IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

No. 11-0282V
Filed: September 9, 2014

SUE RUSSELL, Parent and legal guardian of K.A.,	*	
Petitioner,	*	Ruling on the Record; Vaccine Act Entitlement; Insufficient Proof of Causation; Hepatitis A; Seizure Disorder.
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Sheila A. Bjorklund, Esq., Lommen, Abdo, Cole, King & Stageberg, P. A., Minneapolis Minnesota , for petitioner.
Linda S. Renzi, Esq., U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Gowen, Special Master:

On May 5, 2011, Sue Russell ["petitioner" or "Ms. Russell"] timely filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10 ["Vaccine Act"],[2] on behalf of her minor daughter, K.A. The petition alleges that, as a result of her hepatitis A vaccination on May 23, 2008, K.A. suffered from a tonic-clonic seizure within 24 hours of receipt of the vaccine and subsequently developed intractable seizures. The petition further alleges that K.A.'s injuries persisted for more than six months.

[1] Because this unpublished decision contains a reasoned explanation for the action in this case, I intend to post this decision on the United States Court of Federal Claims' website, in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)). In accordance with Vaccine Rule 18(b), a party has 14 days to identify and move to delete medical or other information, that satisfies the criteria in § 300aa-12(d)(4)(B). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, I agree that the identified material fits within the requirements of that provision, I will delete such material from public access.

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

For the reasons stated herein, I find that petitioner has failed to establish entitlement to an award; and thus the case is dismissed.

I. Procedural History.

This case was originally assigned to Special Master Zane, *see* Notice of Assignment to Special Master Daria J. Zane, filed May 5, 2011, and then reassigned to Chief Special Master Vowell. *See* Notice, filed Sept. 6, 2013. On March 4, 2014 this case was reassigned to the undersigned. *See* Notice, filed Mar. 4, 2014. Petitioner initially filed nine medical record exhibits and her affidavit. Notice of Intent to File CD, filed May 9, 2011; Notice of Filing Exhibit, filed May 19, 2011. Special Master Zane conducted an initial status conference on June 15, 2011, and petitioner filed a Statement of Completion in compliance with the order issued after the status conference. Order, filed June 15, 2011; Petitioner's Statement of Completion, filed July 13, 2011.

On November 18, 2011, Special Master Zane held a second status conference with the parties. Petitioner was ordered to file (1) outstanding medical records requested by respondent by December 1, 2011, and (2) a status report updating the Court on the status of the case and proposing the next steps for moving forward by January 20, 2012. Order, filed Nov. 18, 2011.

Petitioner filed Exhibits 11-14 on November 29, 2011. Notice of Intent to File CD, filed Nov. 29, 2011. Petitioner later filed a status report stating that K.A.'s physicians had decided that it would be beneficial to obtain SCN1A genetic testing for K.A. and had implemented the appropriate steps for approval to obtain the test. Petitioner's Status Report [Pet. Status Rep.], filed Jan. 19, 2012. The status report requested an additional twelve weeks in which to obtain the testing and produce an expert report to support the Petition. *Id.* Special Master Zane issued an Order granting petitioner's request and ordering petitioner to file the results of the genetic testing, as well as an expert report by April 12, 2012, or a status report by that date if the results are not yet available. Order, filed Jan. 27, 2012. After several requests for extension on the filing date,[3] the results of the SCN1A testing were filed on January 15, 2013. Notice of Filing Exhibit 20, filed Jan. 15, 2013.

[3] On April 12, 2012, in accordance with Special Master Zane's previous order, petitioner filed a status report requesting an additional sixty days to obtain the SCN1A testing for K.A.. Pet. Status Rep., filed April 12, 2012. Special Master Zane issued an Order granting petitioner's request and ordering petitioner to file the results of the genetic testing as well as an expert report by June 11, 2012, or a status report by that date if the results are not yet available. Order, filed April 12, 2012. On June 11, 2012, petitioner filed a status report stating that K.A. had received approval for the testing, but that the results and an expert report would not be filed for at least 60-75 days. Pet. Status Rep., filed June 11, 2012. Special Master Zane then issued an order requiring petitioner to file the results of the genetic testing as well as an expert report by August 27, 2012, or a status report by that date if the results are not yet available. Order, filed July 12, 2012. Petitioner requested another extension on August 27, 2012, which Special Master Zane granted, moving the filing date to December 3. Pet. Status Rep., filed Aug. 27, 2012; Order, filed Aug. 28, 2012. A similar extension was requested on December 3, 2012. Pet. Status Rep., filed Dec. 3, 2012.

On January 16, 2013, Special Master Zane held a status conference with the parties. Petitioner's counsel reported that she would be consulting with an expert regarding the SCN1A results. Order, filed Jan. 16, 2013. Additionally, the parties requested time to explore the potential for settlement. *Id.* Special Master Zane ordered the petitioner to file a joint status report by March 15, 2013, to provide a proposed schedule for proceeding. *Id.*

On March 13, 2013, petitioner submitted a Joint Status Report noting that counsel for the parties had consulted. Joint Status Report [J. Status Rep.], filed Mar. 13, 2013. Petitioner stated that she would not be filing an expert report; but instead would be requesting that the Special Master make the entitlement decision based upon the written submissions as permitted under Vaccine Rule 8(d). *Id.* Petitioner requested thirty days to file a written brief outlining the evidence that supported the request for compensation. *Id.* On April 16, 2013, petitioner filed a Motion for a Ruling on the Record accompanied by Exhibits 21-26 (medical literature). Petitioner's Motion for a Ruling on the Record, filed Apr. 16, 2013; Petitioner's Notice of Medical Literature/Exhibits 22-26, filed Apr. 16, 2013. Respondent filed a Response to petitioner's motion on June 12, 2013. Respondent's Response to Petitioner's Motion for a Ruling on the Record [Response], filed June 12, 2013.

