In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 28, 2020

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MICHAEL PAVAN, next friend of J.P., a minor,	*	PUBLISHED
Petitioner,	*	No. 14-60V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Significant Aggravation; Varicella; Chronic Inflammatory Demyelinating Polyneuropathy ("CIDP").
Respondent.	*	
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Scott W. Rooney, Nemes Rooney P.C., Farmington Hills, MI, for petitioner.
Kyle E. Pozza, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

On January 24, 2014, Michael Pavan ("petitioner"), as next friend of J.P., a minor, filed a petition in the National Vaccine Injury Compensation Program.[2] Petitioner alleges that as a result of J.P. receiving the varicella vaccination on January 28, 2011, he suffered a significant aggravation of his Chronic Inflammatory Demyelinating Polyneuropathy ("CIDP"). Amended Petition at ¶¶ 4, 5, & 16 (ECF No. 26); Petitioner's ("Pet.") Post-hearing Brief at 2 (ECF No. 151). Based on a full review of the evidence and testimony presented, I find that petitioner has not established by a preponderance of the evidence that the varicella vaccination significantly aggravated J.P.'s CIDP and therefore, compensation must be denied and the petition dismissed.

[1] In accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012), because this opinion contains a reasoned explanation for the action in this case, **this opinion will be posted on the website of the United States Court of Federal Claims**. This means the opinion will be available to anyone with access to the internet. As provided by 42 U.S.C. § 300aa-12(d)(4)B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). **If neither party files a motion for redaction within 14 days, the entire opinion will be posted on the website and available to the public in its current form.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in 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 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

I. Procedural History

Petitioner, on behalf of the minor, J.P., filed a petition on January 24, 2014. Petition (ECF No. 1). After petitioner filed supporting medical records, an initial status conference was held on March 28, 2014. *See* Initial Order (ECF No. 16). A second status conference was held on August 19, 2014, where petitioner's counsel made an oral motion to amend the petition to include a significant aggravation claim and I granted petitioner's motion. Scheduling Order (ECF No. 24). On September 9, 2014, petitioner filed an amended petition, adding a significant aggravation claim. Amended Petition (ECF No. 26).

On November 5, 2014, respondent filed a Rule 4(c) report, recommending against compensation. Respondent's ("Resp.") Report ("Rept.") at 2 (ECF No. 30). Respondent stated, "there is no appropriate temporal relationship between J.P.'s CIDP and his vaccination. The medical records consistently place the onset of J.P.'s CIDP symptoms in the months prior to his January 28, 2011 vaccinations, making it illogical to conclude that his CIDP was caused by his vaccinations." Resp. Rept. at 11. Additionally, the respondent stated that petitioner had yet to file an expert report that provided any medical or scientific explanation supporting a theory of vaccination causation. *Id.* at 13. Therefore, respondent stated, the petitioner provided insufficient evidence of vaccine causation under the three prongs of *Althen*. *Id.* at 15.

On March 22, 2016, petitioner filed expert reports from Dr. Sheldon Margulies, M.D.,[3] a neurologist, and Dr. David Axelrod, M.D.,[4] an immunologist. Respondent filed expert reports

[3] Dr. Sheldon Margulies is a retired pediatric neurologist. Pet. Ex. 34. He graduated from Stanford University School of Medicine in 1971. *Id.* at 2. Dr. Margulies did his residency at the McGill University Royal Victoria Hospital in Internal Medicine. *Id.* After that, Dr. Margulies had a residence in neurology at the University of California Moffitt Hospital from 1973-1976. *Id.* Dr. Margulies then studied the law and received his Juris Doctorate from the University of Baltimore Law School in 1988. *Id.* Dr. Margulies is board certified in neurology and is licensed to practice medicine in the states of Maryland and New York. *Id.* at 3. From 1982-1989, Dr. Margulies was an Assistant Professor in the Neurology Department at the University of Maryland. *Id.* at 4. He began private practice in Adult and Adolescent Neurology from 1989-2013. During this time, he also maintained volunteer Clinical Assistant Professor positions at the Neurology Department at Howard University Hospital and at the Uniformed Services University of Health Sciences, F. Edward Hebert School of Medicine. *Id.* at 4. During the hearing, Dr. Margulies testified that he has been qualified as an expert in neurology in other court proceedings. Tr. 88. He also testified that he had diagnosed patients with CIDP in the past. Tr. 89. I certified him as an expert in adult and adolescent neurology. Tr. 92.

[4] Dr. David Axelrod is a rheumatologist, allergist and immunologist. Tr. 201; Pet. Ex 35. He graduated from the University of Michigan Medical School in 1974. *Id.* at 2. After graduation, he was a resident of internal medicine at the University of Toronto School of Medicine until 1976. *Id.* He was a Clinical Immunology Fellow at McGill University-Royal Victoria Hospital from 1978-1980. *Id.* Afterwards, he was a Medical Staff Fellow at the Laboratory of Clinical Immunology at the National Institutes of Health ("NIH") from 1980-1982. *Id.* Following his fellowship at NIH, he practiced in adult rheumatology, allergy and immunology from 1991-2018. Tr. 202; Pet. Ex. 35 at 3. Dr. Axelrod had various academic appointments, including as a Principal Investigator in the Division of Gastroenterology, Laboratory of Mucosal Immunology at Walter Reed Army Institute of Research and was the Academic Chief of the Division of Allergy at Mount Carmel Mercy Hospital in Detroit, MI. Pet. Ex. 35 at 3. Dr. Axelrod is licensed to practice medicine in Michigan, Pennsylvania and Maryland. *Id.* Dr. Axelrod testified that he has testified and been recognized as an expert in clinical immunology by other courts and has testified before the Court of Federal Claims in Vaccine cases. Tr. 203-4. During voir dire, Dr. Axelrod stated that he has treated children in the past with allergies and immune deficiencies. Tr. 204. He also stated that he has been involved in the

from Dr. Andrew MacGinnitie, M.D., PhD[5] and Dr. Peter Bingham, M.D.[6] on June 24, 2016. Notice of Filing (ECF Nos. 52 & 53). Another status conference was held on July 12, 2016 where I reviewed the expert reports and ordered the petitioner to file supplemental expert reports addressing multiple issues. Scheduling Order (ECF No. 54). Petitioner filed supplemental expert reports from Drs. Axelrod and Margulies on September 14, 2016. Petitioner Exhibits ("Pet. Ex.") 26 & 27 (ECF Nos. 56 & 57). Respondent filed supplemental expert reports from Drs. MacGinnitie and Bingham on December 5, 2016. Respondent Exhibit ("Resp. Ex.") E & F (ECF Nos. 60 & 61).

On March 9, 2017, the parties filed a joint status report identifying dates in June 2018 for an entitlement hearing. Joint Status Report (ECF No. 70). A hearing order was entered on December 27, 2017. Hearing Order (ECF No. 102).

Both parties submitted pre-hearing submissions. Pet. Prehearing Submission (ECF No. 106 & 125); Resp. Prehearing Submissions (ECF no. 114). An entitlement hearing was held in Washington, D.C. on June 21 & 22, 2018. Mr. Michael Pavan, Ms. Jennifer Pavan, Dr. Sheldon Margulies and Dr. Axelrod testified on behalf of petitioner. Dr. Bingham and Dr. MacGinnitie testified on behalf of respondent.

Petitioner filed updated records after the hearing, including updated medical records and school records for J.P. *See* Pet. Exs. 54-60. On September 19, 2018, petitioner filed a post-

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treatment of children with IVIG. Tr. 205. Respondent did not object to Dr. Axelrod being admitted as an expert, and I admitted him as an expert in clinical immunology. Tr. 205.

[5] Dr. Andrew MacGinnitie is currently an attending physician in Pediatric Allergy and Immunology at Children's Hospital in Boston, Massachusetts. Resp. Ex. B at 3. He graduated from the University of Chicago Pritzker School of Medicine in 1998 and received his Ph.D. in pathology from the same school in 1996. *Id.* at 2. Dr. MacGinnitie did his residency at Boston Combined Residency Program from 1998-2001 in pediatrics and was a fellow in the Allergy and Immunology Division at Children's Hospital in Boston, MA. *Id.* Afterwards, Dr. MacGinnitie became an attending physician at Children's Hospital of Pittsburgh of UPMC and was an assistant professor of pediatrics at the University of Pittsburgh. *Id.* 2-3. In 2011 to the time of the hearing, Dr. MacGinnitie was an attending physician at Children's Hospital in Boston in Pediatric Allergy and Immunology. *Id.* at 3. He was also an assistant professor of pediatrics at Harvard Medical School. *Id.* at 2. He was also the Associate Clinical Director of the Division of Immunology at Boston Children's Hospital. *Id.* at 3. He is licensed to practice medicine in Massachusetts and Pennsylvania. *Id.* at 10. He is also board certified in Pediatrics and Allergy and Immunology. *Id.*; Tr. 281. During the hearing, Dr. MacGinnitie testified that he sees about 1,600 annually. Tr. 281. He also testified that he as seen a few children with CIDP in the past. Tr. 282. The petitioner had no questions for Dr. MacGinnitie. Tr. 283. Respondent offered Dr. MacGinnitie as an expert in pediatric immunologist and I admitted him as such. Tr. 284.

[6] Dr. Peter M. Bingham is a professor of Neurology and Pediatrics at the University of Vermont. Resp. Ex. J. He graduated from Columbia College of Physicians and Surgeons in New York, New York in 1987. *Id.* at 2. Afterwards, he did a residency in pediatrics at Children's Hospital of Philadelphia, followed by a residency in neurology at the same hospital. *Id.* at 2. Dr. Bingham is board certified in neurology/child neurology. *Id.* at 2. He is licensed to practice medicine in Vermont and New York. *Id.* After his residencies, Dr. Bingham became a research fellow for muscular dystrophy at the Hospital of the University of Pennsylvania. *Id.* He has held various teaching positions, including as an Instructor of Clinical Neurology at the University of Pennsylvania School of Medicine and as an Associate Professor of Neurology and Pediatrics at the University of Vermont. *Id.* At the hearing, Dr. Bingham testified that he has treated children with CIDP in the past. Tr. 138. Respondent offered Dr. Bingham as an expert in the field of pediatric neurology. Tr. 138. Petitioner did not object, and therefore, I admitted Dr. Bingham as an expert in the field of pediatric neurology. *Id.*

hearing brief. Pet. Post-Hearing Brief (ECF No. 151). Respondent filed a post-hearing brief on November 30, 2018. Resp. Post-Hearing Brief (ECF No. 154). Petitioner filed a response to respondent's post-hearing brief on January 9, 2019 and additional supporting medical literature. Pet. Post-Hearing Reply ("Pet. Reply") (ECF No. 157); Pet. Exs. 64-69.

This matter is now ripe for adjudication.

II. Legal Standard

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

A petitioner bears the burden of establishing his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

In the present case, petitioner does not allege a Table injury, thus, he bears the burden of establishing actual causation. Furthermore, petitioner alleges that J.P. suffered an off-table significant aggravation of a pre-existing CIDP, as a result of receiving the varicella vaccination on January 24, 2011. Pet. Post-Hearing Brief at 4.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In *Loving*, the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *Althen v. Sec'y of Health & Human Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

In *Sharpe,* the Federal Circuit clarified the *Loving* prongs and what is required by petitioners to successfully demonstrate a cause-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Human Servs.,* 2020 WL 3564251,---F.3d---(Fed. Cir. 2020). *Loving* prong 3 only requires a comparison of a petitioner's current, post-vaccination condition with her pre-existing pre-vaccination condition. *Sharpe* at *5.; *Whitecotton v. Sec'y of Health & Human Servs.,* 81 F.3d 1099 (Fed. Cir. 1996). A petitioner is not required to demonstrate an expected outcome or that their post-vaccination condition was worse than such an expected outcome. *Sharpe* at *5.

Under *Loving* prong four, a petitioner need only to provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Sharpe* at *7; *see also Loving*, 86 Fed. Cl. at 144. In other words, petitioner was required to present a medically plausible theory demonstrating that a vaccine "can" cause a significant worsening" of the condition. *Sharpe* at *7 (citing to *Pafford ex. rel. Pafford v. Sec'y of Health & Human Servs.,* 451 F.3d 1352, 1356-57 (Fed. Cir. 2006). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of her significantly aggravated injury. *Id.*; citing *Walther v. Sec'y of Health & Human Servs.,* 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alterative causation….once petitioner has established a prima facie case").

Loving prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving*, 86 Fed. Cl. at 144. In other words, petitioner has to show that the vaccinations "did" cause a worsening of [petitioner's underlying disorder]. *Id.*

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human*

Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95). In Vaccine Program cases, these factors are used in the weighing of the scientific evidence actually proffered and heard. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Analysis[7]

A. *Loving* Prong One: J. P.'s condition prior to the January 28, 2011 vaccination.

This prong requires an "assess[ment] of the person's condition prior to administration of the vaccine[s]." *Loving*, 86 Fed. Cl. at 143.

[7] Rather than providing a separate summary of the relevant facts before and after the vaccines at issue (drawing from the medical records and the fact witness testimony), I find it appropriate to present that information here, under *Loving* prongs one and two.

J.P. was born at term on December 7, 2007. Pet. Ex. 8 at 40; Transcript ("Tr.") 5. Ms. Pavan testified that J.P. had high bilirubin and had to return to the hospital two days after going home to be treated for his high bilirubin. Tr. 5. Additionally, J.P. developed gastroesophageal reflux disease ("GERD"), anemia and vitamin D deficiency. *Id.*; Pet. Ex. 5 at 2; Pet. Ex. 8 at 33, 40. Ms. Pavan testified that J.P. became extremely fatigued and very pale as a result of his anemia. Tr. 6-7. J.P. began iron supplements in 2008. *Id.* at 7.

