Cassidy Conway has are solely caused by her underlying genetic condition of TSC2. None of her vaccinations caused or aggravated her neurodevelopmental disorder."). Dr. Guggenheim testified that Cassidy's clinical course was characteristic of children with both TS and IS, and that the temporal proximity of the partial complex seizures and the MMR vaccination was due to chance alone. Tr. at 134-35.[17]

The parties seemed to assume that Cassidy's medical prognosis would determine the legal issue of significant aggravation. See Tr. at 157 (Dr. Guggenheim: "And so, the odds were that, because of the infantile spasms, that [refractory epilepsy and poor cognition] was her predicted outcome"); Tr. at 81 (Dr. Kinsbourne: "[T]here is a good chance, more likely than not, that she wouldn't have had seizures subsequently because she didn't have any for such a long time"). Some support appears in the case law for the "prognosis" approach, see Whitecotton, 81 F.3d at 1106 (discussing approvingly in dictum a requirement that, to overcome Respondent's rebuttal case, petitioners would need to show that a vaccinee's post-vaccination condition was worse than would be predicted in the absence of vaccination), but it does not help to resolve the issue of significant aggravation here. Regardless of the fate of the majority of TS sufferers, or even the majority of TS sufferers with IS, there is no way of knowing what would have happened in Cassidy's case if she had not been vaccinated on March 31, 2006. See Knudsen, 35 F.3d at 550 (discussing in an on-Table case Respondent's evidence of an alternative factor, and stating "The bare statistical fact that there are more reported cases of viral encephalopathies than . . . DTP encephalopathies is not evidence that in a particular case a[] [post-DTP] encephalopathy . . . was in fact caused by a viral infection present in the child and not caused by the DTP vaccine").

Although Cassidy was at risk prior to vaccination, the record does not indicate that she was inevitably predestined to develop refractory epilepsy. Even assuming that 75% of individuals who have TS and IS go on to develop intractable epilepsy, Cassidy might have been in the fortunate 25% who did not. See Catherine Chu-Shore et al., The Natural History of Epilepsy in Tuberous Sclerosis Complex, 51 Epilepsia 1236-41 (2010) (Resp't Ex. I). Although many TS-IS patients develop epilepsy, a minority have epilepsy controllable with treatment. Goh et al., supra Pet'r Ex. 24-B, at 236. In addition, not all TS-IS patients develop major mental deficits. Id.

Before vaccination, Cassidy had suffered from infantile spasms, but those were well controlled with vigabatrin. Cassidy had been seizure free for 14 months, and Dr. Guggenheim admitted on cross-examination that the remission of Cassidy's IS was an encouraging sign. Tr. at 241. Before her first seizure, Cassidy appeared to have mild to moderate developmental deficits, but she was considered to be in the mainstream of childhood development. Tr. at 159-

[17] The Goh and the Chu-Shore studies on which Dr. Guggenheim relied are some of the most comprehensive to date on children with TS and IS. As Dr. Kinsbourne noted, however, those studies were conducted at a tertiary care facility for TS patients. Therefore, it is reasonable to assume that the outcomes in that patient population would be more severe than in the general population of TS patients, which includes those who do not suffer serious seizure disorders as a result of their TS and therefore do not seek specialized treatment. See Tr. at 352-53.

61. Her developmental therapists were considering reducing the frequency of visits. Pet'r Ex. 14 at 4.

Post-vaccination, after Cassidy had her first seizure, she experienced daily seizures. Her epilepsy did not respond to medication and her condition significantly deteriorated. Cassidy became severely mentally incapacitated and required significant medical attention. She underwent multiple surgeries to treat her epilepsy, but her seizures did not remit.

Significant aggravation addresses the medical condition of the vaccinee, not the vaccinee's prognosis. § 33(4); see Whitecotton, 81 F.3d at 1107 ("[T]he statute implicitly requires a comparison of the person's pre-vaccination condition with the person's current, post-vaccination condition"). In this case, Cassidy's medical condition was unquestionably worse after vaccination than before it. Following vaccination, she suffered a seizure that led to intractable epilepsy and permanent, serious brain damage. Therefore, Petitioner has established that her alleged injury satisfies the legal standard for significant aggravation. See Loving, 86 Fed. Cl. at 144. Having established that Cassidy's condition was significantly aggravated after her vaccinations, I must determine whether the significant aggravation was caused in fact by her vaccinations, more likely than not.