II. Relevant Medical History.

A. K.A.'s Early Health and Development

Born by cesarean section at 38 weeks gestation on July 10, 2006, K.A. was exposed *in utero* to alcohol, tobacco, cocaine, and Seroquel,[4] and her birth mother was HIV positive. Pet. Ex. 3, p. 6; Pet. Ex. 5, pp. 5, 12. Her birth mother was incarcerated during the third trimester of pregnancy and was tightly controlled for her HIV. Pet. Ex. 3, p. 5. Immediately after birth, K.A. began antiviral therapy, which continued for six weeks after birth. *Id.* K.A. had HIV testing throughout her infancy and consistently tested negative. Pet. Ex. 5, p. 5. On July 13, 2006, K.A. was discharged from the hospital into Ms. Russell's foster care, and Ms. Russell subsequently adopted K.A. on October 15, 2007. Pet. Ex. 9, p. 77.

As a newborn, K.A. experienced fine tremors thought to be a function of her immature neurological system, and, on occasion, her body would shake during times of stress. Pet. Ex. 6, p. 6; Pet. Ex. 12, p. 3. During her infancy, K.A. was regularly seen by her pediatrician, and she received childhood immunizations during her well-child visits at two, four, six, and fifteen months of age. Pet. Ex. 4. K.A. received these childhood immunizations without reported incident. *Id.* She was a healthy child and appeared to develop normally until approximately nine months of age.

According to petitioner, K.A. began exhibiting autistic tendencies at nine months.

[4] Seroquel is the trademark for a preparation of quetiapine fumurate, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY at 1698 (32nd ed. 2012), which is a dibenzothiazepine derivative used as an antipsychotic in the treatment of schizophrenia and other psychotic disorders, *id.* at 1566.

See Pet. Ex. 6, p. 5; Pet. Ex. 9, p. 2. Until then, K.A. appeared to be meeting her developmental milestones: she was smiling at a month, rolled over by two months, sat independently by seven months, was walking by one year, and was cooing and babbling. Pet. Ex. 6, p. 6. During an evaluation done in November 2007, at sixteen months, it was noted that K.A. no longer walked independently, had regressed in her speech development, and had begun to engage in self-stimulating behaviors. *Id.* These self-stimulating behaviors included excessive head banging; K.A. broke several cribs by banging her head against the rails. Pet. Ex. 6, p. 7; Pet. Ex. 14, p. 25. During the November 2007 evaluation, K.A. was diagnosed with autism spectrum disorder and began developmental therapy. Pet. Ex. 6, p. 4.

B. K.A.'s May 2008 Vaccination and Hospitalization

On May 23, 2008, at 22 months of age, during a well-child visit, K.A.'s pediatrician administered a hepatitis A vaccine. Pet. Ex. 2, p. 2. According to petitioner, who is a nurse, within a couple of hours of receiving the shot, K.A. became very irritable and developed a fever of 101º F; the following morning she was running a lower fever.[5] Pet. Ex. 10, p. 2. On May 24, 2008, about 24 hours after receiving her hepatitis A vaccine, Ms. Russell noticed that K.A. was shaking and having an "obvious tonic-clonic seizure." Pet. Ex. 14, p. 24. K.A.'s episode lasted about ten minutes. *Id.* When the police arrived, the seizure activity seemed to be stopping and K.A. began to cry and make "bizarre movements." Pet. Ex. 10, p. 2. K.A. experienced the tonic-clonic seizure while a passenger in petitioner's car. Pet. Ex. 14, p. 24. After transport by ambulance to Children's Hospital,[6] Ms. Russell reported that that K.A.'s behavior had changed in the two weeks before the incident and that she had been screaming throughout the day and at night.[7] Pet. Ex. 14, p. 44. At the hospital, K.A. was noted to have a temperature of 37.7°C (99.86°F). *Id.*, p. 46. A CT scan of the head revealed no structural abnormality, but an EEG conducted several days after the incident demonstrated high voltage rhythmic to semi rhythmic notched activity from the occipital differentials appearing to represent a seizure tendency. Pet. Ex. 5, p. 5.

C. Development of K.A.'s Seizure Disorder After Her May 2008 Hospitalization

In the days following K.A.'s tonic-clonic, or grand mal, seizure, she continued to have seizures and mood swings. Pet. Ex. 5, pp. 2-4. From June 5 to June 10, 2008, K.A. was admitted at the Children's Hospital for continuous video EEG monitoring to clarify intermittent screaming episodes and head banging and rule out seizure activity

[5] Contemporaneous records indicate that K.A. tolerated her immunization well and did not have any fevers, vomiting, or diarrhea. Pet. Ex. 14, p. 24.

[6] K.A. was treated at the Children's Hospitals and Clinics of Minnesota, at both the Minneapolis branch and the St. Paul branch.