At J.P.'s two-year well visit on December 8, 2009, Dr. Anastasi stated that J.P. was developing normally, with "no activity or exercise concerns." Pet. Ex. 14 at 43. On December 17, 2009, J.P. had an acute office visit for congestion. *Id.* at 44. He was assessed with an acute upper respiratory infection and Dr. Gitlin recommended a steam shower, nasal saline spray/drops to relieve congestion or to take a walk in the cool air to break coughing episodes. *Id.* Between December 21, 2010 and April 6, 2010, J.P. was treated for recurring upper respiratory infections associated with coughs and mild fevers. *See* Pet. Ex. 14 at 47-58. On April 4, 2010, in addition to cough, J.P. presented with a rash on both feet between his toes. *Id.* at 58. He was started on Amoxicillin and it was recommended that Lotrimin be applied to his feet for two to three weeks. *Id.*

On April 26, 2010, J.P. was seen by Dr. Becker for abdominal pain with an onset of about ten days. Pet. Ex. 14 at 60. Dr. Becker noted that J.P.'s babysitter observed him "grabbing his lower right side," and J.P. was vocalizing that his stomach hurt. *Id.* Additionally, Dr. Becker noted that J.P.'s parents reported that he "seems more fatigued [in the] past two weeks." *Id.*

On July 21, 2010, J.P. was treated by Dr. Jennifer Becker for fatigue that began approximately one month prior. Pet. Ex. 8 at 55. J.P. received a flu vaccination on September 22, 2010. *Id.* at 57. On October 18, 2010, J.P. was seen by Dr. Becker again for fatigue that had "gotten progressively worse over the past two weeks." *Id.* at 58. Ms. Pavan reported to Dr. Becker that J.P.'s naps were getting progressively longer, from typically two-hour naps to five hours. *Id.* Dr. Becker assessed J.P. with mild fatigue and suspected it was "due to change in sleep/wake cycle." *Id.* She also opined that J.P. may be going through a growth spurt. *Id.*

Ms. Pavan testified that between July 2010 and the beginning of 2011, J.P. had not experienced any additional issues of fatigue or inability to perform activities. Tr. 8. Ms. Pavan explained that J.P. loved to do arts and crafts, like painting, coloring and play-doh. Tr. 8. J.P. enjoyed using the play kitchen, playing cars and monster trucks, and participating in different sporting activities. *Id.* at 9.

J.P. received treatment for a fever and an ear infection in October 2010 and then again in November 2010. Pet. Ex. 8 at 62-5. On January 28, 2011, J.P. was seen for a routine child wellness visit. *Id.* at 67. At this appointment, J.P. had a scaly rash around his toes. *Id.* Dr. Becker assessed J.P. as a "really bright 3-year-old [with] normal growth and development." *Id.* At this appointment, J.P. received his varicella and polio vaccinations. *Id.* at 68.

B. *Loving* Prong Two: J.P.'s condition after the January 28, 2011 vaccinations.

This prong requires an assessment of "the person's current condition (or the condition following the vaccination[s] if that is also pertinent)." *Loving*, 86 Fed. Cl. at 143.

J.P. had a follow-up visit with Dr. Becker on February 1, 2011 for the rash on his feet. Pet. Ex. 8 at 71. Dr. Becker noted the rash had not subsided with over-the-counter antifungal cream and she prescribed ketoconazole to treat the rash. *Id.* at 71.

Ms. Pavan testified that in mid-February 2011, J.P. began to withdraw from activities, he was less interested in participating in physical sports or painting and coloring. Tr. 10. She stated that he became "extremely clingy and emotional." *Id.* Ms. Pavan explained that J.P. went from being fatigued and tired to "completely wiped out…to the point where we would have to carry him around even from the couch to the kitchen table to eat because he physically couldn't walk." *Id.* She testified that J.P. would sleep a full night, but then fall back asleep in the car if they were out running errands. *Id.* at 23.

On March 4, 2011, J.P. was treated by Dr. Becker for fatigue with an onset of two weeks prior to the appointment. Pet. Ex. 8 at 75. Dr. Becker noted that J.P. had decreased energy for music and activities. *Id.* She also noted that he had an increased appetite and thirst, but decreased diapers. *Id.* Dr. Becker assessed J.P. with recurrent malaise and fatigue and stated that if J.P.'s symptoms do not improve after the family vacation, she would do additional lab testing. *Id.* at 75.

Ms. Pavan testified that between April and June of 2011, she and J.P.'s father began to notice more significant physical changes in J.P., like "limb failure, grip issues and fine motor issues." Tr. 28. She explained that J.P. was having coordination issues that made kicking a soccer ball difficult or doing crafts. *Id.* It was around this time that J.P. developed a droop in his left eye. *Id.* at 31. She stated that J.P.'s left eye droop would close almost entirely, and he would complain of vision issues. *Id.*

J.P. returned to Dr. Becker on April 12, 2011 with his father for an assessment of his left eye. Pet. Ex. 8 at 77. Mr. Pavan reported that J.P.'s eyelid appeared to droop four days prior to the appointment, and it appeared to get progressively "more droopey" throughout the day. *Id.* at 77. Mr. Pavan also reported that J.P. appeared to become easily fatigued over the past few months and that J.P. was "less interested in physical activities." *Id.* Dr. Becker noted that recent complete blood count ("CBC") and thyroid stimulating hormone ("TSH") drawn were normal. *Id.* Dr. Becker assessed J.P. with acute ptosis and expressed "clinical concern for possible myasthenia gravis." She recommended J.P. be taken to the Kellogg Eye Center for an evaluation. *Id.* This observation of ptosis beginning on or about April 8, occurred approximately 70 days post vaccination.

On April 15, 2011, J.P. was evaluated by Dr. Wayne Cornblath at the Kellogg Eye Center. Pet. Ex. 4 at 2. Dr. Cornblath indicated that J.P.'s parents noted he was experiencing "variable ptosis." *Id.* He noted that Ms. Pavan reported J.P. was experiencing "some fatigue in the last few months." *Id.* Dr. Cornblath stated, "J.P. has variable ptosis on the left. He has no

ocular motility abnormalities. I was concerned that this represented ocular myasthenia gravis. We will start with an acetylcholine receptor antibody test." *Id.* Dr. Cornblath again noted that Ms. Pavan reported that J.P.'s fatigue increased over the last few months and stated, "It is not clear whether these connect to his ptosis or to the possibility of a generalized myasthenia….Depending on results, I did tell [them] I would also consider a referral to Dr. James Dowling, a pediatric neuro-muscular specialist here." *Id.*

On May 13, 2011, J.P. was evaluated by Dr. James Dowling, a pediatric neurologist at the Pediatric Neuromuscular Clinic at the University of Michigan. Pet. Ex. 11 at 184. Dr. Dowling noted that J.P.'s parents became concerned last fall, as J.P. was demonstrating "excessive fatigue." *Id.* Dr. Dowling wrote, "This became slowly progressive from September onward." *Id.* He stated that J.P. began developing asymmetric ptosis in April, more notable in the left than the right and fluctuating in nature. *Id.* Dr. Dowling noted, "…when [J.P.] does have ptosis, his symptoms of fatigue, clumsiness and decreased appetite are much worse." *Id.* Dr. Dowling stated that J.P.'s test for acetylcholine receptor antibodies was negative and his iron and TSH studies were normal. *Id.* After a physical exam, Dr. Dowling opined that "the most likely diagnosis in this case would be myasthenia gravis. Other considerations would be another autoimmune neurologic condition like CIDP or a mitochondrial disorder like chronic progressive external ophthalmoplegia or a congenital myopathy." *Id.* at 185. He recommended an EMG/nerve conduction study as well as a single-fiber EMG. *Id.* J.P. was also started on a Mestinon[8] therapy. *Id.*

J.P. returned to see Dr. Dowling on June 3, 2011 for further evaluation. Pet. Ex. 11 at 180. Dr. Dowling stated that since J.P. was last at the clinic, J.P. began experiencing fluctuations of eye puffiness and good days and bad days in terms of gross motor skills. *Id.* Since J.P. began the Mestinon therapy there was no obvious change in his symptomology. *Id.* Again, Dr. Dowling wrote, "Of note, J.P.'s symptoms first started in September." *Id.* The physical exam showed some eye puffiness, but no ptosis and mildly decreased muscle tone and muscle bulk. *Id.* Dr. Dowling stated that because of J.P.'s lack of response to the Mestinon therapy an EMG/nerve conduction study is the next step. *Id.* He opined that if the EMG/nerve conduction does not confirm myasthenia, then the leading alternative diagnosis would be mitochondrial cytopathy, but also considered CIDP, given J.P.'s significant fluctuations in symptoms. *Id.*

The EMG performed on June 3, 2011 revealed that the left sural sensory response was absent, and the left median sensory amplitude was reduced. Pet. Ex. 11 at 157. The peroneal motor response was reduced and there was a conduction block with temporal dispersion and prominent slowing of conduction. *Id.* Additionally, the tibial motor response showed a conduction block and temporal dispersion and the left median motor response had a partial conduction block and prominent conduction. *Id.* The conclusion of the study was "electrodiagnostic evidence of an acquired demyelinating neuropathy. The time course is most consistent with CIDP." *Id.* Dr. Dowling informed J.P.'s parents of the results and recommended starting J.P. on IVIG as soon as possible. *Id.* at 178.

[8] Mestinon is the trademark name for pyridostigmine bromide, which is used for the treatment of myasthenia gravis. *Dorland's Illustrated Medical Dictionary* 33nd ed. (2020) (hereinafter "*Dorland's*) at 1562.

J.P. was admitted to the University of Michigan Hospital on June 8, 2011 for initiation of IVIG treatment. Pet. Ex. 11 at 171. On June 9, 2011, J.P. was assessed by pediatric neurologist, Dr. Steven Leber. *Id.* at 162. He stated that he could not elicit deep tendon reflexes, however, noted that exam was limited due to J.P. being shy and upset. *Id.* J.P. was started on a five-day course of IVIG. *Id.* at 163. The same day, J.P. was evaluated by Dr. Wayne Cornblath, a pediatric ophthalmologist. *Id.* at 156. Dr. Cornblath performed an exam of J.P. and stated that there were no signs of optic neuritis and recommended a repeat exam in the next few months. *Id.* at 157.

J.P. was discharged on June 13, 2011 after five days of IVIG treatment. Pet. Ex. 11 at 137. His discharge diagnosis was chronic inflammatory demyelinating polyneuropathy. *Id.* The admission history noted, "Parents report that between October 2010 and April 2011, they noticed a progressive increase in fatigue. They report that Jack was taking naps lasting 4-5 hours and he was tripping/falling more when walking. Prior to the onset of these symptoms, parents that that he had Otis media and a few weeks later received some vaccines (alternate vaccine schedule)." *Id.* at 138. J.P.'s physical exam upon discharged showed he was alert and appropriate for his age and walking around the room playing with toys. *Id.* No tripping was observed, but his knee reflexes were decreased. *Id.* Physical and occupational therapy had evaluated J.P. and cleared him for continuing services. *Id.* J.P. was scheduled for monthly IVIG treatment. *Id.* at 120.

On July 1, 2011, J.P. was readmitted to the hospital for IVIG treatment. Pet. Ex. 11 at 106. Upon admission, J.P. had been experiencing decreased energy and increased his need to sleep. *Id.* Deep tendon reflexes in the biceps and patellar were recorded as decreased. *Id.* at 121. J.P. was discharged on July 5, 2011 and future appointments for additional IVIG treatments were scheduled. *Id.* at 107. The discharge physical exam showed that J.P. was able to move all extremities spontaneously, his strength was 4/5, however, the attending was unable to elicit deep tendon reflexes and J.P. refused to walk. *Id.*

J.P. had a two-day IVIG treatment on July 27-28. Pet. Ex. 11 at 97. Prior to the next scheduled appointment in August, Ms. Pavan reported to Dr. Dowling that J.P. was experiencing more pain in his limbs, is tired and afraid to fall. *Id.* at 95. She reported that typically J.P. had 5-7 good days after the initial five-day treatment, but only two good days after the two-day IVIG in July. *Id.* Ms. Pavan explained to the nurse that J.P. was cold, fatigued, complained of leg and arm pain, was sleeping a lot and wanted to be carried everywhere. *Id.* Dr. Dowling recommend that the treatment schedule be maintained unless things become more severe. *Id.* at 96. J.P. received two days of IVIG treatment on August 24-25th. *Id.* at 90-94.

In September, Ms. Pavan reported to Dr. Dowling that J.P. was experiencing sensory overload with the start of school and his fear and anxiety has greatly increased. *Id.* at 87. Dr. Dowling consulted with Martha Carlson, a developmental neurologist, who recommended that J.P. begin occupational therapy. *Id.* at 88. J.P. had two days of IVIG on September 22-23rd. *Id.* at 81-85. He also received two days of IVIG treatment in October 2011. *Id.* at 75-78.

On November 4, 2011, J.P. was seen by Dr. Dowling for a follow-up appointment. Pet. Ex. 11 at 73. Dr. Dowling noted that J.P. has been very active since his last visit. *Id.* His parents did not report any weakness and J.P. was running, playing and engaging in sports with

his family. *Id.* Dr. Dowling recorded that J.P. had experienced some decreased urination, but his parents continued to push hydration and his urination returned to normal. *Id.* A physical exam showed mild dorsiflexion weakness on strength testing, but able to get onto his toes and his reflexes were reduced. *Id.* Dr. Dowling assessed J.P. with CIDP, who had an "excellent response to IVIG." Dr. Dowling stated that the physical exam showed "possible, mild dorsiflexion weakness, but he does not have foot drop." *Id.* It was recommended that J.P. continue on monthly two-day IVIG treatments. *Id.*

On December 9, 2011, J.P. had his four-year old well child appointment with Dr. Jennifer Becker. Pet. Ex. 8 at 88. Dr. Becker noted that J.P. was currently undergoing intermittent IVIG infusions at the University of Michigan to control his symptoms of fatigue and weakness due to his CIDP. *Id.* Additionally, she stated that he was only voiding once a day. *Id.* Dr. Becker wrote, "Disease is progressing. Started prednisone and Zantac. Neurologist plans for four weeks of prednisone 15 mg once a day for two weeks then two weeks of taper. Will increase IVIG to every two weeks….No longer involved with preschool and anxiety level has improved, though still with many fears." *Id.*

J.P. returned to Dr. Becker on April 25, 2012, where Ms. Pavan reported that J.P. was having sensitivity to sound and touch when his CIDP was "in flare," along with pain, weakness, lack of appetite and no urination sensation. Pet. Ex. 3 at 4.

J.P. had a follow-up appointment with Dr. Dowling on May 25, 2012. Pet. Ex. 9 at 23. Dr. Dowling recorded that after IVIG infusions J.P. is very active, however, towards the end of the month and for several days prior to his next infusion, J.P. prefers to stay in-doors and play sedentary games. *Id.* Dr. Dowling noted that after the past two IVIG treatments, J.P. experienced diffuse pruritus and irritability. *Id.* He stated that after the most recent treatment, J.P. experienced itching and irritability and Benadryl provided some relief. *Id.* A physical exam revealed that J.P. had weakness in his bilateral wrist extensors and ankle dorsiflexors. *Id.* at 24. Dr. Dowling recorded that he was unable to elicit deep tendon reflexes in some areas and J.P. had trace response in his bilateral biceps. *Id.* Dr. Dowling recommended that IVIG monthly infusions continue and occupational therapy and wrist splits, as he was concerned that J.P.'s hands and wrists seemed to have become weaker. *Id.*

In July 2012, J.P. was seen by Dr. Mark Hannibal at the Pediatric Genetics Clinic at the University of Michigan. Pet. Ex. 20 at 16. Dr. Hannibal reviewed J.P.'s medical history and noted that J.P. typically shows some improvement after IVIG treatment, but that his parents have noticed worsening symptoms, like J.P.'s inability to completely open his hands and thumb weakness. *Id.* Dr. Hannibal was unable to elicit reflexes at J.P.'s knees or ankles and observed that J.P. was unable to completely extend his fingers, stating, "there is some resistance felt to full extension, possibly as if there is some mild flexion contractures present." *Id.* at 19. Dr. Hannibal recommended, based on J.P.'s clinical course and mildly dysmorphic features on examination, a chromosomal microarray study to look for deletions or duplications that may be present throughout the genome. *Id.* at 18.