C. Althen Prong 1

Under Althen prong 1, a petitioner must set forth a biologically plausible theory explaining how the vaccine received by the petitioner could cause the injury complained of. See, e.g., Andreu v. Sec'y of Dep't of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). This requirement has been interpreted as "can the vaccine(s) at issue cause the type of injury alleged?" Pafford v. Sec'y of Dep't of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). Evidence should be viewed by the preponderance of the evidence standard and "not through the lens of the laboratorian." Andreu, 569 F.3d at 1380. Although the theory of causation need not be corroborated by medical literature or epidemiological evidence, the theory must be sound, reliable, and reputable – in other words, the theory need not be scientifically certain, but it must have a scientific basis. See id. at 1379-80.

1. Dr. Kinsbourne's Opinion

According to Dr. Kinsbourne, the MMR vaccine stimulated Cassidy's innate immune system to release proinflammatory cytokines, which provoked her TS and caused her to have a seizure. Dr. Kinsbourne testified that persons with TS have a low seizure threshold because tubers are continually inflamed and contain proinflammatory cytokines. Tr. at 28-30. When proinflammatory cytokines are released, perhaps in response to an infection or a vaccination, they further increase the inflammation in tubers. Tr. at 31. This increased inflammation can cause a seizure, which causes the release of more proinflammatory cytokines, which leads to more seizures.[18] Dr. Kinsbourne opined that after vaccination the cytokines would not be

[18] Dr. Kinsbourne's exposition of his theory was at times hard to follow (as was, at times, Dr. Guggenheim's testimony). He stated that the cytokine theory could apply to any of the vaccines Cassidy received on March 31, 2006. Although Dr. Kinsbourne initially asserted he chose the MMR vaccine as the culprit because it is well-known to cause a fever and systemic reaction, he later admitted that this known reaction is viremic. Tr. at 111-14. Dr. Kinsbourne then stated that he chose the MMR vaccine as the likely precipitant of Cassidy's seizure because the wild measles virus can cause encephalopathy. The mechanism of the encephalopathy is not well understood, but it is thought to be mediated though the

localized at the vaccination cite, but either would be transported to the brain by the blood or released in the brain as part of a systemic reaction.[19] Dr. Kinsbourne opined that this reaction could take place within two hours.

To support his opinion that proinflammatory cytokines can cause seizures, Dr. Kinsbourne relied on an article by Nicola Marchi et al., Antagonism of Peripheral Inflammation Reduces the Severity of Status Epilepticus, 33 Neurobiology of Disease 171-81 (2009) (Pet'r Ex. 31-B). The article observed that "systemic inflammation is a common trigger for acute seizures in pediatric and adult patients," and proposed that anti-inflammatory drugs could help treat epileptic patients. Id. at 179. The article reported the results of a study on rats that found increased levels of the proinflammatory cytokine Interleukin type 1 beta (IL-1β) lowered the seizure threshold and increased the severity of seizures. Dr. Kinsbourne claimed that Marchi et al.,"directly demonstrated the causal role of IL-1β (in generating seizure activity) by administering an antagonist to IL-1β and seeing seizure activity decrease." Pet'r Ex. 32 at 2.

In the study, the authors administered a seizure-inducing agent at sub-convulsive levels. When they also administered an agent that raised IL-1β levels, the rats had seizures. The authors found seizures either were prevented or their severity reduced by administering a third chemical, one that blocks IL-1β. They also noted that the IL-1β raising agent they used had the same effect on IL-1β levels as seen with infection and injection with bacterial toxins. Marchi et al., supra Pet'r Ex. 31-B, at 179. Their conclusion was that IL-1β, and inflammation, in general, can contribute to seizure causation by lowering the seizure threshold.