[7] When Ms. Russell returned to the Children's Hospital with K.A. on June 5, 2008, 12 days after the first tonic-clonic seizure, she again noted the change in K.A.'s behavior. She stated that for the past 2-3 weeks (which would include the week prior to the tonic-clonic seizure), K.A. had recurrent spells, progressive developmental interruption, and was "just not herself." Pet. Ex. 14, p. 122.

as an etiology for these episodes. Pet. Ex. 7, p. 93. The video EEGs conducted for 24 hours each on June 6, 9 and 10 showed diffuse slowing and poor organization during wakefulness with multiple episodes of high amplitude 300-400 volt sharp 2.5 to 4 hertz rhythmic activity lasting 5 to 15 seconds with posterior dominance. *Id.* The EEG recordings were considered abnormal but did not show specific epileptiform discharges and no specific seizure activity was noted. *Id.* The abnormalities in her EEGs were described as implying "bilateral cortical dysfunction," possibly related to "genetic, metabolic, degenerative, structural, vascular, or other epileptogenic pathologies." *Id.* K.A. began seeing Dr. Steve Janousek, MD, a pediatric neurologist, for the treatment of her seizures. Pet. Ex. 5. Dr. Janousek prescribed several different anticonvulsant medications in the year following K.A.'s first seizure. *Id.*, pp. 5, 23, 33, 49, 71. Keppra, in particular, seemed to greatly increase her irritability or sleepfulness and her mood seemed to improve when taken off of it. *Id.*, pp. 40-41.

After nearly a year with little success on anticonvulsant medications, on March 19, 2009, K.A. was again admitted at the Children's Hospital for a 24-hour EEG, which was noted to be moderately to markedly abnormal with high voltage electrographic seizure activity, both generalized and right occipital with spread to the left occipital region without obvious clinical correlate. Pet. Ex. 7, p. 77. Clinical correlation of the record indicated diffuse cerebral dysfunction with a tendency for seizures of both generalized and focal right occipital onset. *Id.,* p. 76.

At this time her medication was changed to Prednisone[8], to which she responded well with improvement in symptoms and on her EEG. When K.A. began Prednisone she no longer experienced grand mal seizures and she was more alert, with visual interaction and some babbling. *Id.*, p.82. When Dr. Janousek lowered her dose of prednisone, K.A. had a mild deterioration of function, which prompted Dr. Janousek to suggest an intravenous immunoglobulin (IVIG) course. *See id.*, p.86. Given that her initial response to immune therapy with Prednisone had been positive, a course of IVIG therapy was undertaken. On April 16, 2009 K.A. began IVIG therapy. *Id.*, p. 97. After undergoing two days of IVIG therapy, K.A. saw Dr. Janousek, who noted that her mother had seen a significant improvement in K.A.'s interaction, which was evident during the visit, and her video EEG revealed no subclinical seizures (although it still revealed some abnormality). *Id.*, p. 104. On June 11, 2009, Dr. Janousek again noted K.A.'s positive response to IVIG, highlighting that K.A.'s mother and therapists saw improvement and positive effects immediately following the IVIG and lasting about three weeks. *Id.*, p. 122. The positive effects of IVIG would begin to wear off at the three-week mark, at which point her self-stimulatory behavior increased. *Id.* K.A. continued to receive IVIG therapy every three weeks which continued to be effective when the dose was renewed. *Id.*

After the onset of her seizure condition, K.A. continued to see her primary care physicians at South Lake Pediatrics for sick and well-child visits. *See* Pet. Ex. 4, pp. 20-

[8] Prednisone is a synthetic glucocorticoid derived from cortisone, administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY at 1509 (32nd ed. 2012).

36. On July 17, 2009, at her three-year-old well-child exam, K.A. received her second hepatitis A vaccine without incident. *Id.*, p. 32.

K.A. continued to do well on the IVIG therapy and later subcutaneous immunoglobulin therapy (SCIG), but at an October 4, 2010 visit, Dr. Janousek noted that K.A. had been experiencing behavioral degeneration toward the end of the intervals between IVIG injections over the course of the last several months. *Id.*, p. 197. K.A. had become more irritable with increased seizure-like activity. *Id.* After an IV dose of immunoglobulin on October 4 and continued more frequent SCIG thereafter, K.A. responded with fewer seizures and improved interaction and attention. Pet. Ex. 8, p. 13. K.A. was noted to have an "amazing response to therapy with immunoglobulin." *Id.*, p. 15; *see* Pet. Ex. 8 Supp., p. 6. K.A.'s positive responses to SCIG and IVIG would last for variable amounts of time so that the frequency of her dosing was increased from the original plan in response to her deterioration three to four weeks after the prior dose. Each time she received an IVIG administration she would become calmer and more focused, her speech patterns would improve, and her seizures would stop. Pet. Ex. 8 Supp., p. 4.

Around K.A.'s fourth birthday, her mother began to notice pubertal changes, Pet. Ex. 8, p. 11, and in early 2011, K.A. began seeing an endocrinologist for "early puberty and bone age acceleration," Pet. Ex. 7, p. 103.