On October 15, 2012, J.P. had an appointment at the Neurology Clinic at Boston Children's Hospital. Pet. Ex. 15. J.P. was seen by neurologist, Dr. Peter Kang and Dr. Margaret

Moscato, a neuromuscular fellow. *Id.* at 5. They recounted his medical history and performed a physical exam. *Id.* at 4. They were unable to elicit reflexes at the patellae and ankles and observed bilateral reduced grip strength. *Id.* Additionally, they reviewed MRIs from July 2012 which showed extensive abnormal enhancement of ventral and dorsal roots of all visualized nerves in the cervical spine. *Id.* They stated, "J.P.'s electrodiagnostic studies were in keeping with the diagnosis of an acquired demyelinating polyneuropathy and the history of progression and exam are consistent with chronic inflammatory demyelinating polyneuropathy (CIDP). *Id.* They opined that given J.P.'s response to IVIG, it is less likely that he has an inherited neuropathy. *Id.* at 5. They recommended that J.P. maintain IVIG treatments and suggested that the treatments either occur every three weeks or he receive the full amount in one dose rather than a divided dose. *Id.* Additionally, they suggested that J.P. catch up on immunizations if there is an outbreak of the relevant disease in his area and noted that, "but for most routine immunizations, there is no convincing evidence that they trigger either the initial development of CIDP or a relapse of CIDP." *Id.*

Dr. Dowling modified J.P.'s IVIG treatment to every three weeks in May 2013. Pet. Ex. 11 at 499; Pet. Ex. 14 at 267. On July 1, 2013, J.P. was evaluated by neurologist Dr. Marc Patterson. Pet. Ex. 11 at 499. He stated that, "[J.P.] first began to experience symptoms that were likely attributable in retrospect to his CIDP in the latter half of 2010. However, it was not until March 2011 when he had obvious fatigue, increased clumsiness and falls, as well as increased appetite and thirst and emotional lability, that his weakness declared itself." *Id.* After a review of J.P.'s medical history and diagnostic tests, Dr. Patterson wrote, "J.P. has a history and laboratory investigations, including imaging, consistent with a diagnosis of CIDP. I suspect that he has third nerve[9] involvement which has alternated and which is consistent with his imaging studies; this can occur as an atypical manifestation of CIDP." *Id.* at 503. J.P. was also seen by Dr. Salman Kirmani, with the Medical Genetics Division at the Mayo Clinic. *Id.* at 490. She stated that J.P.'s mitochondrial workup showed that he had a variant of unclear significance in the ATP6 gene, but that it is "likely a benign polymorphism." *Id.* Dr. Kirmani also noted that the diagnosis of CIDP was initially questioned because of "some atypical clinical symptoms and lack of response to IVIG, but more recently he has shown a typical pattern and has responded very well to IVIG." *Id.*

Mr. Pavan testified that J.P. continues to be treated at the Mayo Clinic once a year for an evaluation of his CIDP. Tr. 76. He stated that Dr. Patterson explained that CIDP is "life-long disease" and that the "nerve damage that [J.P.] suffered to his extremities, primarily his hands, fingers, and to a certain extent his shoulders and legs, the damage is permanent." *Id.*

C. *Loving* Prong Three: Did J.P. experience a significant aggravation of his condition?

This section will address whether J.P.'s condition became markedly worse after the vaccinations at issue. To the extent to which the term "significant aggravation," as used in *Loving,* implies vaccine causation, that will not be addressed in this section. The role of the

[9] The "third nerve" is a reference to the oculomotor nerve, which controls all extrinsic eye muscles. *Dorland's* at 1258.

vaccinations, if any, in causing the change in J.P.'s condition will be addressed under *Loving* prongs five and six (*Althen* prongs two and three).

The petitioner conceded that J.P. had CIDP prior to receiving the vaccinations. Pet. Post-Hearing Brief at 4. Petitioner's expert, Dr. Sheldon Margulies, asserted that J.P.'s symptoms were "extremely mild, given that he had gone four months without any symptoms whatsoever, that in all likelihood it would have continued and may have even spontaneously resolved." Tr. 102. Additionally, J.P.'s treating physician at the Mayo Clinic, placed J.P.'s onset of CIDP to the fall of 2010, prior to him receiving the vaccinations. *See* Pet. Ex. 11 at 499.

Respondent's expert, Dr. Bingham, agreed that J.P. likely had CIDP before he received the vaccinations on January 28, 2011. Tr. 154. He also agreed that J.P.'s symptoms worsened after the January vaccines were administered, however, he stated that the vaccine did not cause the exacerbation of symptoms. Tr. 144, 154-55.

There is no doubt that J.P.'s condition became markedly worse in the time period following the varicella vaccination. But the relevant question of whether the vaccine was the cause of J.P.'s condition becoming worse is a question of vaccine-causation, which will be addressed below.

D. *Loving* Prong Four (*Althen* Prong One): Petitioner has not established a reliable and reputable theory of how the varicella vaccinations can cause the significant aggravation of CIDP.

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Knudsen* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added).

1. Petitioners' Experts' Opinions Regarding *Loving* Prong Four (*Althen* Prong Four): Dr. Margulies and Dr. Axelrod

Dr. Margulies explained that chronic inflammatory demyelinating polyneuropathy ("CIDP") is an inflammatory condition affecting the myelin of the peripheral nerves. Tr. 94. In his second report, he wrote, "The pathogenesis of CIDP is still unclear. Pathology demonstrates a demyelination of peripheral nerves with inflammation carried out by white blood cells and antibodies…The pathophysiology is felt to involve an autoimmune process as it resembles experimental autoimmune neuritis and it responds to immunosuppressive treatments. However,

neither the target antigen nor the cell population involved in the inflammatory attack has been identified, but it is likely that both B and T cells lymphocytes are involved." Pet. Ex. 27 at 3. He explained that the pathology of CIDP demonstrates that the myelin is affected with primarily cellular (T-cell) infiltration and inflammation and edema of the peripheral nerves. Tr. 112.

During the hearing, Dr. Margulies explained that the pathophysiology of CIDP is inflammatory, primarily T-cell. Tr. 94. He stated that it causes symptoms related to disturbances of the peripheral nerve, usually bilateral weakness or clumsiness. *Id.* at 95. He also stated that some may experience sensory symptoms and absent or depressed reflexes. *Id.* Dr. Margulies stated that CIDP is a chronic condition treated with immunosuppressive, including IVIG or plasmapheresis. *Id.* Dr. Margulies testified that there is probably some component of antibodies in the pathophysiology, as demonstrated by the disease responding to IVIG treatment. Tr. 95. However, he reiterated that CIDP is primarily a T-cell mediated disease. *Id.*

Dr. Margulies opined that the varicella vaccination was the cause of J.P.'s CIDP exacerbation. Tr. 96. He testified that the varicella virus is a neurotropic virus[10] that lives in the peripheral nerves. *Id.* He stated that because the varicella virus is a neurotropic virus "the fact that antibodies against the virus and antibodies against peripheral nerves should overlap does not surprise me." Tr. 109. Dr. Margulies largely deferred offering an opinion on the medical theory of causation to Dr. Axelrod. However, he testified that he came to the conclusion that the varicella vaccination exacerbated J.P.'s CIDP largely on the temporal relationship between the vaccine and when J.P.'s CIDP symptoms began to become more pronounced. Tr. 106-07. He stated, "…given that [J.P.] had gone four months without any symptoms whatsoever, that in all likelihood it would have continued and may have even spontaneously resolved." Tr. 102. Dr. Margulies stated, "I think given that he was doing so well for so long, and within a few weeks of a vaccination it became worse, in my opinion, there is a causal relationship between the two." Tr. 107.

Dr. Axelrod testified that CIDP is a demyelinating disorder involving the peripheral nerves. Tr. 206. He explained that like adults, children have myelin sheath that cover the peripheral nerves. Tr. 207. He stated that CIDP is a rare disorder, but the myelin sheath is affected in both adults and children. Tr. 208. Dr. Axelrod agreed with Dr. Margulies that varicella is a neurotropic virus and that the varicella vaccine, although attenuated, contains the same structure as the wild virus, otherwise it would not be effective as a vaccine. Tr. 212-13.

Dr. Axelrod opined the immune system's idiotype ("id")/anti-idiotype ("anti-id") response to the varicella vaccine interacts with the neuronal tissue to cause damage, including demyelinating disease. Pet. Ex. 24 at 2. He explained that glycoprotein B in the varicella vaccine associates with the myelin-associated glycoprotein ("MAG"), which is a structure that forms part of the myelin. *Id.* He stated that even after the vaccine product has been cleared through the body, through the mechanism of epitope spreading, "Damage to the nervous system through these homologous structures exposes other structures of the nervous tissues, to which the immune system can react and through which the immune system can continue to cause damage to the nervous system." *Id.*

[10] A neurotropic virus is one that has a predilection for and causes infection in nerve tissue. *Dorland's* at 1258.

In his second report, Dr. Axelrod clarified his theory and explained, "Damage to the myelin from an immune response can occur if the immune response (antibody, cellular or a combination of antibody and cellular) to a drug causes an immune response to the myelin basic peptides, myelin associated glycoprotein or any other structures that are components of the myelin sheath." Pet. Ex. 26 at 3. He observed that the Suenaga et al.,[11] article found that the varicella zoster vaccine contains glycoprotein B that associates with the myelin-associated glycoprotein. Pet. Ex. 26 at 3. The article describes MAG as "a cell-surface molecule that is preferentially expressed in neural tissues, especially on the myelin sheath and plays an important role in the regulation of axonal growth." Pet. Ex. 39 at 2; Pet. Ex. 24 at 2; Pet. Post-Hearing Brief at 16. Dr. Axelrod explained that because the glycoprotein B of the varicella zoster vaccine are structurally similar to MAG, they bind together and then incorporate the virus into the cells, causing infection. Tr. 222-23.

He opined that the development of anti-idiotype networks after vaccination can lead to damage of the myelin. Pet. Ex. 26 at 4. He wrote, "Antibodies to the attenuated live varicella zoster vaccine can result in the formation of immune responses to the structures upon the varicella zoster vaccine that can result in anti-idiotypic responses (antibody and cellular) that interacts with the structures to which the varicella zoster interacts, such as the myelin associated glycoprotein ("MAG") of the peripheral nerve myelin." *Id.* at 4; Tr. 214-22.

At the hearing, Dr. Axelrod explained that an immune response generally has both an idiotypic and an anti-idiotypic component. Tr. 225. The immune system network theory, developed by Jerne[12], "postulates that the immune system functions as a regulatory network, which is based on id/anti-interactions occurring between lymphocytes." Pet. Ex. 62 at 3. Idiotype are "the set of epitopes displayed by the variable regions of a set of antibody molecules." Pet. Ex. 36 at 9. The article by Hemp[13] explains Jerne's theory of the immune network theory:

> The specific binding sites of an antibody are located in the three-dimensional structure created by the variable regions of the antibody's two light and two heavy chains. This part of the antibody is referred to as the idiotypic determinant. This antigen-specific "idiotype" of each antibody determines its unique recognition of its antigen. However, the idiotype itself can serve as an antigen and be recognized by anti-idiotypic antibodies (anti-id), which can function as a critical part of a regulatory network….[T]his unique ability of antibodies both to recognize an antigen and be recognized by other antibodies as an antigen creates a balanced network that acts to regulate the humoral arm of the immune system. Anti-id are proposed to maintain homeostasis of the adaptive humoral

[11] Suenaga, T., et al., *Myelin-associated glycoprotein mediates membrane fusion and entry of neurotropic herpesviruses*, 107 PNAS 866-871 (2010). [Pet. Ex. 39].

[12] Jerne, N.K., *Towards a Network Theory of the Immune System,* 125 C Ann. Immunol (Insl. Pasleur), 373-389 (1974). [Pet. Ex. 36].

[13] Hemp, Christiane S., *Protective role of anti-idiotypic antibodies in autoimmunity-Lessons for type 1 diabetes,* 45(4) Autoimmunity, 320-331 (2012). [Resp. Ex. K]

immune responses by neutralizing idiotypic antibodies and regulating idiotypic antibody secretion.

Resp. Ex. K at 3.

Dr. Axelrod explained that an idiotypic antibody is an antibody that directly reacts to a foreign antigen. Tr. 219. The anti-idiotype is a cell or antibody which recognizes the idiotypes on antibodies. Pet Ex. 66 at 1[14]; Tr. 219. Dr. Axelrod stated that the "antibodies that are formed to the varicella zoster vaccine are structurally similar to the structure that they bind to on the myelin-associated glycoprotein and the anti-idiotypic response, which is structurally similar to the varicella zoster glycoprotein B, is capable of binding to the binding site on the myelin-associated glycoprotein." Tr. 236, 245. In other words, the anti-idiotype, which resembles the varicella vaccine antigen, attaches to the MAG and has the capacity to cause damage. Tr. 237-8. Petitioner's post-hearing brief explained, "The hyper-variable region of anti-idiotype antibodies and T-cell receptors to the glycoprotein B bind to the MAG…This interaction can result in damage to the myelin at the MAG binding sites for glycoprotein B on the MAG." Pet. Post-Hearing Brief at 16.

Dr. Axelrod explained that in a normal immune response, the idiotypic response is to protect, along with the anti-idiotypic response. Tr. 239-40. He testified that an idiotype in J.P.'s case would prevent the binding of glycoprotein to the MAG, protecting the cells from being infected. Tr. 239-240. In his second report, Dr. Axelrod wrote that the id/anti-idiotypic networks, "tend to limit immune response and return the immune response to a normal state." Pet. Ex. 26 at 4; Tr. 255. He testified that if anti-idiotypes do not fix complement,[15] then they would act primarily as regulatory cells, to dampen an immune response. Tr. 220, 240. However, in the context of CIDP, the anti-idiotype can bind to the MAG, which can fix complement and trigger an antibody dependent cellular cytotoxicity, which causes damage to the myelin. Tr. 226.