Dr. Kinsbourne also relied on an article by Annamaria Vezzani, Inflammation and Epilepsy, Epilepsy Currents, Vol. 5, No. 1 (Jan./Feb. 2005), 1-6 (Pet'r Ex. 24-F). The article summarized the results of studies on the inflammatory response observed during and after seizure activity. One paragraph of the article mentioned TS, noted increased proinflammatory cytokine levels in TS patients, and hypothesized that "an inflammatory response in tubers may be directly related to epileptogensis in these lesions." Id. at 4. The author concluded that persistent presence of proinflammatory signals in the brain may contribute to brain injury, and therefore play a role in epileptogenesis and the acute manifestation or reinforcement of seizures. Id. at 5.

2. Dr. Guggenheim's Opinion

Dr. Guggenheim testified that it is well established that vaccination can lead to a local reaction, swelling, and redness, which can sometimes evolve into systemic reactions such as fever and malaise, and that these reactions likely are mediated by cytokines. Tr. at 175-77. She challenged, however, the notion that proinflammatory cytokines could themselves induce a seizure. Tr. at 176-79.

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immune system. Tr. at 114. There was no allegation, however, that Cassidy suffered a post-vaccine encephalopathy, at least not within the meaning of the Vaccine Act. See 42 C.F.R. § 100.3(b)(2).

[19] Dr. Kinsbourne was not entirely clear concerning how cytokines produced in response to vaccination could have reached Cassidy's brain within a few hours. Dr. Kinsbourne opined that cytokines can break down the blood brain barrier. Tr. at 357; Pet'r Ex. 31. He also testified that vaccinations could cause a local reaction, a systemic reaction, or both. Tr. at 76-77.

Dr. Guggenheim opined that the only mechanism by which a cytokine reaction could induce seizures was through fever. Tr. at 327. If fever were to occur immediately after vaccination, it would be accompanied by a noticeable systemic reaction. See Tr. 176-77, 327.[20] Although it is not understood how elevated body temperature leads to seizures, it is accepted that it happens. Tr. at 210. Dr. Guggenheim also understood that the MMR vaccine could cause seizures in rare circumstances, but stated that that phenomenon is mediated through fever and would take from a few days to 14 days after the vaccination to occur. Tr. at 263-64. Thus, a fever-mediated reaction was not applicable to Cassidy.

Dr. Guggenheim opined that no evidence showed that cytokines alone could cause seizures, although she admitted that the medical literature documented some association between seizures and cytokines. She conceded that tubers have inflammation within them. Tr. at 185. Dr. Guggenheim questioned Dr. Kinsbourne's reliance on the Marchi et al. article because, although it found that a high dose of an IL-1β blocker mitigated seizures, another agent, and not IL-1β, actually caused the seizures. Resp't Ex. M at 2. She doubted the probative value of the rest of Petitioner's literature, noting that, "In virtually all of these studies, the sequence is that something is done to the animal model to initiate seizures[,] . . . [such as] the injection of one or another type of toxin . . . . And then they find in that tissue the presence of an inflammatory response." Tr. at 177.[21] Dr. Guggenheim opined that "the presence of this cytokine inflammatory microglial response is a consequence to inducing seizures, and not a cause of seizures." Tr. at 177.

Dr. Guggenheim saw little evidence that a cytokine reaction as described by Dr. Kinsbourne could have happened in as little as two to three hours. Dr. Guggenheim did not elaborate on the temporal issue because, whether it was "two hours or two days, . . . it would [not] make a difference in my opinion because I think it's her underlying disease that resulted in her having bad epilepsy." Tr. at 158. She stated that she knew of no evidence, even anecdotal, contraindicating vaccination for TS patients because of heightened risk of a seizure. Tr. at 344-45.

Dr. Guggenheim agreed that, in a TS patient, an initial partial complex seizure would be a critical event, and the patient would almost certainly go on to have more seizures. Tr. at 325. Dr. Guggenheim stressed, however, that in patients with TS and infantile spasms, the likelihood of developing refractory epilepsy with a disabling outcome was at least 75%, Tr. at 147-48, 229, and the likelihood of having another seizure was as high as 98%, Tr. at 322.