D. K.A.'s Pediatric Immunology Visits

On October 10, 2009, K.A. was seen by a pediatric immunologist, Ralph Shapiro M.D., for "evaluation of her immune system as related to her diagnosis of intractable seizure disorder and IVIG therapy." Pet. Ex. 8, pp. 2-4. Dr. Shapiro ordered several Laboratory studies to be drawn. *Id.*, p. 4. At her follow-up on November 5, Dr. Shapiro noted that the lab studies showed no evidence of an ongoing inflammatory disorder and that her autoimmune screening was negative at that time. *Id.*, p. 5. Dr. Shapiro discussed with Ms. Russell the possibility of K.A. having a sodium channel defect coded for by the SCN1A gene. *Id.* On October 29, 2012, K.A. was tested for the SCN1A mutation and no mutation was detected, essentially eliminating an SCN1A defect as an explanation for the seizure disorder. Pet. Ex. 20, p. 1.

Dr. Shapiro also noted that he discussed with Ms. Russell the possibility of the seizure disorder being a vaccine related injury and recommended that she consult with an attorney experienced in the program. *Id.*

III. Discussion

A. Legal Standard to Establish Entitlement to Compensation

The Vaccine Act provides for the establishment of causation in one of two ways. *See Munn v. Sec'y of Health & Human Servs*., 970 F.2d 863, 865 (Fed. Cir. 1992). First, a petitioner may demonstrate (i) that the injury suffered is one listed in the

Vaccine Injury Table ("Table injury"), *see* 42 U.S.C § 300aa-14(a); (ii) that the injury occurred within the time provided within the Table; and (iii) that the injury meets the requirements of section 300aa-14(a). *Munn*, 970 F.2d at 865. In such a case, causation is presumed. *Id*. Second, where the complained-of injury is not listed in the Vaccine Injury Table ("off-Table claim"), petitioner may prove causation in fact. *See* 42 U.S.C. §§ 300aa-13(a)(1), -11(c)(1)(C)(ii)(I). In such a case, petitioner must prove by a preponderance of the evidence that the vaccine at issue caused the injury. *See Shyface v. Sec'y of HHS*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999); *Munn*, 970 F.2d at 86.

Eligibility for compensation in an off-table claim is established when petitioner demonstrates by a preponderance of the evidence that the injured party (1) received a vaccine set forth in the Vaccine Injury Table; (2) received the vaccine in the United States; (3) sustained, or had significantly aggravated, any illness, disability, injury, or condition caused by the vaccine; and (4) that the condition persisted for more than six months. *Id.*; §§ 13(a)(1)(A), 11(c)(1). To establish *prima facie* entitlement to compensation in an off-table claim, the petitioner must prove that the vaccine was not only a but-for cause of the injury but also a substantial factor in bringing about the injury. *See Shyface v. Sec'y of HHS*, 164 F.3d 1344, 1352 (Fed. Cir. 1999). The vaccination need not, however, "be the sole factor or even the predominant factor" that caused the injury. *Pafford v. Sec'y of HHS*, 451 F.3d 1352, 1357 (Fed. Cir. 2006).

In *Althen v. Sec'y of HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005), the Federal Circuit set forth three factors that a petitioner must establish by a preponderance of the evidence to prove causation in fact in off-Table injury cases: "(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 showing of proximate temporal relationship between the vaccination and the injury." In order to prevail on an off-Table claim, all three *Althen* factors must be satisfied by preponderant evidence. *Id.*; *Stone v. Sec'y of HHS*, 690 F.3d 1380, 1381-82 (Fed. Cir. 2012).

Petitioner's theory of causation must be supported by a "'reputable medical or scientific explanation.'" *Althen*, 418 F.3d at 1278. (citing *Grant v. Sec'y of HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992)). While petitioner 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." *Andreu v. Sec'y of HHS*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). Where submitted, this evidence should not be viewed with the purpose of establishing that causation is medically or scientifically certain, but rather with the purpose of evaluating whether causation is logically and legally probable. *See id.* Causation is evaluated on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y of HHS*, 35 F.3d 543 (Fed. Cir. 1994).

B. Analysis of *Althen* Factors

In her Petition, Mrs. Russell alleged that as a result of the hepatitis A vaccine,

which K.A. received in Minneapolis on May 23, 2008, she developed a tonic-clonic seizure within 24 hours of receipt of the vaccine and subsequently developed intractable seizures. She asserted that the residual effects of the vaccine injury have continued for more than six months. Petition, paras. 1-3.

In this case, petitioner did not submit an expert report, but instead petitioner elected to rely on the submitted medical records and medical literature to satisfy all three *Althen* factors and thereby to establish causation.

Petitioner contends that the submitted medical literature "coalesces" to provide a reasonable medical theory proving that the hepatitis A vaccine can cause seizures in a susceptible child, thus satisfying the first *Althen* factor. *Id.* at 11. To satisfy the second *Althen* factor, petitioner relies on the opinion of one of K.A.'s treating physicians that her seizure disorder could be vaccine related. *Id.* at 12. To satisfy the third *Althen* factor, petitioner relied on a case report of a 5 year old boy who had seizures in the 24 hours *prior* to his hepatitis A diagnosis as well as the manufacturer's insert listing febrile seizure as a possible adverse event following receipt of vaccination. *Id.* at 14.

There is no question in this case that K.A. received a hepatitis A vaccine in the United States, suffered a grand mal seizure within approximately 24 hours of receiving the vaccine and has continued to be symptomatic for more than six months. The question is whether the vaccine caused the seizures and subsequent seizure disorder, and whether sufficient evidence is contained within the medical records and medical literature submitted by petitioner to satisfy the Althen prongs without the support and explanation of an expert opinion.