Dr. Axelrod also clarified that he is proposing a theory similar to molecular mimicry, because, "…the antibodies that are initially formed to the varicella virus are structurally similar to whatever the structure is that it binds to on the MAG. The anti-idiotypic response, which is structurally similar to the varicella zoster glycoprotein, is capable of binding to whatever that site is on the MAG." Tr. 245. Dr. Axelrod clarified that the Suenaga article shows that the varicella cells can bind to the MAG and "that is how he connected the idiotypic network to both the vaccine and the MAG place to attach." Tr. 233. He stated, "…because the structures are similar…one of the responses to the MAG receptor and the other to the glycoprotein B, which is what allows the anti-idiotypic response to possibly cause damage at the level of the myelin glycoprotein." Tr. 246.

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[14] William, W.M. & Isenberg, D.A., *Idiotypes and autologous anti-idiotypes in human autoimmune disease-Some theoretical and practice observations,* 17 Autoimmunity, 343 (1994). [Pet. Ex. 66].

[15] Fixing complement is the process in which IgM antibodies activate the complement system by binding several C1 proteins to the Fc region of an IgM antibody which has already bound itself to an antigen. The binding of two or more C1 molecules together can initiate a cascade of chemical reactions that produce a C3 convertase, thus activating a complement system reaction against a specific antigen.

Dr. Axelrod acknowledged that T-cells play an important role in CIDP in children. Tr. 247. He explained that T cells are part of the id/anti-id immune response. Tr. 235-37. During the hearing, he referenced the article by Mendlovic et al.,[16] to show that there is an interaction between T cells and the idiotypic network. Tr. 239. The study examined the capacity of T cells in patients with systemic lupus erythematosus ("SLE") to proliferate to a specific idiotype that was found to play a role in the pathogenesis of SLE and its anti-idiotypic monoclonal antibody. Pet. Ex. 42 at 5. The authors of the study compared the T cell proliferation in patients with SLE to healthy donors and first-degree relatives. *Id.* The study found that T cells in healthy patients proliferated to the SLE idiotypes at a higher rate than the SLE-diagnosed patients. *Id.* Put another way, "the percentage of SLE patients whose T cells proliferated to the id antibody was significantly lower than shown in healthy controls." *Id.* at 3. The authors hypothesized that the lower T cell proliferation in SLE patients to the id and anti-id antibodies could be because T cells are already being stimulated and their capacity to undergo further proliferation is significantly reduced. *Id.*

Post-hearing, petitioners filed an article by Seledtsov and Seledstova,[17] where the authors proposed that immune memory is based on id/anti-id interactions occurring between B-cell receptors ("BCRs") and T-cell receptors ("TCRs") following clearance of an antigen that elicited immune responses, to support Dr. Axelrod's theory. Pet. Post-Hearing Brief at 28; Pet. Ex. 62. The authors acknowledged that Jerne's original theory only focused on immunoglobulins "with little reference to T cells," but then proposed that TCRs can form three-dimensional antigenic images recognizable by BCRs, while some BCRs with certain Id/anti-Id specificities could directly activate specific T cells. Pet. Ex. 62 at 3. The authors explain:

> Direct BCR-TCR interactions leading to their cross-linking, together with co-stimulatory signals, could provide both growth and differentiation stimuli for individual B- and T-cells. As a result, new memory B- and T-cells, as well as new effector T-cells and plasma cells could be generated and further implicated in the Id/anti-id immunoregulation network.

Pet. Ex. 62 at 4.

The authors wrote, "TCR-specific antibodies present in high concentrations could also induce apoptosis in target T-cells or kill them via complement and/or FcR-dependent mechanisms. Consistent with this scenario, there are published data to suggest that anti-id TCR specific antibody responses can be induced by T cell vaccination in multiple sclerosis patients and that these responses are likely to contribute to the suppression of myelin basic protein-reactive T cells in vaccinated patients." *Id.*

According to petitioners, these articles demonstrate that the id/anti-Id theory involves both the production and proliferation of antibodies and T-cells. This is critical to petitioner's

[16] Mendlovic, S. et al., *Anti-DNA idiotype- and anti-idiotype-specific T cell response in patients with systemic lupus erythematosus and their first degree relatives,* 82 Clin. Exp. Immunol., 504-508 (1990). [Pet. Ex. 43].

[17] Seledtsov, V. and Seledtsova, G., *A Possible Role for Idiotype/anti-idiotype B-T cell Interactions In Maintaining Immune Memory*, 8 Front. Immunol., doi:10.3389/fimmu.2017.00409 (2017). [Pet.Ex. 62].

theory, as CIDP is known to be primarily T-cell mediated in children. Pet. Post-Hearing Brief at 28.

Dr. Axelrod testified that J.P.'s CIDP was exacerbated by a primary adaptive immune response, which caused the development of idiotypes, and then the development of anti-idiotypes which have the capacity to bind to some part of the myelin associated glycoprotein, which subsequently results in damage to the myelin. Tr. 274. He argued that the immune system likely cleared the vaccine within a short period of time, however, the anti-idiotypic response which is structurally similar to the varicella zoster remains, causing the exacerbation of the underlying condition. Tr. 276.

2. Respondent's Experts' Opinions Regarding *Loving* Prong Four (*Althen* Prong One): Dr. Bingham and Dr. MacGinnitie

Dr. Bingham agreed that J.P. likely had CIDP prior to the vaccinations he received on January 28, 2011 and that there was a worsening of symptoms related to his illness in February-March, however, he did not believe that the varicella vaccination worsened his CIDP. Resp. Ex. C at 4.

Dr. Bingham testified that CIDP is an autoimmune condition of the Schwann cells, which make up the myelin of the peripheral nerves. Tr. 140. He explained that it affects a person's movement and sensation. *Id.* Dr. Bingham testified, "[CIDP] has an interesting temporal course…the idea that it has its own ups and downs. [It's] hard to understand why it may remit, why the symptoms may get worse." *Id.* He explained that common symptoms are change in gait, numbness and pain sometimes. *Id.*

Dr. Bingham also testified that CIDP is not monophasic, unlike Guillain-Barre syndrome ("GBS"). Tr. 141-42. He explained that GBS has some similarities with CIDP, "…in the sense that GBS is also an inflammation of peripheral nerves and of Schwann cells and has a similar pathology." *Id.* at 141. But where GBS is monophasic, CIDP is different in its time and course. Tr. 142. He agreed that GBS and CIDP are on the same spectrum of diseases. Tr. 161. Dr. Bingham stated that CIDP can be considered a progressive condition. Tr. 143. He explained that a person can continue to get worse over a period of time, but it is unknown what causes the worsening of symptoms or the transition of CIDP to a more progressive illness. Tr. 145.

Dr. Bingham agreed that the varicella virus is a neurotropic virus which can affect central nervous system pathology, but not affect the peripheral nerve. Tr. 152. He testified that he has not found that the varicella vaccine can cause peripheral nerve disease. Tr. 153. He explained that the Schwann cells, which he described as the, "peripheral nervous system version of myelin," are attacked. Tr. 156. Dr. Bingham stated that CIDP presenting in children is extremely rare and acknowledged that epidemiologic studies would have difficulty picking up on pediatric CIDP. Tr. 194. He reiterated, that in his opinion, the varicella vaccination did not significantly aggravate J.P.'s CIDP. Tr. 143.

Dr. MacGinnitie opined that anti-idiotypes are antibodies that act to block the immune response or downregulate the immune system, so damage caused by anti-idiotypes would be

"very unlikely." Tr. 286-87. Dr. MacGinnitie acknowledged that some of the articles cited by Dr. Axelrod indicate that the id/anti-idiotype network could generate T-cells, but that these articles are focused on other illnesses outside of CIDP and instead, demonstrate that anti-Id antibodies are protective against autoimmune disease. Tr. 254-56.

Further, Dr. MacGinnitie stated that the idiotype/anti-idiotype antibody is irrelevant in this case, as CIDP is a T-cell mediated disease, particularly in children and the petitioner's theory focuses on B cells (antibodies). Tr. 296. Dr. MacGinnitie stressed that, "CIDP in children does not involve antibodies but rather is caused by auto-reactive T-cells, a distinct arm of the immune system." Tr. 294-96. Resp. Ex. A at 4. Respondent cited to the article by Karimi et al.,[18] which reviewed articles and reviews on CIDP, and explained the understood pathophysiology of CIDP as the following:

> The immune development starts with the loss of tolerance to self-antigens by mechanisms such as molecular imitation or cytokine stimulation and activating T-cell recognition of autoantigens, which encompasses both cellular and humoral response. CIDP appears to be mainly T-cell mediated with no reports of anti-bodies in childhood and a candidate autoantigen in only about 20% of adults.

Resp. Ex. G-2 at 2.

Dr. MacGinnitie also cited to an article by Matsumura et al.,[19] which studied biopsied sural nerves from nine patients diagnosed with CIDP. Resp. Ex. G-1 at 1. They analyzed the infiltrating cells in the peripheral nerves and found the presences of macrophage-associated demyelination and the presence of T cells in the endoneurium which correlated with activity of demyelination. *Id.* The study found the presence of CD4-positive cells and CD-8 positive cells, with the CD8-positive cells being more numerous than CD-4 positive cells. *Id.* at 6. The authors wrote, "B cells were not detectable in the endoneural[20] area of the nerves from any patients." *Id.* Immunoglobulin deposits (IgG, IgM, and IgA) were not identified on the myelin sheath of any of the patients. *Id.* at 6-7. Further, C1q could not be detected on the myelin or elsewhere in the endoneurium. *Id.* The authors stated, "Our data indicated that the mononuclear cell infiltrates were composed of macrophages and T lymphocytes of both helper/inducer and cytotoxic/suppressor phenotypes." *Id.* at 8. The authors concluded, "that CD8-positive cells may have a function to sustain the demyelinating activity of [CIDP]." *Id.* at 8.

Dr. MacGinnitie explained that the idiotype/anti-idiotype theory is completely theoretical. Resp. Ex. A at 6. He wrote that although, "anti-idiotype antibodies can be generated, there is no consistent, reliable medical evidence that they play a role in autoimmune diseases, such as CIDP." *Id.* at 6. Dr. MacGinnitie testified that it was his understanding that anti-idiotype antibodies actuall*y downregulate* the immune system. Tr. 307. Dr. MacGinnitie

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[18] Karimi, N., et al., *Chronic Inflammatory Demyelinating Polyneuropathy in Children: A Review of Clinical Characteristics and Recommendations for Treatment,* 3(2) J. Pediatr. Rev. e2269 (2015). [Resp. Ex. G- 2].

[19] Matsumuro, K. et al., *Chronic inflammatory demyelinating polyneuropathy: histological and immunopathological studies on biopsied sural nerves,* 127 J. of Neurol. Sci. 170-178 (1994). [Resp. Ex. G-1].

[20] Endoneural means within a nerve. *Dorland's* at 616.

explained that most of the articles petitioner filed in support of Dr. Axelrod's theory, demonstrate that anti-idiotype antibodies are protective against autoimmune disease. Tr. 286-87

He explained that Dr. Axelrod's id/anti-id theory is almost exclusively defined for antibodies, which would not necessarily fit the known pathophysiology of pediatric CIDP. Tr. 296-7. Dr. Axelrod acknowledged that while some of the literature he had cited indicated that there could be anti-idiotype T cells, he described the articles as "tangential to the illness we're describing today." Tr. 297.

Dr. MacGinnitie agreed that the Suenaga article demonstrates that the varicella zoster antigen can bind to the myelin associated glycoprotein. Tr. 328. He stated, however, that most patients that are infected with varicella (prior to the vaccine) can recover without any neurologic damage. *Id.*

Dr. MacGinnitie reiterated that the anti-idiotype antibodies function to downregulate the immune response. Tr. 330. Further, Dr. MacGinnitie stressed that pediatric CIDP is mediated by autoreactive T-cells and Dr. Axelrod's proposed mechanism, involving anti-idiotype antibodies does not fit the observed illness. Resp. Ex. E at 3.

3. Discussion and Conclusion Regarding *Loving* Prong Four (*Althen* Prong One):

Consistent with the description of CIDP by Dr. Margulies and Dr. Bingham, the Karimi et al. article, describes CIDP as "an acquired neuropathy, characterized by a chronic rapidly progressive, proximal and distal symmetric weakness, accompanied by hyporeflexia and sensory symptoms." Resp. Ex. G-2 at 2. CIDP often has similar presentations to other types of acute inflammatory demyelinating neuropathies, like Guillain-Barre syndrome ("GBS") also known as acute inflammatory demyelinating polyneuropathy ("AIDP"), except that in CIDP, the symptoms can advance for eight weeks or more and symptoms can come and go over time while GBS is monophasic and tends to develop to nadir within a few weeks and then recede. Tr. 142-3; Resp. Ex. G-2 at 2.

CIDP is much less common in children than in adults in whom it is also a rare disease. Resp. Ex. G-2 at 3. When it occurs in children, it generally appears between the ages of 5-18 and may cause long-lasting disability if not treated quickly. *Id.* Several children have more recurrent relapses than adults, but they mostly have more response to treatment. *Id.* Karimi et al., cited to a review article by Dr. Anne Connolly, which illustrated two clinical types of CIDP in children. Resp. Ex. G-2 at 3. The Connolly[21] article stated, "Some children demonstrate a progression to maximal weakness over the course of 3 months or less and tend to have a monophasic course. Recovery with long-term remission is common in this group. Other children progress over a longer period of time and are more likely to have a relapsing remitting course." Court Exhibit ("Ct. Ex.") 1 at 3.

[21] Anne M. Connolly, *Chronic Inflammatory Demyelinating Polyneuropathy in Childhood,* 24 Pediatr. Neurol. 177-183 (2001). [Court's Exhibit 1].

CIDP in children presents with symmetric, mostly motor neuropathy, evolving over several weeks or months. Resp. Ex. G-2 at 3. In children, compared to adults, CIDP may appear more sub-acutely and with numerous relapses. *Id.* at 5. The article by Vanasse et al.,[22] describes the course of CIDP in children as being characterized, "by remissions and relapses in 60-80% of affected patients." Pet. Ex. 75 at 2.

In his post-hearing brief, petitioner attempted to clarify Dr. Axelrod's theory, stating, "Dr. Axelrod has proposed that B-cells, in conjunction with T-cells and antibodies are involved in the development of J.P.'s CIDP through the idiotype/anti-idiotype mechanism." Pet. Post-Hearing Brief at 18. Respondent argued that CIDP in children is primarily mediated by auto-reactive T cells, making Dr. Axelrod's theory of anti-idiotype antibodies irrelevant to the development or exacerbation of CIDP. Resp. Post-Hearing Brief at 18-19.