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[20] Dr. Kinsbourne's report stated, and he insisted at hearing, that Cassidy's mother reported localized swelling at the site of the vaccination on March 31, 2006. See Pet'r Ex. 24 at 2 (Dr. Kinsbourne's Report), Tr. 52-54, 77 ("I do believe that the local inflammation that the mother reports is relevant to this because certainly, IL-1β would have been involved in that as part of the mechanism of creating it. And that would be found in the bloodstream."). In fact, the record contains no such report by Cassidy's mother and no other evidence of a localized inflammatory response or, for that matter, a general inflammatory response, around the time of vaccination. Dr. Guggenheim, who also referred to Cassidy's mother's report of inflammation, explained that she adopted this allegation from Dr. Kinsbourne's report, but that she too could find no evidence of such inflammation in Cassidy's case. Tr. at 155-56.

[21] See, e.g., Annamaria Vezzani et al., Functional Role of Inflammatory Cytokines and Antiinflammatory Molecules in Seizures and Epileptogenesis, 43 Epilepsia 30-35 (2002) (Pet'r Ex. 31-C). "Our study shows that limbic seizures in rodents rapidly and reversibly induce inflammatory cytokines in glia in the hippocampus." Id. at 34.

3. Analysis

In evaluating whether a petitioner has presented a legally probable medical theory, "the special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324. Assessing the reliability of an expert's opinion in Vaccine Act cases can be challenging, because often there is scant evidence directly supporting the expert's opinion. See Althen, 418 F.3d at 1280 (noting that the "field [is] bereft of complete and direct proof of how vaccines affect the human body"). Consequently, most expert opinion will require extrapolation from existing data and knowledge. The weight to be given to an expert's opinion is based in part on the size of the gap between the scientific evidence and the opinion proffered. Cedillo v. Sec'y of Dep't of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010). A special master is not required to rely on a speculative opinion that "'is connected to existing data only by the ipse dixit of the expert.'" Snyder v. Sec'y of Dep't of Health & Human Servs., 88 Fed. Cl. 706, 745 n.66 (2009) (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)). In assessing an expert's asserted chain of a causation, a "'court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.'" Cedillo, 617 F.3d at 1339 (quoting Joiner, 522 U.S. at 146).

According to Petitioner's theory, Cassidy had a lowered seizure threshold such that the proinflammatory cytokines released in response to vaccination caused agitation of her tubers, which caused her to have a seizure. Vaccination, it is agreed, promotes cytokine release, and there is evidence (disputed, but nevertheless) that these inflammatory agents can cross the blood brain barrier within hours. Tr. at 357; see Pet'r Ex. 31 at 1-2 (citing Marchi and Barrientos studies). There is no reliable evidence, however, that cytokines produced by external factors, such as vaccines, increase seizure activity in patients with TS by stimulating the epileptogenicity of tubers, or otherwise.[22] The absence of reliable evidence that cytokines, or any exogenous agent, cause seizures in TS sufferers is fatal to Petitioner's cause. Some individuals with TS are likely to develop seizure disorders, to be sure, but this is due to their underlying genetic disorder, not, according to the most reliable and persuasive evidence in this record, by the production of cytokines in response to an exogenous agent such as a vaccine. See Tr. at 330-32, 344-45.

Dr. Kinsbourne's assertion that cytokine-induced inflammation can trigger seizures in TS patients because of their hypothetically low seizure threshold lacks reliable support and is implausible. Dr. Kinsbourne reasoned that, because vaccination arguably makes seizures more likely in the general population (in association with fever), vaccination must make seizures even more likely in a child with TS. Without some reliable evidence to support the hypothesis, this is mere speculation. A special master must consider all relevant and reliable evidence, but Daubert and the decisions requiring its application in cases under the Vaccine Act require the

[22] The Vezzani article cited by Dr. Kinsbourne does not lend support to the critical component of his theory. The article mentions "the possibility that proinflammatory components of tubers may reflect downstream effects of the TSC1 or TSC2 gene mutations." Vezzani, supra Pet'r Ex. 24-F, at 4. In other words, proinflammatory cytokines and markers of immune system activation in IS and TS patients may be caused by the genetic mutations that are known to cause TS. The Vezzani article describes an endogenous process occurring in the brain that is caused by genetic mutations, as described by Dr. Guggenheim. Vezzani's hypothesis does not support the proposition that cytokines produced by factors outside the brain somehow trigger seizures in TS patients.

rejection of mere speculation as the basis for proving entitlement under prong 1 of Althen. See Cedillo, 617 F.3d at 1339.