1. *Althen* Prong One

The first *Althen* factor requires the petitioner to provide a medical theory "causally connecting the vaccination and the injury," and, thus, answering the question "can the vaccine at issue cause the injury alleged?" *Pafford v. Sec'y of HHS*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (quoting *Pafford v. Sec'y of HHS*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004)). While medical literature can be used in some cases to show a causal connection between the vaccine and the injury, the first *Althen* factor is ordinarily satisfied by an explanation of a plausible medical theory by an expert. *See, e.g.*, *Hibbard v. Sec'y of* HHS, 698 F.3d 1355, 1364 (Fed. Cir. 2012); *Andreu*, 569 F.3d at 1375. The role of a qualified expert is initially to explain a theoretical basis for a cause and effect relationship between the vaccine and its potential to cause the harm at issue. As is often stated, the role of expert opinion in the first *Althen* prong is to explain how the vaccine could cause the injury.

Medical literature is usually used to support the opinion of an expert rather than to stand alone. While it is possible that some medical study could so directly fit with the facts developed in petitioner's medical records that no further explanation would be necessary, that situation would be unusual in a contested case and indeed is not the case here. The medical literature submitted in support of this Petitioner's case leaves

unanswered many questions relevant to causation that would have been better addressed by expert opinion.

In this case, petitioner was given multiple opportunities, over the course of nearly 14 months, to file an expert report.[9] She chose, instead, to rely on medical literature to establish the causal theory required by the first *Althen* factor. Petitioner essentially argues that a causal theory can be inferred from various parts of the submitted literature sufficient to satisfy the first prong of *Althen.* Petitioner's Motion, p. 11.

After review of the record, and specifically the submitted medical literature, I have concluded that there are too many unanswered questions to satisfy the initial *Althen* criteria without expert opinion and explanation. I have therefore concluded that petitioner has failed to prove, by a preponderance of the evidence that the hepatitis A vaccine can cause a seizure disorder. I will review below each of the medical or scientific references produced in order of their importance to the presentation of petitioner's theory of causation.

a. *Immunology and Epilepsy* article

Immunology and Epilepsy, Souhel Najjar, MD, *et al.*, *Immunology and Epilepsy*, REVIEWS IN NEUROLOGICAL DISEASES, 5(3): 109-16 (2008), filed as Pet. Ex. 26, ["Najjar, Pet. Ex. 26" p.114-115] details the immune mechanisms known or thought to be involved in the generation of some forms of epilepsy. The article provides an explanation of an autoimmune basis for some seizure disorders. It discusses the critical role of microglia and pro-inflammatory cytokines in providing the immune response to a foreign invader within the central nervous system. Counsel draws the attention of the court to a particular mechanism of autoimmune action triggered by microglia in the brain as described in this article:

> "Microglial cells may be pathogenic players in acute and chronic forms of epilepsy…Activated microglia can produce pro-inflammatory cytokines, which can also stimulate microglia to produce more cytokines in an autocrine loop. However, overproduction of cytokines and ongoing over-activation of microglial cells can cause a "cytokine storm" of inflammation that can lower the seizure threshold and destroy neurons". *Id.* p 115

The *Najjar* review also included reference to Landau Kleffner Syndrome which is described as a clinical diagnosis based upon acquired loss of language skills, behavioral problems, seizures and EEG abnormalities. *Id.* at 114. Significantly, the article indicates that corticosteroid treatment appears to be the most effective therapy to improve language function and IVIG therapy appears capable of reducing EEG spikes. *Id.* The medical record from Children's Hospital and Clinics of Minnesota from August 27, 2009, after summarizing K.A.'s history lists developmental regression, epilepsy,

[9] Orders filed on January 27, 2012, on April 12, 2012, on July 12, 2012, and on August 28, 2012, each gave petitioner more time to secure and expert in conjunction with SCN1A testing results. *See supra*, note 3.

autism and suspected Landau Kleffner Syndrome in the differential diagnosis. Pet. Ex. 14, p. 726. And consistent with the description in the article, corticosteroid and IVIG treatments were most effective in addressing K.A.'s seizures and developmental disabilities. The effectiveness of the immune modulating therapy in this case certainly suggests an autoimmune etiology for her condition as is suggested by the Najjar article and one of K.A.'s treating physicians described her condition as suspected Landau Kleffner Syndrome. Pet. Ex. 14, p. 276. The course of the syndrome in K.A.'s case does appear to track the symptoms of Landau Kleffner syndrome as described in the *Najjar* article, which symptoms significantly also include her pre-vaccine symptoms. Finally, the article acknowledges that the etiology of the disorder remains unknown.