Petitioner acknowledged that CIDP in children is primarily T-cell mediated but argued that B-cells are also involved in the immunopathogenesis of CIDP. Pet. Reply at 5. Petitioners stated, "Even though CIDP in children may be primarily T-cell mediated, both antibodies and cells with anti-idiotypic activity can cause damage to the peripheral myelin, such as in the case of CIDP." Pet. Reply at 6. Petitioner argued that because there is molecular mimicry between the varicella zoster vaccine glycoprotein B and the anti-idiotype antibody response, both of which share the structures to bind to Myelin Associated Glycoprotein ("MAG"), this binding of the anti-idiotypic antibody or T-cell receptor to the MAG would cause damage to the myelin. *Id.* at 9.

The Vanasse et al. article, filed by petitioner, suggests that "both cellular (T cells) and humoral immune factors (B cells) are implicated in the pathogenesis of [CIDP], but explains that T-cells appear to be the primary mechanism:

> Inflammatory infiltrates consisting primarily of macrophages and T cells suggest a T cell-mediated delayed hypersensitivity reaction. Also, markers of T cell activation such as interleukin-2 (IL-2) and tumor necrosis factor alpha (TNF-α) have been observed in the serum of patients [with CIDP]. The observation of increased levels of soluble adhesion molecules, chemokines and matrix metalloproteinases (MMPs) in the serum/and or CSF of patients may also be an indicator of the active T cell migration across the blood-nerve barrier, which is necessary for the T cells to infiltrate the nerves.

Id. at 2.

The same article also explained that other studies demonstrated a role for B-cells in the pathogenesis of CIDP in "only a proportion of patients." Vanasse referenced different studies that showed anti-myelin IgG targeted the myelin protein P0. *Id.* The Anti-P0 IgG antibodies could be detected in 6 out of 21 patients with CIDP. *Id.* Vanasse et al., cited to other studies where antibodies directed against the gangliosides and other glycolipids such as GM1 and LM1,

[22] Vanasse, M., et al., *Chapter 121: Chronic inflammatory demyelinating polyneuropathy,* Handbook of Clinical Neruol. Vol. 112 (3rd Series) (2013). [Pet. Ex. 75].

which are widely distributed within the nervous system, could be detected in up to 15% of patients with CIDP. *Id.*

The Karimi et al article., explains that, "Both the cellular and humoral components of the immune system seem to be involved in the pathogenesis of CIPD." Resp. Ex. G-2 at 3. However, it explains, "CIDP appears to be mainly T cell-mediated with no reports of antibodies in childhood and a candidate autoantigen (P0 myelin protein) in only 20% of adults." *Id.* The article states:

> In adults with CIDP, both monoclonal and polyclonal autoantibodies (ganglioside and sulfatide auto antibodies, acidic glycolipids, proliferating non-myelinating human, Schwann cells, and b-tublin autoantibodies) have been revealed in subgroups of patients, *but these have not been detected in children* and thus have not usually been tested for.

Id. (emphasis added).

The Dalakas[23] article, also filed by respondent, explains that no pathogenic autoantibody or single triggering antigen has been identified in CIDP. Resp. Ex. I-2 at 5. The article also describes the demyelinating process in CIDP as being primarily a T cell process:

> When autoimmunity develops, the putative antigen is processed by antigen-presenting cells, such as macrophages, which via costimulatory molecules, cause clonal expansion of T cells, release of cytokines and chemokines, upregulation of adhesion molecules on endothelial cells, and transmigration of T cells across the blood-nerve barrier to the myelin sheath. These T cells may have a role in local immunoregulation or cytotoxicity. Resident macrophages, activated by cytokines, invade the myelin fiber via their Fc receptors, leading to macrophage-mediated demyelination.

Id. at 6.

However, as petitioner observed, the Dalakas article acknowledges the possible role of B cells in CIDP. Resp. Ex. I-2 at 5; Pet. Post-Hearing Brief at 20. Specifically, the Dalakas article states, "Other evidence also supports a link between humoral factors and CIDP pathogenesis. In particular, complement-fixing IgG and IgM deposits are found on the myelin sheath of nerves in patients with CIDP, suggesting that pathogenic antibodies may have a role in recognizing myelin antigens." Resp. Ex. I, Tab 2 at 5. The article explains, "Consistent with this hypothesis, antibodies to various glycolipids or to myelin protein P0 are more frequently detected in the serum of patients with CIDP than in controls." *Id.* at 5.

Although petitioner is correct in noting that the three articles discussed above identify a possible role of antibodies in the pathogenesis of CIDP, they do not support Dr. Axelrod's theory that the anti-idiotype would associate with the myelin-associated glycoprotein ("MAG") to cause CIDP. Specifically, Dr. Axelrod opined that the varicella vaccine contains glycoprotein B that associates with the myelin associated glycoprotein expressed on neural tissues. This association

[23] Dalakas, M., *Advances in the diagnosis, pathogenesis and treatment of CIDP*, 7 Nat. Rev. Neurol. 5070517 (2011). [Resp. Ex. I, Tab 2].

between the glycoprotein B and MAG then causes infection of the cells, leading to damage to the gangliosides. *Id*. However, both the Vanasse and Dalakas articles identify the myelin protein P0 as a more likely target for antibodies in CIDP. Further, the articles are also consistent in endorsing a T-cell mediated process in CIDP in children.

The other problem with Dr. Axelrod's theory is that it does not adequately explain how the id/anti-idiotype mechanism generates an immune response that could lead to the autoimmune disorder, CIDP. Dr. MacGinnitie's main criticism of Dr. Axelrod's theory is that the role of the anti-idiotype antibody is actually *protective* against autoimmune disorders, thus such a response would not generate the T-cell activity that is discussed in the literature as the pathogenesis of CIDP. *See* Resp. Ex. A at 6.

Key to understanding Dr. Axelrod's theory is the concept of molecular mimicry. On questioning by the Court, Dr. Axelrod endorsed the concept of molecular mimicry as the mechanism by which the anti-idiotypes bind to and damage the myelin on the peripheral nerves. He explained:

> This is sort of a molecular mimicry theory…because the antibody—I'm speaking of the antibody, but it could be the cells as well—that are initially formed to the varicella virus, are structurally similar to whatever the structure is that it binds to, on the myelin-associated glycoprotein, and the anti-idiotypic response, which is structurally similar to the varicella zoster glycoprotein, which is capable of binding to whatever that site is on the myelin-associated glycoprotein. So, to some extent, it's molecular mimicry. I mean, based on molecular mimicry. That's right.

Tr. 244-5.

However, as Dr. McGinnitie explained and the literature appears to support, the role of the anti-idiotype is to down regulate the immune response not to enhance it. Thus, the anti-idiotype, even if molecular mimicry was demonstrated would not appear to be a component of the immune system that would attack the nerve cells but rather would play a role in down regulating the immune response and potentially be protective against autoantibodies that would attack neural the myelin.

Most of the articles submitted by petitioner prior to trial relating to the idiotype/anti-idiotype immune theory were several decades old and the articles petitioner filed post-hearing attempted to refute Dr. MacGinnitie's assertions that Dr. Axelrod's id/anti-idiotype antibody theory was irrelevant to a T-cell mediated disease, like CIDP and that the idiotype/anti-idiotype network is on the "fringe of current immunology." Tr. 329.

In his post-hearing brief petitioner, noted that the Seledtsov and Seledtsova article was written in April 2017 and stated, "This article further refutes respondent's proposition that idiotypic networks are somehow not mainstream, or is a speculative theory." Pet. Post-Hearing Brief at 19, 28. However, the Seledtsov and Seledstova article is about a possible role for the idiotype/anti-idiotype network in maintaining immune memory. Pet. Ex. 62. The authors state that the id/anti-id interactions can induce T-cell responses. *Id.* at 3. The authors wrote, "We

speculate that plasticity of BCR and TCR repertoires and structural similarities of target antigen receptors in B and T cell compartments are important prerequisites that can facilitate contact and communication between B-and T-cells through direct id/anti-Id BCR-TCR interactions." *Id.* at 2. Direct BCR-to-TCR interactions lead to growth and differentiation of memory B and T cells. *Subsequently, plasma cells originated from memory B cells produce IgG antibodies, which shield TCRs, thereby inhibiting not only growth and differentiation activity of memory B and T cells, but also the functionality of effector T cells, including helper T cells.* *Id.* at 3 (emphasis added). This mechanism described could downregulate memory cell expansion. *Id.* at 4. The authors theorize that, "potentially auto-aggressive lymphocytes are initially depleted or suppressed by immunoregulatory mechanisms. Consequently, under normal conditions, a self-reactive lymphocyte clone is unlikely to achieve the quantitative threshold level necessary to generate functionally significant Id/anti-Id T-B cell interactions." *Id.* at 4. Thus, while this article suggests that the idiotype/anti-idiotype mechanism remains the subject of some discussion in immunology, it appears to suggest a role in suppressing immune activity rather than being a source of autoimmunity, as observed by Dr. MacGinnitie.

Petitioners also referenced the article by Raychaudhuri et al.[24] article to demonstrate the role of T-cells in id/anti-idiotype immune response. Pet. Ex. 63 at 1. The authors of the Raychaudhuri article used two anti-idiotype antibodies against an antitumor antibody that recognized a tumor-associated antigen to "study the protective ability against tumor growth of two anti-idiotype antibodies made against antitumor antibody." *Id.* at 2. The authors found that, "one of the anti-idiotype antibodies can induce protective immunity," and is "effective in controlling tumor progression." *Id.* at 4-5. The authors stated, "The demonstration of the presence of both regulatory and effector T cells in anti-idiotype immunized mice agrees with the concept that effector and regulatory lymphocytes recognize different or overlapping determinants or antigen." *Id.* at 5. They concluded, "The finding that two anti-idiotype antibodies induce similar B cell idiotype profiles and have different effects on tumor growth in vivo emphasize the role of regulatory network interaction in response to anti-idiotype antigens." *Id.* This article focused on the treatment of cancer and did not discuss the promulgation of autoimmune disease.

Post-hearing, respondent filed the Hempe article to demonstrate that anti-idiotype antibodies are protective against autoimmune diseases. Resp. Ex. K; Resp. Post-Hearing at 14-15. The Hemp article explained the idiotype/anti-idiotype reaction in patients that received the tetanus vaccine:

> The initial injection of vaccine antigen triggered an increase in tetanus toxoid antibody titer. This increase of idiotypic antibody titer was followed by an increase in anti-Id and subsequent decrease in the titer of free tetanus toxoid antibody. This apparent decrease of tetanus toxoid antibody titer was caused by competition of anti-Id for the tetanus toxoid binding site on the idiotypic antibody. There is also a real decrease of tetanus toxoid antibody, which was caused by the anti-Id induced inhibition of secretion of the idiotypic antibody.

[24] Raychaudhuri, S., et al., *Analysis of the Tumor-Related Network Response Induced by the Tumor and by Internal Image Antigens (Ab2b)*, 139 The J. of Immunol. 271-278 (1987). [Pet. Ex. 63].

Resp. Ex. K at 5.

This article demonstrates that the anti-id can actually down-regulate the secretion of the idiotypic antibody. *Id.* The Hemp article continued, stating that the protective role of anti-Id against autoimmune diseases is based on two major observations from studies of auto-immune diseases. *Id.* at 6. The first observation is that anti-Id specific to autoantibodies are present in patients during remission and/or in healthy individuals, and the second observation is that anti-Id are absent during periods of active disease. *Id.*

Even accepting that the id/anti-idiotype immune response includes both cellular and humoral responses, the articles discussed above demonstrate that this mechanism is more likely to be protective against autoimmune conditions. For example, the Seledtsov article specifically suggests that IgG antibodies that are produced from the original id/anti-idiotype response may restrict the functionality of T-cells. The Hemp article also demonstrates that anti-idiotypic antibodies inhibits the functionality of autoantibodies that are acting as autoantigen presenting cells, therefore limiting the proliferation of autoantibodies. These articles tend to refute Dr. Axelrod's theory that the anti-idiotype antibody can cause damage to peripheral nerve myelin. *See* Pet. Reply at 6. Instead, they demonstrate that anti-idiotype antibodies appear to target potentially autoreactive cells that are present in autoimmune conditions and downregulate them.

The petitioner has failed to provide preponderant evidence that the id/anti-id theory, facilitated by molecular mimicry, presented by Dr. Axelrod, can cause an exacerbation of CIDP. The literature presented by both parties suggests that the role of anti-idiotypes appears to be to suppress or regulate an immune response, not to stimulate one. The role of anti-idiotypes is not in attacking antigens, whether self or foreign, but to reduce the number of cytotoxic T-cells or B-cells and thereby return the system to homeostasis after the immune system has completed its response to a foreign antigen, such as the varicella virus or its vaccine counterpart. Additionally, even though petitioner recognized that the literature presented suggested a prominent role of T-cells in pediatric CIDP, Dr. Axelrod did not adequately address how the anti-idiotype response would cause T cells to attack the peripheral nerve myelin.

Therefore, I find that petitioner has not established *Loving* prong four (*Althen* prong one).

E. *Loving* Prong Five (*Althen* Prong Two): Petitioners have not established a logical sequence of cause and effect or a temporal association between the varicella vaccination and the significant aggravation of J.P.'s CIDP.

Loving prong five requires a petitioner to show a "logical sequence of cause and effect, showing that the vaccination was the reason for the significant aggravation. *Loving,* 86 Fed. Cl. at 144; see also *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Loving* at 144.*; Broekelschen,* 618 F. 3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Human Servs.*, 9556 F.2d 1144, 1148 (Fed. Cir. 1992).

This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148.

1. Petitioners' Experts' Opinions Regarding *Loving* Prong Five (*Althen* Prong Two)

Dr. Margulies explained that some symptoms of CIDP include motor disturbances, weakness and sensory disturbances. Tr. 97. Additionally, there may be bladder or bowel and autonomic disturbances. *Id.* Dr. Margulies testified that based on the medical record and the testimony from Mr. and Ms. Pavan, it appears that J.P. was experiencing fatigue, which dated back to 2010, pre-dating the vaccinations at issue. Tr. 98-9. He testified that J.P.'s sole symptom of CIDP in 2010 was fatigue, but in mid-February, J.P. developed upper extremity changes, clumsiness with handling utensils and he was getting reluctant to walk. Tr. 106.

In his second report, Dr. Margulies stated that the absence of any mention of fatigue between October 25, 2010 and January 28, 2011 suggested that "[J.P.] was clearly improving, even fully recovering, particularly as it is known that the evolution of CIDP is more favorable in children than adults, with an 80-100% response rate to standard treatments." Pet. Ex. 27 at 3. Dr. Margulies continued, stating that, "The fact that [J.P.] dramatically deteriorated within weeks of his January 28, 2011 vaccination strongly suggests that absent the vaccination, he would have continued to do well." *Id.* at 3.