Indeed, were Dr. Kinsbourne's hypothesis true, TS patients predictably would experience seizures following vaccination. This is not what occurs. Tr. at 223; Tr. at 341-45. The problem with arguments like Petitioner's is that, if credited, the argument proves too much – if TS truly predisposed individuals to adverse vaccine reactions, the phenomenon would be common among TS sufferers. According to the record in this case, such a phenomenon is unknown. Dr. Guggenheim testified, "I've never heard of any general knowledge within my community of pediatric neurology that . . . you've got to watch out for kids with [TS] because they get febrile – fever triggers their seizures more easily than other kids." Tr. at 344-45. She testified that current pediatric practice was to administer vaccines to children with TS. Tr. at 215-17. Dr. Kinsbourne's testimony was consistent on this point. See Tr. at 107-08 (when asked if having TS was a sufficient reason to withhold the MMR vaccine, Dr. Kinsbourne replied "I haven't thought about it. All I can say is I don't think the medical community has come to that conclusion.").

To the same effect, if Cassidy's TS were such that the release of proinflammatory cytokines were sufficient to trigger a seizure, that reaction presumably would have occurred in response to any number of antigens to which she was exposed, not only to the vaccination she received on March 31, 2006. The release of proinflammatory cytokines is not limited to vaccinations; the immune system releases inflammatory cytokines in response to other antigens it encounters. See Tr. at 28. The medical literature on which Dr. Kinsbourne relied, for example, stated that the drugs used to stimulate the release of proinflammatory cytokines in the experimental models would have the same effect as the body's response to an infection. Marchi et al., supra Pet'r Ex. 31-B, at 179. Thus, seizures also could be triggered by an infection, such as Cassidy's March 2, 2006, croup infection for which she was hospitalized for two days. Petitioner's theory does not explain why Cassidy's relatively mild immune response to her March 31, 2006, vaccinations could have caused her to have a seizure, but her immune response to the severe croup infection only four weeks earlier did not.[23]

Dr. Kinsbourne testified, "I can't give a totally watertight logical explanation of this. I can just say that this sort of thing happens in medicine all the time." Tr. at 116. This explanation rings hollow when there is no evidence in the record that patients with TS experience seizures as a result of vaccination, and no evidence that Cassidy's seizures were triggered by the release of inflammatory agents, whether from vaccination or illness.[24]

Petitioner has not established more likely than not that cytokines released by the immune system in response to vaccination could provoke the tubers in a TS patient's brain and

[23] This analysis also is relevant to prong 2.

[24] Questioned about the lack of evidence of an inflammatory response to Cassidy's vaccination, Dr. Kinsbourne stated that there would not necessarily be evidence of inflammation. Tr. at 78 ("So it would be my opinion that in this special case of low seizure threshold, you could get an effect of an infection or a vaccination even without the systemic findings."). The medical research he cited, however, was predicated on "the fact that systemic inflammation is a common trigger for acute seizures in pediatric and adult patients worldwide." Marchi et al., supra Pet'r Ex. 31-B, at 179. The medical literature in the record does not support the proposition that a mild inflammatory process resulting in no manifestations of systemic inflammation could contribute to seizure causation.

cause a seizure. Accordingly, Petitioner has not established a biologically plausible theory of causation under Althen.

D. Althen Prong 2

The second prong of Althen requires a petitioner to prove "'a logical sequence of cause and effect show[ing] that the vaccination was the reason for the injury.'" Andreu, 569 F.3d at 1374 (quoting Althen). The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." Knudsen, 35 F.3d at 548-49. Under prong 2, petitioners are not required to show "epidemiologic studies, rechallenge, the presence of pathologic markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect . . . ." Capizzano v. Sec'y of Dep't of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second Althen factor. Capizzano, 440 F.3d at 1325-26; Andreu, 569 F.3d at 1375-77 (treating physician testimony). In this case, no treating physician identified vaccination as the cause of Cassidy's seizure in late March 2006, or her subsequent decline.[25] Petitioner relies on Dr. Kinsbourne's testimony to establish prong 2.