Nowhere in the article is there any reference to a causal connection between any vaccine and the microglial activation or Landau Kleffner Syndrome. While a qualified expert may have been able to explain that such a connection is plausible, no such testimony is included in the record.

b. Manufacturer's package insert for VAQTA vaccine (Brand name of Hepatitis A Vaccine manufactured by Merck)

The manufacturer's package insert for the VAQTA vaccine provides prescribing information as well as a description of adverse reactions to the vaccine. Merck Sharp & Dohme Corp., *VAQTA (Hepatitis A Vaccine, Inactivated): Suspension for Intramuscular Injection*, MERCK & CO., INC. (1996), filed as Pet. Ex. 24, ["Merck, Pet. Ex. 24"] at 1. The Merck package insert discusses the results of two controlled medical studies of the hepatitis A vaccine. Significantly, it reports on temperature greater than 98.6°F in 12.4% of recipients within 1 to 14 days. In the case at bar, Ms. Russell reported a fever of 101°F on the evening of the vaccination and the hospital recorded 37.7°C or 99.86°F when examining the child after the grand mal seizure. Pet. Ex. 10, p. 2.

More importantly, the studies identified serious adverse events "judged to be vaccine related by the study investigator" to include febrile seizures in .05% of the cases studied. The results of these studies would suggest that the vaccine could cause seizures in a very small percentage of recipients. Because of the fact that the seizure events were judged to be vaccine- related by the study investigators and not mere random reports of an adverse outcome, they should be given more weight than, for example, undocumented VAERS[10] reports. But without more detail, it is difficult to give these conclusions significantly more weight, particularly as the package insert does not define the criteria the study investigators relied upon when judging an event to be vaccine related.

c. *Hepatitis A Vaccine (Intramuscular Route),* Mayo Clinic

This article provides information from Mayo Clinic on the hepatitis A vaccine and

[10] VAERS is the Vaccine Adverse Event Reporting System, a database maintained by the Centers for Disease Control.

describes the purpose of the drug and the disease it prevents, the risks to consider before taking the vaccine, instructions for proper use, precautions, and side effects. Mayo Clinic, *Hepatitis A Vaccine (Intramuscular Route)*, THOMPSON HEALTHCARE, INC. (2013), filed as Pet. Ex. 23, ["Mayo Clinic, Pet. Ex. 23"] at 1-5. This submission merely lists seizures under an "[i]ncidence unknown" category in a discussion of possible side effects of the vaccine. Viewed most liberally, this submission may indicate some recognition by the Mayo Clinic that seizures could occur post vaccination but it most likely only reflects the information from the package insert and does not discuss any criteria for drawing a conclusion of causal connection.

d. *Hepatitis A Virus Infection Presenting with Seizures*

This article analyzes a case report of a 5-year-old boy who experienced tonic-clonic seizures during the course of a hepatitis A infection.[11] Sebahat Cam, MD, *et al.*, *Hepatitis A Virus Infection Presenting with Seizures*, THE PEDIATRIC INFECTIOUS DISEASE J., 24(7): 652-53 (2005), filed as Pet. Ex. 22, ["Cam, Pet. Ex. 22"] at 652. This case report discussed the presentation of a five year old boy who was admitted to the hospital with generalized tonic-clonic convulsions that had occurred four times over 24 hours. *Id.* Alternative causes such as head trauma, prior history or drug intake were ruled out by history. *Id.* On examination he had slight jaundice, mild tenderness on palpation over the right upper quadrant, and nuchal rigidity. He was afebrile when presenting to the hospital and throughout his stay. *Id.* He had elevated liver function tests and IgM and IgG antibodies to hepatitis A in his serum. *Id.* Serology for other viral causes were negative. *Id.* A lumbar puncture was done and IgM for hepatitis A was positive as was the RNA for hepatitis A in the cerebral spinal fluid. *Id.* The presence of Hepatitis A antibody and RNA in the cerebral spinal fluid, with no other reasonable explanation, caused the physicians to conclude that a hepatitis A infection caused the seizures. *Id.* There was no known time of onset of the hepatitis infection, as the seizures were the initial presenting symptom leading to the diagnosis of hepatitis. In two years of follow up with this patient he did not have additional seizures. *Id.* at 652-53.

While this article documents a rare finding of hepatitis A antibody in the cerebral spinal fluid, and presents a conclusion that hepatitis caused the seizures in this young boy, it provides no more than a loose association between seizures and a wild hepatitis infection. It does not present the case of a vaccine stimulated seizure disorder or, for that matter, a chronic seizure disorder at all. It does report on a series of seizures occurring on one day that led to the diagnosis of hepatitis A through physical examination, and identification of significant laboratory markers of hepatitis which in turn led the doctors to conclude that hepatitis caused the seizures.

e. *Adversomics*

The fifth submitted article, *Adversomics*, discusses the possibility that adverse

[11] The boy experienced four convulsions lasting 1-10 minutes in the 24-hour period before admission to the hospital and diagnosis. Pet. Ex. 22 at 652.

events and reactions to vaccines may be genetically predetermined. Gregory A. Poland, MD, *et al.*, *Adversomics: The Emerging Field of Vaccine Adverse Event Immunogenetics*, THE PEDIATRIC INFECTIOUS DISEASE J., 28(5): 431-32 (2009), filed as Pet. Ex. 25, ["Poland, Pet. Ex. 25"] at 1.[12] The article is essentially an exhortation to the medical community to conduct further studies using enhanced technologic capabilities to address the problems associated with vaccine immunogenetics. The article describes the difficulty of studying large enough groups, and matching of adverse outcomes with individual characteristics, and genetic susceptibilities in order to better understand the causes of adverse outcomes after vaccines. The authors suggest that a wide variety of factors may influence "immune, inflammatory, idiosyncratic and other responses to vaccines." *Id.* at 1. They generally discuss work done with cytokines and smallpox vaccine in their lab and describe some genetic associations with adverse events associated with the MMR vaccine. However, it does not discuss the hepatitis vaccine, adverse reactions to it or any known genetic susceptibilities to the vaccine. While the article's advocacy of further study of adverse outcomes potentially associated with vaccines is a laudable goal, it does not provide insight into a potential mechanism or causal relationship between the hepatitis A vaccine and seizures. To the extent that the authors propose the likelihood of genetic susceptibilities as a vulnerability to vaccine adverse events, there were no such genetic abnormalities either related to the hepatitis A vaccine discussed in the article or documented in K.A.'s medical records.