Dr. Margulies stated that prior to receiving the vaccination, J.P. was asymptomatic for at least four months. Tr. 106. He testified that J.P. was doing well and within a few weeks of the vaccination, he experienced an exacerbation of the CIDP. Tr. 107. He stated that in middle of February, J.P. "seemed to have a qualitative change in his activities and, behavior, in that he was developing more symptoms." Tr. 99. He stated, "…there was something more than just fatigue." *Id.* Additionally, J.P. was getting reluctant to walk. *Id.* Dr. Margulies explained that he would have expected J.P.'s trajectory of the disease to remain asymptomatic. *Id.* During cross-examination, Dr. Margulies acknowledged that J.P.'s medical records indicated that he kept having recurrences, but he also noted that between October 2010 and February 2011, J.P. went through a longer period of time without any symptoms of the CIDP. Tr. 122. He testified that it could have been possible that J.P. would have a recurrence of symptoms absent the vaccinations and that his disease was relatively mild prior to the vaccinations. *Id.* He stated that it was significant that J.P. gets the vaccinations and "a couple of weeks later, [J.P.] is on a steady, progressive, downhill deterioration." Tr. 122.

Dr. Margulies testified that varicella vaccine exacerbated J.P.'s CIDP. Tr. 96. He stated that varicella is a neurotropic virus and "it lives in the peripheral nerves." *Id.* When asked about the relationship between the varicella virus and the peripheral nervous system, Dr. Margulies reiterated that the varicella vaccine affects the peripheral nerves and "the fact that antibodies against the virus and antibodies against the peripheral nerves should overlap does not surprise me." Tr. 109. However, later Dr. Margulies acknowledged that the pathology of CIDP, "is it affects the myelin with primarily cellular infiltration and inflammation and edema of the peripheral nerves." Tr. 112.

Dr. Axelrod stated that J.P.'s response to the varicella vaccine is a considered a primary immune response, because he had never been exposed to varicella or received prior varicella vaccinations. Tr. 263; Pet. Post-Hearing Brief at 22. He explained that the live attenuated varicella vaccine contains altered structures to which an immune response develops that prevents the attachment of the varicella zoster virus to the structures at the nerve for fusion and intracellular replication. Pet. Ex. 26 at 3. He stated that the varicella zoster virus contains glycoprotein B which binds with the myelin-associated glycoprotein (MAG) and causes damage to the structures of the myelin. *Id.* The anti-idiotype, which is structurally similar to the varicella zoster glycoprotein B, is capable of binding to the myelin-associated glycoprotein and can cause damage, which would exacerbate the demyelinating condition. Tr 242-5; Pet. Post-Hearing Brief at 21-22. Dr. Axelrod relied upon the Suenaga article to support his theory that molecular mimicry between glycoprotein B in the varicella virus and the MAG, which "exposes other structures of the nervous system tissues, to which the immune system can react." Pet. Post-Hearing Brief at 22. This, in his opinion was the cause of the exacerbation of J.P.'s CIDP. *Id.*

2. Respondent's Experts' Opinions Regarding *Loving* Prong Five (*Althen* prong two)

Dr. Bingham agreed that J.P.'s CIDP began prior to the vaccines administered on January 28, 2011. Tr. 145. He stated that, based on the medical record and testimony by J.P's parents that it appeared that J.P had a "more up-and-down course, or a more relapsing and remitting course, and then [the CIDP] became more progressive." Tr. 144. He testified that what causes worsening or a transition to a more progressive course is unknown. Tr. 145.

Dr. Bingham cited to the Vedeler et al.[25] paper, which states, "The time course of CIDP is variable. Most often the disease is chronic progressive, especially in older patients. A relapsing course can be seen especially in younger patients." Resp. Ex. I-4 at 2. Essentially, Dr. Bingham testified that J.P.'s clinical course was consistent with some pediatric CIDP cases described in the literature. He testified that the vaccination that J.P. received in January 2011 did not play a role in the change in his symptom course subsequent to the vaccination. Tr. 145. While he agreed that the severity of J.P.'s CIDP is rare, the medical literature does provide support for such cases. Tr. 190-91.

Dr. MacGinnitie testified that J.P.'s pre-existing CIDP is an autoimmune disease in which the immune system attacks the myelin and that if there was a reaction to the varicella vaccines, it would be a secondary response, which would be a much more vigorous and more rapid response than seen in a primary response. Tr. 285, 291. He explained that prior to receiving the vaccines in January, J.P. had already developed a primary immune response against the myelin. Tr. 290. He testified that because of J.P.'s pre-existing condition, he still had memory B and T cells, even if J.P.'s symptoms had resolved. Tr. 330. If the vaccine had acted as trigger to the existing T and B cells specific to the myelin, then one would expect a faster response. Tr. 290-91.

[25] Vedeler, CA, et al., *Chronic inflammatory demyelinating polyneuropathy (CIDP)*, 127 (Suppl. 196) Acta Neurol. Scand., 48-51 (2013). [Resp. Ex. I-4].

Dr. MacGinnitie agreed that J.P.'s immune response to the varicella vaccine would be considered a primary response to the vaccine, but because his understanding of Dr. Axelrod's theory "was that the glycoprotein on varicella reacts with glycoprotein on myelin and since CIDP is a demyelinating disease, there's already existing cells ready to attack the myelin, and that is why he thought this would be a secondary response and therefore occur much more rapidly." Tr. 326.

Dr. MacGinnitie testified that it was his understanding that CIDP is remitting and relapsing condition and that the records demonstrate that J.P. had previous episodes of fatigue associated with his CIDP and then episodes of improvement. Tr. 331. He stated that, "[J.P.] already had a demyelinating immune response and that would not have gone away in four months." *Id.* Therefore, it was unlikely that the primary immune response to the varicella vaccination could cause an exacerbation of J.P.'s CIDP.

3. Discussion and Conclusion Regarding *Loving* Prong Five (*Althen* Prong Two)

CIDP occurring in children is less common than in adults and is in fact quite rare. Resp. Ex. G-2 at 3. Clinical manifestations can include, gait disturbances, falling and fatigue. *Id.* at 3; Ct. Ex. 1 at 1. The Karimi article explained that cranial nerve dysfunction has also been reported. Resp. Ex G-2 at 3. The authors described various oculomotor symptoms that some children with CIDP have experienced, including ptosis. *Id.* at 3. The article states, "Exceptionally, facial weakness was found in 20-33% of children." *Id.*

The Karimi paper also noted that, "Children who initially progressed to their nadir of weakness over one to three months had a tendency to a monophasic course and were more likely to recover entirely. Children who initially progressed over more than three months had a tendency to a more chronic, relapsing-remitting course." Resp. Ex. G-2 at 5. The Connolly article, cited by Karimi et al., explains two major clinical types of CIDP in children:

> The first was a monophasic disorder getting maximal weakness over three months and the second was a disorder that progressed even more slowly, but predisposed to having a relapsing and remitting course.

Resp. Ex. G-2 at 2.

The Connolly article states, "Some children demonstrate a progression to maximal weakness over the course of 3 months or less and tend to have a monophasic course. Recovery with long-term remission is common in this group. Other children progress over a longer period of time and are more likely to have a relapsing remitting course." Ct. Ex. 1 at 3. Further, Connolly noted that another study found that the duration of the initial onset of the weakness correlated inversely with disability. Ct. Ex. 1 at 4. Specifically, "Children who initially progressed over more than 3 months tended to have a more chronic relapsing, remitting course." *Id.* at 4. Both the Karimi and Connolly articles explain that first-line treatments for childhood CIDP are IVIG, corticosteroids and plasmapheresis. Resp. Ex. G-2 at 5; Ct. Ex. 1 at 4.

Prior to his diagnosis, J.P. was seen by pediatric neurologist, Dr. James Dowling, on May 13, 2011 for further evaluation for fatigue and ptosis. Pet. Ex. 11 at 184. Dr. Dowling recorded J.P.'s history and wrote, "[J.P.'s] parents first became concerned last fall. He was demonstrating excessive fatigue. This became slowly progressive from September onward. It is most notable now for the fact that he is wanting to run around less and he is less interested in doing active endeavors. They have also noticed that he has become more clumsy." *Id.* After a physical exam, Dr. Dowling recorded his impression and wrote, "In summary, [J.P.] is a 3-year-old with progressive fatigue and fluctuating asymmetric ptosis. The most likely diagnosis in this case would be myasthenia gravis. Other considerations would be another autoimmune neurologic condition like CIDP…" *Id.* at 185. J.P. returned to see Dr. Dowling on June 3, 2011 for a re-evaluation of his condition. *Id.* at 180. Dr. Dowling wrote that, "[J.P.] has had both good and bad days in terms of gross motor skills. There are times when he has been either unable to unwilling to go down the stairs as other days when he is perfectly fine. Other neurologic symptoms recently have included frequent mood swings and also diminished appetite." *Id.* Dr. Dowling wrote, "Of note, [J.P.]'s symptoms first started in September. *Id.* Dr. Dowling considered J.P.'s medical history and noted that J.P. was scheduled for an EMG later that day. He wrote, "Other considerations given his significant fluctuations would be a metabolic condition or a neuropathy like CIDP." *Id.* After the EMG study was performed on June 3, 2011, the diagnosis of CIDP was confirmed. *Id.* at 178.

On June 8, 2011, J.P. was admitted to the University of Michigan Hospital for treatment of CIDP. Pet. Ex. 11 at 171. Dr. Dowling examined J.P. upon admission and recorded J.P.'s history of present illness and wrote, "Parents report that between October of 2010 and April 2011, they noticed a progressive increase in fatigue." *Id.* He also recorded, "[J.P.'s] symptoms wax and wane." *Id.*

On July 1, 2013, J.P. was evaluated by a pediatric neurologist, Dr. Patterson, at the Mayo Clinic. Pet. Ex. 11 at 497. Dr. Patterson noted that J.P. first began to experience symptoms "were likely attributable in retrospect to his CIDP, in the latter half of 2010." *Id.* at 499. He noted that it was not until March 2011 when J.P. had obvious fatigue, increased clumsiness and falls, as well as increased appetite and thirst and emotional lability, that J.P.'s weakness declared itself. *Id.* Dr. Patterson also reviewed J.P.'s past medical records, including his EMG/NCV studies from 2011 and 2012, as well as J.P.'s brain and cervical spine MRIs. *Id.* at 501. Dr. Patterson concluded, "[J.P.] has history and laboratory investigations, including imaging, consistent with a diagnosis of CIDP." Dr. Patterson referred J.P. to Dr. Salam Kirmani, for a genetic assessment. *Id* at 497. Dr. Kirmani, assisted by Dr. Kochlar, noted, "Briefly, Jack has been diagnosed with CIDP. Initially, the diagnosis was questioned because of some atypical clinical symptoms and lack of response to IVIG, but more recently responded very well to IVIG." *Id.* Eventually, J.P. began receiving IVIG treatments more frequently. Tr. 29. He continues to receive occupational and physical therapy. Tr. 36. In 2018, J.P.'s treating physicians at the Mayo Clinic explained that J.P. has a severe case of CIDP, and it will be a life-long condition. Tr. 76.

The medical records are clear in this case that the onset of J.P.'s symptoms were slow with relapses. The onset of his CIDP appears to be consistent with the medical literature submitted in this case, that a cohort of children may have develop symptoms over a longer-

period of time and that this cohort is more likely to have a relapsing and remitting course. Further, none of J.P.'s treating physicians appeared to associate his CIDP or progressive symptoms to the vaccination. While J.P.'s condition did change after he received the varicella vaccine, the change in his condition appears to be consistent with a course of the disease which has been well described in the literature as noted above. Petitioner's argument that the varicella vaccination induces an anti-idiotype response that associates with the myelin-associated glycoprotein, persists after the vaccine has been cleared and continued to cause further and persistent damage is also unpersuasive.

More importantly, however, as discussed above, the petitioner failed to demonstrate a persuasive medical theory as to how the vaccine could cause an aggravation of CIDP. Accordingly, I cannot conclude that there was logical cause and effect relationship between the vaccine and the worsening of his condition.

As such, petitioners have failed to provide preponderant evidence that a logical sequence of cause and effect that the varicella vaccine J.P. received caused an exacerbation of his CIDP.

F. *Loving* Prong Six (*Althen* Prong Three): Petitioner has not established an acceptable temporal association between the varicella vaccine and the exacerbation of J.P.'s CIDP.

The final *Loving* prong requires petitioner to establish a "proximate temporal relationship" between the significant aggravation of their condition and the received vaccine. *Loving* at 144; *see also Althen*, 418 F.3d at 1281. That term has equated to the phrase, "medically-acceptable temporal relationship." *Althen* at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.,* 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

1. Petitioner's Experts' Opinion Regarding *Loving* Prong Six (*Althen* Prong Three)

J.P. received the varicella vaccination on January 28, 2011. Pet. Ex. 1. Ms. Pavan testified that in mid-February 2011, J.P. went from being fatigued and tired to completely wiped out to the point where she and her husband would have to carry him around. Tr. 10. She described his behavior from February 2011 to March 2011, stating, "It just slowly and progressively, [J.P.'s] emotional being, his physical being, meaning fatigue and being able to engage in the activities that we routinely did, decreased." Tr. 12. As the medical records show, J.P. was diagnosed with CIDP on June 3, 2011. Pet. Ex. 11 at 157, 180.

Dr. Margulies stated that three weeks following the administration of the varicella vaccine, J.P. suffered another episode of fatigue. Pet. Ex. 23 at 2. He stated that five weeks after the vaccination, J.P. suffered the left eye droop, which was his first objective sign of CIDP. *Id.* He opined, "Given the close timing of the January 28, 2011 varicella vaccination and the onset of fatigue followed shortly thereafter by clear evidence of CIDP….it is my opinion that the

varicella vaccination…initiated the immune reaction that included J.P.'s CIDP." *Id.* In his second report, Dr. Margulies clarified that J.P.'s parents reported excessive sleepiness and fatigue for several weeks prior to the March 4, 2011 appointment, "placing his symptoms within the time period expected for a post-vaccination illness." Pet. Ex. 27 at 3. During the hearing, Dr. Margulies testified that J.P. received the vaccination on January 28, 2011 and three weeks later, [J.P.'s] parents noticed changes mid-February. Tr 110. He stated that three weeks was within the medical standard of temporal relationship between a vaccination and an exacerbation or flare-up of symptoms. *Id.*

Dr. Axelrod opined that a recurrence of J.P.'s demyelinating condition within 21 days following the administration of the varicella vaccine was "consistent with a primary immune response." Pet. Ex. 24 at 2. He stated that, "J.P. received the varicella…vaccine and 21 days later he developed fatigue, followed by neurologic findings. This time interval is consistent with primary adaptive immune responses to the vaccine." *Id.* at 2-3. At the hearing he testified that he would expect the time frame for a primary adaptive immune response to the varicella zoster vaccine within 10 to 25 days, "but at least [within] a week for sure." Tr. 248. He stated that if J.P. presented with bouts of falling within 14 days or 20 days of the vaccination, that would also fit the medically appropriate time frame. Tr 248-9.