1. Dr. Kinsbourne's Opinion

Dr. Kinsbourne's testimony on prong 2 focused on the MMR vaccine, but he asserted that his proinflammatory cytokine theory actually could apply to any or a combination of the vaccines administered on March 31, 2006. Dr. Kinsbourne focused on MMR because it is known to cause seizures under certain conditions (not present here, see supra). Tr. at 114. He testified that Cassidy's TS resulted in a lower seizure threshold that left her vulnerable (as of March 31, 2006) to seizures triggered by the production of cytokines, due to vaccination. Tr. at 33-34; Tr. at 38; Tr. at 78. Cassidy's mild reaction to the MMR vaccine therefore was able to cause a seizure and epilepsy. Tr. at 78, 103-04.

Dr. Kinsbourne recognized that a temporal relationship alone was insufficient to establish causation but stated, "[A]ny physician who sees an infection or a vaccination followed by a seizure within two or three hours cannot help but be impressed by the importance of that relationship. So then one sees to what extent one can explain this in terms of existing knowledge." Tr. at 117. Dr. Kinsbourne stated that he could not give a "watertight" explanation of why Cassidy had a seizure in response to her March 31, 2006, vaccinations but not previous vaccinations, musing that, "one could argue that it had to do with the evolution of the tubers." Tr. at 116. He did not specify how the evolution of Cassidy's tubers affected her response to vaccination, or explain why that evolution would not have caused seizures "but for" vaccination. He predicted that, without the March 2006 vaccinations, Cassidy's mental development more likely than not would have been adequate because her IS was well controlled with medication. Tr. at 81, 84-85. Since Cassidy's outcome deviated from his prediction, he concluded that vaccines must have caused the change.

[25] The April 12, 2006, resident's intake notes stated, "The patient also had MMR immunization two hours prior to seizure onset, and it is worth exploring potential relationships as a precipitant." Pet'r Ex. 9 at 6; see Tr. at 87. The note merely indicates that the temporal association between vaccination and seizure warrants further exploration, not that there is a probable causal link. Cedillo, 617 F.3d at 1348; cf. Andreu, 568 F.3d at 1375-76 (testimony of treating physician could establish prong 2 in that case).

2. Dr. Guggenheim's Opinion

Dr. Guggenheim rejected Dr. Kinsbourne's cytokine theory because the record contained no evidence of a local or systemic reaction to the vaccination. Tr. at 327-28. Because Cassidy showed no evidence of an acute encephalopathy (in response to a toxic insult), fever, rash, or other adverse symptoms at the time of vaccination and onset of seizures, Dr. Guggenheim opined that Cassidy's seizures occurred due to the natural progression of her TS, unrelated to her vaccinations. Tr. at 156-57, 335.

Dr. Guggenheim opined that Cassidy's course was consistent with the expected clinical progression of TS. Specifically, in TS patients who suffer from IS in infancy, seizures typically begin within two or three years after cessation of the IS. Tr. at 149-50.[26] Although Dr. Guggenheim admitted that complex partial seizures (such as Cassidy suffered post-vaccination), can be causally related to epilepsy, she opined that such a relationship was unlikely the cause of Cassidy's epilepsy, which in her view was in fact TS.

Dr. Guggenheim testified that Cassidy likely had an ongoing epileptic process, caused by TS, which resulted in her seizure. As she explained the effect of TS on the brain, the cells that become tubers are present within a few months of conception. Tr. at 136-37. The tubers are formed when otherwise healthy cells are directed to the wrong part of the brain during cell migration. Tr. at 138-39.[27] As the brain matures, the mislocated cells set up reverberating electrical networks that can evoke spontaneous electrical activity. Tr. at 138-39. "So this is the core of the neurological aspect of tuberous sclerosis. It's genetically determined." Tr. at 139. Dr. Guggenheim testified that, because the disorder was completely genetic, she did not think of outside factors as affecting its development or as "triggering" epilepsy. Tr. at 294. While she admitted that TS patients are predisposed to have epileptic seizures, she testified that the medical community did not view TS patients as more susceptible to having seizures induced by outside factors. Tr. at 342-45.

3. Analysis

Petitioner has not established prong 2. The medical record lacks evidence that Cassidy's vaccination caused an inflammatory response within hours, which in turn caused Cassidy to suffer a seizure. The medical record, moreover, does not support Dr. Kinsbourne's assertion that Cassidy had a lowered seizure threshold. In addition, the progression of Cassidy's condition is inconsistent with Petitioner's theory of causation, and consistent with the natural course of Cassidy's TS.