f. Evaluation of the Evidence

The literature submitted by Ms. Russell suggests an immune mediated cause of seizure disorders such as that suffered by K.A., and does provide some support for the notion that the hepatitis A vaccine "can cause" seizures in relatively rare instances. The microglial generated cytokine storm theory suggests a possible mechanism, assuming that some element of the vaccine invaded the brain and thereby triggered the storm. However, neither the theory nor the means by which some part of the vaccine may have entered the brain has been endorsed or explained by a qualified expert in this case. The notion of a hepatitis A vaccine cause is arguably supported by the Merck studies, in which investigators concluded that .05% of the study subjects were considered to have had vaccine- related seizures. However, there was no reported data as to whether the seizures reported progressed to chronic seizure disorders or were self-limited occurrences. As noted above, the package insert did not describe the basis upon which the investigators concluded that .05% of their study population suffered vaccine related seizures.

Expert testimony is almost always helpful in synthesizing and explaining the literature while relating it to the medical conditions at issue. It would have been helpful here. Without expert testimony it is difficult to find a connection between the proposed

[12] While the article is published in the Pediatric Infectious Disease Journal at pages 431-32, petitioner filed an Author Manuscript, which is paginated 1-4.

cytokine storm mechanism and the vaccine in question.[13] The *Najjar* article discusses the immune response to foreign invaders of the central nervous system, but does not discuss particular pathogens or describe how the antigen contained in the vaccine or any other part of the vaccine would cross the blood brain barrier in order to stimulate the microglial and cytokine response described.

While the Vaccine Act does not require that petitioner describe a specific mechanism, nor does it require proof to a scientific certainty, it does require petitioner to articulate a theory that links the vaccine and the condition in question and that is reasonably supported by a sound and reliable medical or scientific explanation. *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548 (Fed. Cir. 1994). If a cytokine storm mechanism is relied upon as a theoretical basis for the initiation of a seizure disorder, a reasonable explanation would require an expert or treating physician to explain how that mechanism could occur secondary to a vaccine and, in particular, to this vaccine. The Merck data could be seen as supportive of a well-developed medical opinion, but is insufficient by itself to establish the first prong of *Althen* without more information as to the criteria used to establish a causal link between the vaccine and seizures, and whether any of the seizures developed into the type of full blown disorder seen in this case.

Accordingly, I have concluded that the evidence submitted is not sufficient to establish a causal theory and satisfy *Althen* prong one.

2. *Althen* Prong Two

The second *Althen* factor requires petitioner to establish that the vaccine was the reason for the injury—not only a but-for cause of the injury but also a substantial factor in bringing about the injury. *See Shyface v. Sec'y of HHS*, 164 F.3d 1344, 1352 (Fed. Cir. 1999). Testimony from treating physicians can be probative when evaluating the second *Althen* factor as "treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006).

Expert testimony, which, as petitioner argues, may be provided by a treating physician, is generally also helpful in establishing *Althen* prongs 2 and 3. To be helpful, it needs to be more than the expression of a mere possibility of connection; it should contain an explanation of the logical sequence of cause and effect showing that the vaccination was the cause for the injury. *Knudsen*, 543 F.3d at 548. 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, but there needs to be a sound and reliable medical or scientific explanation for any conclusion in favor of causation. *Id.* at 548-49.

[13] The fact that a special master, acting as a medical expert, may interpret a medical study without assistance does not mean that he *must* conclude that a particular study, or aspects of a study, can be understood absent such assistance. *Moberly v. Sec'y of HHS*, 85 Fed. Cl. 571, 597 (2009).

Petitioner argues that Dr. Shapiro, a pediatric immunologist, whose credentials would be appropriate to opine on causation in this case, stated in the records that "the etiology of K.A.'s seizures was likely the hepatitis A vaccine." Petitioner's Motion, p. 12. However, Dr. Shapiro's notes from a November 5, 2009 visit actually do not go that far. Rather, they state, "[w]e also discussed the possibility that this is [a] vaccine related injury. In light of that, I gave a call to a colleague who does a lot of vaccine injury work," (referring to an attorney with considerable experience in the vaccine program). Pet. Ex. 8, p. 5. Dr. Shapiro's notes from a November 8, 2011, visit also say, "[s]She has a seizure disorder thought to be Immune mediated. She has had a remarkable response to therapy, SCIG (subcutaneous immunoglobulin) seems to be holding her fairly well but at intervals of 2-3 months she begins to breakthrough and responds again to IV dose of Immunoglobulin." Pet. Ex. 8, p. 22.