2. Respondent's Experts Opinions' Regarding *Loving* Prong Six (*Althen* prong three)

Dr. Bingham acknowledged that J.P.'s CIDP became worse after he received the January 28, 2011 vaccination, but testified that the vaccination did not cause a change in J.P.'s symptom course. Tr. 146; 154. Dr. Bingham also agreed that J.P. evidenced fatigue three weeks after he received the varicella vaccine and that if the vaccine was the cause of an immune reaction, three weeks would be a medically appropriate timeframe. Tr. 192. However, he stated that linking a vaccination to CIDP really depends on the theory of what is known to occur in the body and whether the vaccination could cause the rare condition of pediatric CIDP. Tr 194-5.

Dr. MacGinnitie explained that Dr. Axelrod's proposed timeframe of 10-25 days after exposure is inconsistent with a T-cell mediated disease, such as CIDP. Resp. Ex. A at 3-4. He wrote that "T-cell mediated responses are significantly more rapid, typically occurring within 1 week." *Id.* at 4. In his second report, Dr. MacGinnitie, wrote, "…for T-cells, cellular response are typically in decline by day 10-11 after exposure." Resp. Ex. E at 1-2. Dr. MacGinnitie opined that, "This time course is not consistent with onset in late February 2011….as the onset." *Id.* at 2.

During the hearing, Dr. MacGinnitie testified that J.P. had a primary immune response to the varicella vaccine, and 18 to 20 days would be a possible primary immune response. Tr. 293; 326. However, he opined that this case involved a secondary immune response, which one would expect to see much more rapid and vigorous. Tr. 290. He stated that, "In this case, I would expect by January…2011, J.P. had many T cells and B cells specific for myelin and that if they were triggered by a secondary immune response, we would see a very vigorous, very rapid response." Tr. 291. Dr. MacGinnitie testified that if there was a secondary immune response, one would have expected to see additional damage to the myelin more quickly, which did not

occur in this case. Tr. 292. He explained that pediatric CIDP, according the medical literature, appears to be primarily T-cell mediated. Tr. 296. He testified that a T-cell response to a stimulus appears to "peak at about day seven and by day fourteen, the T-cell response is already improving. And so in this case, that would put 21 days for onset, even of a primary immune response, really out of what is typically seen." *Id.*

3. Discussion and Conclusion Regarding *Loving* Prong Six (*Althen* Prong Three):

In this case, J.P. received the varicella vaccination on January 28, 2011. Pet. Ex. 1. Mr. and Ms. Pavan both testified that starting mid-February 2011, they noticed that J.P. became more fatigued and his activity level significantly decreased. Tr. 9; 44; and 58. This is approximately 21 days after J.P. received the vaccine.

During the hearing, I agreed that approximately 18-20 days after J.P. received the varicella vaccine, he demonstrated a relapse in symptoms that were related to his pre-existing CIDP. Tr. 293. Further, respondent's expert agreed that 21 days after a person receives a vaccination is within the "outer" range for primary immune response. Tr. 293. Dr. MacGinnitie accepted that the onset of the worsening of his condition appeared in mid-February. Tr 327

However, Dr, MacGinnitie emphasized that with a T-cell mediated disease, like CIDP, when there were T-cells primed one would expect "to see damage to the myelin more quickly than in this case." Tr. 292. Thus, concluding that the onset of J.P.'s exacerbation of symptoms 21 days after receiving the varicella vaccine would be too remote to demonstrate a proximate temporal association with the vaccine.

This program has generally accepted that a proximate temporal association for an immune response to an initial exposure to a vaccine is between 3 and 42 days. In this case, petitioner has presented sufficient evidence to establish that J.P.'s symptoms of CIDP were exacerbated within 21 days of receiving the varicella vaccination. However, proximate temporal association alone does not suffice to show causal link between vaccination and injury. *Grant v. Sec'y of Health & Human Servs.,* 956 F.2d 1144 (Fed. Cir. 1992).

G. Conclusion

I have great sympathy for J.P. and admiration for the care and concern his parents have shown for him over the prolonged and debilitating course of this disease. It is not without difficulty that I have come to this conclusion, however, after carefully reviewing the testimony and submitted literature, I unfortunately must conclude that the evidence presented is insufficient to demonstrate that the varicella vaccination played a causal role in exacerbating J.P.'s underlying condition.

Accordingly, petitioner's claim must be and is hereby **DISMISSED.** In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court is directed to enter judgment forthwith.[26]

IT IS SO ORDERED.

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

[26] Entry of judgment is expedited by each party's filing notice renouncing the right to seek review. Vaccine Rule 11(a).

ELSEVIER

Review Article

Chronic Inflammatory Demyelinating Polyneuropathy in Childhood

Anne M. Connolly, MD

Chronic inflammatory demyelinating polyneuropathy (CIDP) in children is relatively rare. However, it has been recognized for many years. In patients presenting with this disease, subacute onset of weakness usually develops over at least 2 months and often progresses to a loss of ambulation. Some children's initial presentations may mimic Guillain-Barré syndrome. Dysasthesias are common. Males are affected more than females, and antecedent illnesses or vaccinations occur in approximately half of patients. Physical examination reveals diffuse, proximal greater than distal weakness, with an absence or depression of muscle stretch reflexes. Electrophysiology confirms demyelination, and spinal fluid examination demonstrates albuminocytologic dissociation. The clinical presentation, diagnosis, and prognosis of childhood CIDP are reviewed. Treatment and immunologic features are also discussed in this article.

Connolly AM. Chronic inflammatory demyelinating polyneuropathy in childhood. Pediatr Neurol 2001;24:177-183.

Introduction

Although chronic inflammatory demyelinating polyneuropathy (CIDP) remains a relatively rare cause of weakness in childhood, the collective experience reported in the last 20 years sheds a great deal of light on the clinical manifestations and diagnosis of this disorder. Diagnosis of CIDP is important because immune-modulating therapies are effective. In this article the clinical, electrophysiologic, pathologic, and immunologic features of CIDP in childhood are reviewed.

Clinical Presentation and Diagnosis of Childhood CIDP

Children with CIDP present with a subacute onset of symmetric proximal and distal weakness that progresses over at least 2 months. The two mandatory clinical research criteria for the diagnosis include the following: (1) progressive or relapsing motor and sensory dysfunction of more than one limb and (2) hyporeflexia or areflexia, which usually involves all four limbs [1]. Onset as early as infancy is well documented in patients with CIDP [2,3]. Most [3-6], but not all [7], studies demonstrate that males are affected twice as often as females. As many as 50% of children lose or, in children with onset in the first year, have delay in their ability to ambulate [3,5,6,8,9]. Loss of ambulation is more common in children than in adults and in younger children [6]. Fatigue and sensory symptoms, including dysasthesias and sensory loss, are common. Large-fiber sensory loss is more common than small-fiber loss. In a retrospective study of 13 children, two clinical courses have been described [4]. Some children demonstrate a progression to maximal weakness over the course of 3 months or less and tend to have a monophasic course. Recovery with long-term remission is common in this group. Other children progress over a longer period of time and are more likely to have a relapsing remitting course. Ryan et al. [7] also reported two courses (monophasic and relapsing) in their 16 children. Hattori et al. [8] have demonstrated that those children with acute presentation over 2-3 months tend to have a good response to corticosteroids.

Simmons et al. [6] demonstrated that in one third of the 15 children with CIDP they studied, the initial presentation mimicked acute inflammatory demyelinating polyneuropathy (AIDP) with initial progression of weakness occurring within 1 to 4 weeks. These children went on to fulfill

From the Departments of Neurology and Pediatrics; St. Louis Children's Hospital; Washington University School of Medicine; St. Louis, Missouri.

Communications should be addressed to:
Dr. Connolly; Department of Neurology; Box 8111;
Washington University School of Medicine;
660 S. Euclid Ave., St. Louis, MO 63110.
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Table 1. Electrophysiologic features that distinguish CIDP from HMSN-1 and HNPP

Disease	Conduction Velocity	Conduction Block*	Motor Distal Latencies	F Waves	Sensory
CIDP	Nonuniform slowing < 80% of LLN if CMAP is ≥ 80% of LLN; < 70% of LLN if CMAP is ≤ 80% of LLN	Common	Nonuniform; prolonged[†]	Nonuniform; absent or prolonged[‡]	Focal; nonuniform slowing
HMSN-1	Marked slowing < 50% of LLN	Uncommon	Uniformly prolonged	Uniformly slowed	Uniformly slow or absent
HNPP	May be normal or minimally slowed at nonentrapment sites	Common	Uniformly prolonged	Uniformly prolonged	Uniformly slow

* Conduction block has been defined variably from study to study. In a pathologic study by Feasby et al. [54], electrophysiology was compared with demyelination pathologically. Their criteria for definite conduction block are similar to the research criteria published by the American Academy of Neurology [1] and include the following: (1) if the negative peak duration changes by no more than 15%, the CMAP amplitude with proximal stimulation must be 20% less than with distal stimulation; (2) if the negative peak duration increases by more than 15%, then the CMAP amplitude with proximal stimulation must be 30% less than with distal stimulation.

† Prolonged to 125% of ULN if CMAP is ≥ 80% of LLN; prolonged to 150% of ULN if CMAP is ≤ 80% of LLN.

‡ Absent or prolonged to > 120% of the LLN when the distal CMAP is ≥ 80% of the LLN; prolonged to > 150% of LLN when the distal CMAP is ≤ 80% of the LLN.

Abbreviations:
CIDP = Chronic inflammatory demyelinating polyneuropathy
CMAP = Compound muscle action potential
HMSN-1 = Hereditary motor sensory neuropathy type 1
HNPP = Hereditary liability to pressure palsy
LLN = Lower limit normal
ULN = Upper limit normal

clinical criteria for CIDP because they had relapses or late progression of weakness.

The clinical diagnosis of CIDP should be supported by laboratory testing and electrophysiology [1,10], including spinal fluid examination because this test detects albuminocytologic dissociation in most children. Nerve conduction studies initiated to search for differential nerve conduction velocity slowing, absent F-waves, and conduction block are helpful in distinguishing this neuropathy from inherited neuropathies.

Incidence and Prevalence of CIDP

The incidence and prevalence of CIDP in childhood are difficult to estimate. Formal epidemiologic studies of CIDP are rare. Recently Lunn et al. [11] reported an adult prevalence of 1 in 100,000 for definite, and probable CIDP in southeast England [11]. A second study by McLeod et al. [12] in New South Wales, Australia, revealed that the estimated incidence of CIDP was 0.15 in 100,000 and prevalence was 1.9 in 100,000. In this study, age at the time of the survey was analyzed, and six patients under 20 years of age were included. This percentage corresponded to a childhood prevalence of 0.48 in 100,000 [12]. The higher overall incidence in the second study relates to the fact that the researchers included possible as well as probable and definite patients with CIDP.

Differential Diagnosis of Childhood CIDP

Relatively few conditions mimic the full clinical presentation of a child with CIDP. Hereditary polyneuropathies, which are much more common in children than is CIDP, should be considered. These include hereditary motor sensory neuropathies (HMSN), hereditary liability to pressure palsies, Krabbe's disease, and metachromatic leukodystrophy. The history in these children usually reveals long-standing weakness without relapses. Children with hereditary neuropathies usually manifest distal more than proximal weakness. In contrast, children with CIDP usually present with both proximal and distal weakness. Although sensory loss exists in children with CIDP, it is usually more severe in children with hereditary sensory neuropathies. As many as one third of children with CIDP may exhibit sensory symptoms at presentation [3,4,8]. Physical examination of parents should be performed because it frequently will demonstrate distal weakness and sensory loss in the dominantly-inherited motor sensory neuropathies type I and II (HMSN type I and II). However, children with autosomal-recessive neuropathies, such as metachromatic leukodystrophy or Krabbe's disease, can also display symptoms that mimic CIDP because symptoms of peripheral nervous system may precede the central nervous system involvement [13]. Although pes cavus is associated more commonly with hereditary neuropathies, this finding may also be present in children with CIDP who have early onset of weakness [14].

Electrophysiologic studies may distinguish children

Table 2. Treatment of children with CIDP: results of immune modulating therapy with prednisone, human intravenous immunoglobulin (IVIG), and plasma exchange

Series	Number of patients	Corticosteroid # Treated/ # Improved (%)	IVIG # Treated/ # Improved (%)	PE # Treated/ # Improved (%)
Colan, 1980	5	5/5 (10%)	NU	NU
Sladky et al. 1986 [3]	6	6/6 (100%)	NU	NU
Beydoun et al. 1990 [48]	2	NU	NU	2/2 (100%)
Uncini et al. 1991 [49]	5	4/4 (100%)	NU	NU
Baba et al. 1993 [14]	6	6/6 (100%)	NU	NU
Nevo et al. 1996 [4]	13	13/13 (100%)	3/6 (50%)	3/3 (100%)
Simmons 1997	12	5/7 (71%)	7/8 (88%)	4/4 (100%)
Hattori 1998 [6]	10	7/9 (78%)	1/2 (50%)	1/2 (50%)
Ryan et al. 2000 [7]	16	11/11 (100%)	3/4 (75%)	1/1 (100%)
TOTAL	75	57/61 (93%)	14/20 (70%)	11/12 (92%)

Abbreviation:
NU = Not used

with CIDP from those with inherited neuropathies (Table 1). Thus if examination of the parents reveals weakness, a genetic and/or electrophysiologic study of the parents should also be performed. Some parents who are asymptomatic by history may exhibit minimal clinical findings but reveal characteristic electrophysiologic changes. Finally, acquired myopathies, such as dermatomyositis, may mimic CIDP because the characteristic rash of dermatomyositis may be absent in children. However, in contrast to children with CIDP these children will display normal sensory examinations and normal nerve conduction studies. Creatine kinase levels may be elevated in children with acquired myopathies, but usually they will be normal in children with CIDP.

Associated atypical features, including predominantly distal involvement, central nervous system demyelination, and prominent cranial nerve dysfunction were reported in a recent large series of adults and children with CIDP [15]. However, it was not possible to discern whether these features were present in the children or the adults of that series. Autoimmune diseases may coexist in children. An atypical form of CIDP with prominent axonal involvement developed in a 12-year-old child after an initial diagnosis of myasthenia gravis at 2 years of age [16]. As we begin to understand more subtle presentations, it is likely that some atypical presentations will be documented in children as is true for adults [15,17].