In the hours after her vaccination, Cassidy exhibited no symptoms of localized or generalized inflammation, when presumably, the inflammatory process posited by Dr.

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[26] Dr. Guggenheim recalled two TS-IS patients she had treated, one who remained seizure free for one year and one who remained seizure free for two-and-a-half years. Tr. at 149-50; see also Chu-Shore et al., supra Resp't Ex. I, at 1237 (two years of age was too young to determine if child would have another type of seizure after IS).

[27] The brain starts out as a flat disk of cells. Tr. at 137. As it develops, it turns into a tube, and then a bicycle wheel before it turns into its easily recognized semispherical shape. Tr. at 137-38. Throughout this process, cells are constantly reorganizing, and this is called cell migration. Tr. at 138.

Kinsbourne was under way. She was evaluated by medical professionals on April 1 and 5, 2006, and none of them noted a fever, inflammation, or malaise. To explain this discrepancy, Dr. Kinsbourne opined that the vaccine could have caused Cassidy to have a seizure without causing a noticeable systemic reaction because Cassidy's seizure threshold was low due to her TS. Tr. at 78.

Dr. Kinsbourne offered no objective evidence that Cassidy's seizure threshold was "low" or that TS patients are prone to having seizures triggered by exogenous factors. Dr. Kinsbourne recognized that both vaccination and infection could cause the release of proinflammatory cytokines required to agitate the abnormal cells in Cassidy's brain. One month before her vaccinations, however, Cassidy had an infection so severe that she was hospitalized for a day and a half. He offered no explanation for why, if Cassidy had a lowered seizure threshold, her severe infection did not generate seizures, but her vaccine reaction four weeks later did. See Tr. at 116.[28]

In contrast, Dr. Guggenheim explained that TS develops without any known relationship to external factors. See Tr. at 223 ("[I]t all comes from what's – from a neurologic perspective, what's in our brain to start with. It isn't modified, to our knowledge, by any external forces."); Tr. at 331-32.[29] Dr. Guggenheim explained that while TS patients are predisposed to seizure activity, the medical community does not view external factors as causal agents in precipitating their seizures.[30]

Dr. Guggenheim testified that the tubers and other malformed brain tissue led to the seizures, and there was no relationship between this development and Cassidy's vaccination.[31] The TS disorder itself determined the timing of Cassidy's seizure in March 2006. In contrast to Dr. Kinsbourne's speculative explanation of what may have happened, Dr. Guggenheim's testimony was consistent with the information in Cassidy's medical record, and with medical knowledge about TS. See e.g., Holmes et al., supra Resp't Ex. C, at 621-23.

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[28] Dr. Kinsbourne also opined that the one seizure Cassidy suffered shortly after her vaccination caused the entire decline in her condition, leading to severe and permanent brain damage. See Tr. at 103 ("[O]nce that first seizure occurred, as happens so often in tuberous sclerosis because of the low seizure threshold, unfortunately, it perpetuated into a very severe epilepsy"). Because insufficient evidence supports the theory that Cassidy's seizure was "triggered" by vaccination, I need not resolve the question of whether her initial, post-vaccination seizure caused the subsequent train of events documented in Cassidy's medical records.

[29] Dr. Kinsbourne appeared to share the view the tubers develop according to their own, genetically determined pattern, stating: "tubers have their own development[,] [s]o they might over time become more epileptogenic or less." Tr. at 63. His testimony that Cassidy's tubers had developed to the precise point on March 31, 2006, that her vaccination triggered a seizure within hours lacks any reliable support.

[30] On cross-examination, counsel sought to persuade Dr. Guggenheim that a theory espoused by Petitioner ("double hit") was supported by one of the studies offered in evidence by Respondent. See Tr. at 217-226; Holmes et al., supra Resp't Ex. C. Dr. Guggenheim's answers made it even clearer that, based on medical science, the events that result in TS occur "in the early state of in utero brain development," not later in life. Tr. at 219-21.

[31] Three months after Cassidy's seizures started, a July 2006 MRI first depicted two tubers on Cassidy's brain. Dr. Guggenheim testified that the tubers would have been present since birth, and that they finally reached a size visible on an MRI had no bearing on the occurrence of seizures. Tr. at 331-32.