Without further explanation by Dr. Shapiro, these comments do not demonstrate "a logical sequence of cause and effect showing that the vaccination was the cause of the injury," *Althen,* 418 F. 3d at 1278*,* and are insufficient to meet the second prong of *Althen.* If Dr. Shapiro did, in fact, believe that the vaccine was linked to K.A's seizure disorder, it is unfortunate for petitioner that Dr. Shapiro was unwilling to express this opinion or to provide an explanation as to how this vaccine could and did cause K.A.'s seizure disorder. The child's responsiveness to immune therapy, and her relative unresponsiveness to first line epileptic medications, suggest that her condition is related to a malfunction of the immune system by which an element of the immune system attacked and damaged the brain, giving rise to seizures. This factor would be supportive of causation if petitioner had offered the opinion of an appropriately qualified medical professional to explain how the vaccine caused the onset of the seizure disorder, and how that function of the immune system would have been stimulated by the hepatitis A vaccine. A treating physician's diagnosis concluding that the hepatitis A vaccine caused K.A.'s seizure disorder *could* be sufficient proof of causation. *See Moberly*, 85 Fed. Cl. at 604; *Capizzano,* 440 F.3d at 1326*.* However, Dr. Shapiro's chart notes did not affirmatively state such an opinion, and petitioner did not file a report from him setting forth that opinion with an appropriate explanation. A review of the record also fails to show any indication that Dr. Janousek or any of the treating doctors at Children's Hospital held the opinion that the vaccine caused K.A.'s seizure disorder. As the Federal Circuit held in *Paterak v. Sec'y of HHS*, 527 Fed. App'x 875, 883 (Fed. Cir. 2013), "the statutory standard requires more than just proof of a 'plausible' or 'possible' causal link between the vaccine and the injury."

It also would have been helpful if petitioner had presented medical opinion distinguishing the seizure disorder, alleged to have begun 24 hours after the vaccination, from the behavioral disturbances and neurodevelopment regression that were well underway before the vaccine was given. An explanation for the lack of re-challenge effect when K.A. received the second dose of hepatitis A vaccine without incident on July 17, 2009, would also have been helpful.

K.A.'s records contain confounders including that K.A. was exposed to harmful

substances as well as HIV *in utero*. Pet. Ex. 5, pp. 5, 12. However, there is no evidence of record that her birth mother's physical condition or recreational ingestions had a causal effect in producing seizures that did not begin until many months after birth.

The record does reflect that K.A. began experiencing developmental issues at nine months, which caused her to engage in severe self-stimulating behaviors, including head-banging, Pet. Ex. 6, pp. 5-7. The vaccine was received at 22 months. Her mother mentioned, on more than one occasion, in the records, that K.A.'s behavior had changed in the weeks prior to her receipt of the hepatitis A vaccine and subsequent grand mal seizure. Pet. Ex. 14, pp. 44, 122. If petitioner is relying upon a Landau Kleffner Syndrome diagnosis, it would certainly seem that the developmental and behavioral issues that presented in the weeks before the vaccine could well have been part of the syndrome and the seizures a later manifestation of that continuum. While the Vaccine Act "does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case," the elimination of alternative causes may be key to establishing causation when no definitive mechanism for the harm is understood. *Walther v. Sec'y of HHS*, 458 F.3d 1146, 1149-50 (Fed. Cir. 2007). Petitioner "may be required to eliminate potential alternative causes where the petitioner's other evidence on causation is insufficient." *Id.* In this case the logical leap from Dr. Shapiro's statement of a possible association with the vaccine is one too far when he did not provide a report describing the medical explanation for a conclusion that the vaccine did in fact cause the seizure disorder, and did not explain how the confounding circumstances could be distinguished.

Accordingly, the undersigned finds that petitioner has failed to establish a logical sequence of cause and effect showing that K.A.'s hepatitis A vaccine was the reason for her seizures. Thus, petitioner does not satisfy the second *Althen prong*.

3. *Althen* Prong Three

The third *Althen* factor requires that petitioner demonstrate a proximate temporal relationship between the vaccination and the injury—that the injury "occurred within a medically acceptable time frame." *Pafford*, 451 F.3d at 1358. Again, it would be helpful to establishing causation to have expert opinion indicating that the time frame for the onset of symptoms was appropriate. Without testimony as to the suspected causal relationship between the vaccine and the seizures, it is difficult to determine if the time frame was appropriate for the suspected immune process to develop and cause injury in the brain. There is no evidence in the record as to the time frame that would be appropriate for a cytokine storm to cause an autocrine loop resulting in a seizure disorder. Nor is there any explanation as to how the child's pre-vaccine symptoms, also consistent with the Landau Kleffner Syndrome and that certainly were not caused by the vaccine, could be separated from the post-vaccine seizure manifestations of the syndrome. The close temporal relationship between the vaccine and K.A.'s initial grand mal seizure may be supportive evidence in a case where the testimony established a

logical cause and effect along with the appropriate time frame for the suspected immune process to take place. As it has been concluded that the evidence in this case was insufficient to make that connection, the proximity of the event by itself is not helpful to the petitioner.

IV. Conclusion

Petitioner has failed to satisfy any of the *Althen* factors, and has thus failed to establish by a preponderance of the evidence that the hepatitis A vaccine caused K.A.'s seizure disorder. Petitioner has failed to demonstrate entitlement to compensation. **I therefore hold that petitioner's claim is dismissed. The clerk shall enter judgment accordingly.**

IT IS SO ORDERED.

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