Cassidy's epilepsy was consistent with the natural course of her TS. Dr. Guggenheim testified that she had seen and other medical professionals had reported children who "respond[] to a treatment for infantile spasms and [are] seizure free, but then after a few months, or as long as several years, will start developing other types of seizures." Tr. at 147. Dr. Kinsbourne agreed that, "[A]ll her seizures are caused by her tuberous sclerosis. If she didn't have that [genetic] mutation, more likely than not she wouldn't have any epilepsy. That's not in dispute." Tr. at 80. Also undisputed is that the cells in Cassidy's brain that developed into tubers certainly were present long before her vaccinations in March 2006. See Tr. at 62 (Dr. Kinsbourne: "I'm sure whatever cells give rise to them have a history way back before birth"); Tr. at 331-32 (Dr. Guggenheim: "the abnormal cells [had to have been there since about six months post conception] because they came from the process of cell migration").

In his expert report, Dr. Kinsbourne asserted that, "After so prolonged a period of freedom from seizures, it would be far-fetched indeed to invoke coincidence as an explanation for the onset of breakthrough seizures immediately after vaccinations, particularly in view of continued anti-epileptic treatment." Pet'r Ex. 24 at 5. However, other than the "conspicuous timing" of the seizures, Tr. at 40, Dr. Kinsbourne did not present supporting evidence for his theory. It may be far-fetched to invoke coincidence to explain why Cassidy's seizure occurred in close temporal proximity to her vaccination. But it is equally far-fetched to use coincidence to explain why Cassidy's TS resulted in a seizure on March 31 but not on March 1, 2006, when she was hospitalized with an infection. See Tr. at 116 ("I can just say that this sort of thing happens in medicine all the time").

In sum, Dr. Guggenheim's opinion is more persuasive than Dr. Kinsbourne's, which appears to be based almost entirely on the "conspicuous timing" of the onset of seizures. Dr. Kinsbourne identified scant evidence that the release of proinflammatory cytokines in fact resulted in Cassidy's seizure, or that Cassidy suffered from what he termed a low seizure threshold. It appears much more likely that Cassidy's TS caused the seizure on March 31 than that the vaccinations, in the absence of fever, somehow triggered a seizure. Dr. Kinsbourne's failure to explain why Cassidy's severe infection one month before vaccination, which according to his own theory would have caused a similar biological reaction as vaccination, did not cause a seizure, tends to negate the assertion of cause and effect between cytokine production and seizures in Cassidy's case.

Accordingly, Petitioner has not satisfied prong 2 of the Althen test.

E. Althen Prong 3

To show causation, a petitioner must establish that the injury occurred within a time frame that is consistent with the theory of causation set forth. Pafford, 451 F.3d at 1358. A temporal relationship between receipt of a vaccine and alleged onset of symptoms, without more, is insufficient to establish a causal relationship in a cause-in-fact case. Grant, 956 F.2d at 1148. What constitutes an appropriate temporal association is a question of fact and will vary with the particular theory of causation advanced. Id.; de Bazan, 539 F.3d at 1352.

Here, Dr. Kinsbourne asserted that the proinflammatory cytokine reaction he described could happen within a few hours. See Tr. 38. Dr. Guggenheim was dubious but did not carefully consider the timing of onset. She stated that she had not dissected out the temporal

association because if the seizures started at two hours or two days, her opinion would still be that it was TS alone that resulted in Cassidy's refractory epilepsy. Tr. at 158.

Were Petitioner able to establish the other two prongs of Althen, the record would support a finding that Cassidy's reaction occurred in a timeframe medically consistent with Petitioner's cytokine theory of causation, particularly without refutation on this point from the Secretary.

IV. CONCLUSION

Petitioner has not set forth a plausible or reliable theory of significant aggravation of a pre-existing medical condition due to vaccination, or established a logical cause and effect relationship between vaccination and such injury. Accordingly, Petitioner has not established entitlement to compensation for significant aggravation of a pre-existing condition under the Vaccine Act, and her petition must be **DISMISSED**.

IT IS SO ORDERED.

s/ Dee Lord
Dee Lord
Chief Special Master