Electrophyisologic Features of CIDP

Research criteria set by the ad hoc subcommittee of the American Academy of Neurology demand that electrophyiologic data prove demyelination is the predominant feature in CIDP (Table 2) [1]. Thus the following three of four conditions must be met: (1) a slowing of motor conduction velocity; (2) partial conduction block abnormal temporal dispersion in one or more motor nerves; (3) prolonged distal latencies in two or more nerves; (4) absent or prolonged minimal F-wave latencies. These research criteria have been helpful in characterizing patients and have formed the basis for most of the clinical CIDP research in the last 10 years. These research criteria have held up well for recent studies of children with CIDP. It is important to note, however, that in some patients these criteria may be too restrictive [15]. Electrophysiologic studies in children suspected of having CIDP should include the study of four motor nerves and the results must be compared with the well-established childhood normal values [18].

Asymmetric findings, conduction block, and/or abnormal temporal dispersion are all helpful in distinguishing CIDP from hereditary neuropathies such as HMSN type I [19]. Although it may be more difficult to distinguish hereditary liability to pressure palsies from CIDP electrophysiologically, recent work suggests that the incidence of distal conduction block and prominent sensory involvement are helpful (Table 1) [20].

Pathogenesis of CIDP

Extensive pathologic and clinical evidence demonstrate that CIDP is an immune-mediated disease. The pathologic features in the nerve include mononuclear infiltrates, segmental demyelination on teased fiber preparations, and, in long-standing patients, onion bulb formation [7,21-23]. The precise mechanism by which the immune system is disrupted is more difficult to discern. However, the majority of the clinical and basic science research suggests that the humoral immune system is predominantly involved. In one 18-month-old patient with CIDP, cerebrospinal fluid (CSF) IgG synthesis rate was markedly elevated and oligoclonal bands were identified in her CSF, which suggested ongoing inflammation. This patient responded well to prednisone, and her CSF IgG synthesis normalized [9].

In adults with CIDP, both monoclonal and polyclonal

autoantibodies have been demonstrated in subsets of patients. Ganglioside and sulfatide autoantibodies [24], acidic glycolipids [25], proliferating nonmyelinating human Schwann cells [26], and β-tubulin [27-29] autoantibodies have been found in subsets of adults with CIDP. Recently autoantibodies to peptides spanning two extracellular domains of peripheral myelin protein-22 were described in 41% of adults with CIDP and 58% of adults with acute demyelinating polyneuropathy [30].

The role of any of these autoantibodies in the pathogenesis of CIDP is unknown. Autoantibodies may or may not be pathogenic. The concept of "natural" autoantibodies has been well established [31-36]. In other humorally mediated autoimmune diseases, passive transfer of sera has been considered the gold standard for proof of pathogenesis. For example, passive transfer of sera in myasthenia gravis demonstrates that humoral immunity is sufficient to transmit the disease [37]. Passive transfer of sera from patients with CIDP to marmoset monkeys has been reported. Transfer of the IgG subfraction led to electrophyisologic evidence of motor conduction velocity slowing [38]. Recently Yan et al. [39] used the method of intraneural injection of human sera into tibial branch of the rat's sciatic nerve to passively transmit the disease. In this study, purified IgG from sera of four of 12 CIDP patients was able to produce electrophysiologic evidence of conduction block in the rat's nerve [39]. They also demonstrated that activated P2-specific $CD4^+$ T cells, if given before IV injection of the same purified IgG, would also cause demyelination electrophysiologically. Interestingly, these four patients also manifested IgG and complement 3d binding on immuncytochemical studies of human nerve, and all four responded to plasma exchange [39]. This work strongly supports the notion that disruption of the humoral immune system plays a major role in CIDP. Activated T cells may be responsible for the disruption of the blood-nerve barrier.

Treatment of CIDP

Our early understanding of treatment for CIDP heralds largely from adult studies in which immune-modulating therapies, including prednisone, azathioprine, plasma exchange, and human IV immunoglobulin (IVIG) have all been demonstrated to be effective [21,40-48]. One of these series included 10 children [46]. Another large series included at least one child, but the children were not analyzed separately [47].

More recently pediatric series have highlighted effective management of children with CIDP [3-7,14,49]. The results of treatments used in children are summarized in Table 2. These children met clinical and electrophysiologic criteria or clinical and pathologic criteria for CIDP. Although prednisone results in improvement in strength for the majority (93%) of children, other immune-modulating therapies, including IVIG and plasma exchange, are clearly effective as well. Because of the small numbers of children affected, a multicenter trial would have to be used to directly compare treatment modalities. In adults, large comparative trials have been performed. In an adult series of 20 patients, IVIG has been studied carefully in a crossover study with plasma exchange and was proven to be equally effective [42]. In another blinded study of 30 adult CIDP patients the effectiveness of IVIG was confirmed [50]. Although controlled studies of CIDP in childhood still need to be performed, these results and the childhood reports (Table 1) suggest that IVIG may be an effective, first-line approach to treatment of childhood CIDP. More recent studies of other immune-modulating treatments, including β-interferon, have demonstrated benefits in adults with CIDP [51,52].

Prognosis of Childhood CIDP

The majority of children have a good short-term prognosis and nearly all indicate response to some immune-modulating therapy. Nevo et al. [4] reported that the duration of the initial onset of the weakness correlated inversely with disability. Thus children who initially progressed to their nadir of weakness over 1-3 months tended to have a monophasic course and were more likely to recover completely. Children who initially progressed over more than 3 months tended to have a more chronic, relapsing, remitting course [4]. Hattori et al. [8] also demonstrate two subsets of children based on type of onset with six of 10 children presenting between 1 and 3 months from onset. This group responded well to steroids (six of six). Two children in this subgroup did not initially respond to plasma exchange (one child) or IVIG (one child). However, when each child was changed to corticosteroids, they did improve [8]. These authors suggested that the group presenting between 1 and 3 months may be best treated with corticosteroids. The follow-up study by Simmons et al. [5] demonstrated that 10 of 12 children had relapsing courses with an average of 4.7 relapses (range-1-15). The Simmons et al. [5] follow-up study of 12 children demonstrated that all of them experienced an excellent response to immunotherapy and, with a minimum follow-up period of 12 months, only two had any disability based on modified Rankin score. These two children each displayed a score of 1/6, which is consistent with minor symptoms with no restriction in lifestyle [5]. A retrospective study of 16 children by Ryan et al. [7] also suggests a good prognosis (follow-up from 4 to 283 months) for children regardless of the initial onset.

Long-term prognosis for children with CIDP is incompletely understood because few studies have followed children into adulthood. McCombe's early work [46] reported follow-up information on eight of 10 children who presented between 2 and 10 years of age. Although treatment in these children is not specifically discussed, only one experienced minor disability and seven had no disability. However, long-term follow-up did indicate three of these eight children suffered relapses of weakness

in adult life [46]. One recent series of 100 patients, including some children (age range 10-82 years of age), recognized a number of prognostic factors; younger age at onset (less than 30 years old) correlated with a better outcome. Pain at onset and infectious prodromal illnesses also predicted a better outcome. Most importantly, axonal loss on electrodiagnostic studies predicted poor prognosis ($P < 0.0001$) [53]. Although the precise outcomes of the children in this study cannot be deciphered, this important work demonstrates the prognostic value of electrophysiology in CIDP.

Summary

The diagnosis of childhood CIDP depends on careful history, examination, and confirmatory electrodiagnostic and laboratory testing. The hallmarks are subacute weakness and hyporeflexia or areflexia. Electrophysiologic studies should confirm demyelination as the prominent abnormality. The majority of the immunologic research suggests that the humoral immune system is predominantly affected. Therefore directing immune-modulating therapy at the humoral immune system is important. Human IVIG, plasma exchange, and daily prednisone have all been proven to be effective. More work needs to be done to determine whether a particular onset (subacute vs chronic) has predictive value for what type of therapy to use initially. Prognosis for initial improvement in strength with immune-modulating treatment is excellent. Although it is clear long-term remission is possible, longer follow-up studies are necessary to determine what percentage of children remit completely and whether relapses in adulthood occur in subsets of children.

References

[1] **Subcommittee of the Am Academy of Neurology AIDS Task Force**. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991;41:617-8.

[2] **Pasternak** JF, Fulling K, Nelson J, Prensky AL. An infant with chronic, relapsing polyneuropathy responsive to steroids. Dev Med Child Neurol 1982;24:504-24.

[3] **Sladky** JT, Brown MJ, Berman PH. Chronic inflammatory demyelinating polyneuropathy of infancy: A corticosteroid responsive disorder. Ann Neurol 1986;20:76-81.

[4] **Nevo** Y, Pestronk A, Kornberg AJ, Connolly AJ, Iqbal I, Shield LK. Childhood chronic inflammatory demyelinating neuropathies (CIDP): Clinical course and long term follow up. Neurology 1996;47: 98-102.

[5] **Simmons** Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: II. Long-term follow-up, with comparison to adults. Muscle Nerve 1997;20:1569-75.

[6] **Simmons** Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: I. Presentation, electrodiagnostic studies, and initial clinical course, with comparison to adults. Muscle Nerve 1997;20:1008-15.

[7] **Ryan** MM, Grattan-Smith PJ, Procopis PG, Morgan G, Ouvrier RA. Childhood chronic inflammatory demyelinating polyneuropathy: Clinical course and long-term outcome. Neuromusc Disord 2000;10:398-406.

[8] **Hattori** N, Ichimura M, Aoki S, et al. Clinicopathological features of chronic inflammatory demyelinating polyradiculoneuropathy in childhood. J Neurol Sci 1998;154:66-71.

[9] **Faleck** H, Cruse RP, Levin KH, Estes M. Response of CSF IgG to steroids in an 18-month-old with chronic inflammatory polyradiculoneuropathy. Cleve Clin J Med 1989;56:539-41.

[10] **Dyck** PJ, Arnason B. Chronic inflammatory demyelinating polyneuropathy. In: Dyck PJ, Thomas P, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1993:2104-14.

[11] **Lunn** MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: A prevalence study in south east England. J Neurol Neurosurg Psychiatry 1999;66:677-80.

[12] **McLeod** JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. Ann Neurol 1999;46:910-3.

[13] **Nevo** Y, Pestronk A, Lopate G, Carroll SL. Neuropathy of metachromatic leukodystrophy: Improvement with immunomodulation. Pediatr Neurol 1996;15:237-9.

[14] **Baba** M, Takada H, Tomiyama M, et al. Chronic inflammatory demyelinating polyneuropathy in childhood. No To Shinkei 1993;45: 233-40.

[15] **Rotta** FT, Sussman AT, Bradley WG, Ram Ayyar D, Sharma KR, Shebert RT. The spectrum of chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2000;173:129-39.

[16] **Kimura** K, Nezu A, Kimura S, et al. A case of myasthenia gravis in childhood associated with chronic inflammatory demyelinating polyradiculoneuropathy. Neuropediatrics 1998;29:108-12.

[17] **Uncini** A, Di Muzio A, De Angelis MV, Gioia S, Lugaresi A. Minimal and asymptomatic chronic inflammatory demyelinating polyneuropathy. Clin Neurophysiol 1999;110:694-8.

[18] **Miller** RG, Kuntz NL. Nerve conduction studies in infants and children. J Child Neurol 1986;1:19-26.

[19] **Lewis** RA, Sumner AJ. Electrophysiologic features of inherited demyelinating neuropathies: A reappraisal. Ann N Y Acad Sci 1999;883: 321-35.

[20] **Andersson** PB, Yuen E, Parko K, So YT. Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. Neurology 2000;54:40-4.

[21] **Dyck** P, O'Brien PC, Oviatt KF, et al. Prednisone improves chronic inflammatory demyelinating polyneuropathy more than no treatment. Ann Neurol 1982;11:136-41.

[22] **Krendel** DA, Parks HP, Anthony DC, St. Clair MB, Graham DG. Sural nerve biopsy in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1989;12:257-64.

[23] **Chou** SM. Immunohistochemical and ultrastructural classification of peripheral neuropathies with onion-bulbs. Clin Neuropathol 1992;11:109-14.

[24] **Fredman** P, Vedeler CA, Nyland H, Aarli JA, Svennerholm L. Antibodies in sera from patients with inflammatory demyelinating polyradiculoneuropathy react with ganglioside LM1 and sulphatide of peripheral nerve myelin. J Neurol 1991;238:75-9.

[25] **Ilyas** AA, Mithen FA, Kalakas MC, Zi-Wei C, Cook SD. Antibodies to acidic glycolipids in Guillain-Barre syndrome an chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 1992;107: 111-21.

[26] **van Schaik** IN, Kwa MSG, deJonge RR, Baas F, Vermeulen M. Investigation of serum response to myelin and non-myelin components in inflammatory neuropathies. Neurmusc Disord 2000;10:363.

[27] **Connolly** AM, Pestronk A, Trotter JL, Feldman EL, Cornblath DR, Olney RK. High titer selective serum anti-β-tubulin antibodies in chronic inflammatory demyelinating polyneuropathy. Neurology 1993; 43:557-62.

[28] **Connolly** AM, Pestronk A, Mehta S, et al. Serum IgM monoclonal autoantibody binding to the 301-314 amino acid epitope of β-tubulin: Clinical association with slowly progressive demyelinating polyneuropathy. Neurology 1997;48:243-8.

[29] **Connolly** AM, Pestronk A. Anti-tubulin autoantibodies in

acquired demyelination polyneuropathies. J Inf Dis 1997;176 (Suppl 2):S157-9.

[30] **Gabriel** CM, Gregson NA, Hughes RA. Anti-PMP22 antibodies in patients with inflammatory neuropathy. J Neuroimmunol 2000; 104:139-46.

[31] **Avrameas** S. Natural autoantibodies: From "horror autotoxicus" to "gnothi seauton." Immunol Today 1991;12:154-9.

[32] **Avrameas** S, Ternynck T. The natural autoantibodies system: Between hypotheses and facts. Mol Immunol 1993;30:1133-42.

[33] **Dighiero** G, Lymberi P, Holmberg D, Lundquist I, Coutinho A, Avrameas S. High frequency of natural autoantibodies in normal newborn mice. J Immunol 1985;134:765-71.

[34] **Mamula** MJ, Lin R, Janeway CA, Hardin JA. Breaking T cell tolerance with foreign and self co-immunogens: A study of autoimmune B and T cell epitopes of cytochrome $c^{1.}$ J Immunol 1992;149:789-95.

[35] **Martin** T, Duffy SF, Carson DA, Kipps TJ. Evidence for somatic selection of natural autoantibodies. J Exp Med 1992;175:983-91.

[36] **Miller** DJ, Rodriguez M. A monoclonal autoantibody that promotes central nervous system remyelination in a model of multiple sclerosis is a natural autoantibody encoded by germline immunoglobulin genes. J Immunol 1995;154:2460-9.

[37] **Toyka** KV, Drachman DB, Griffin DE, et al. Myasthenia gravis. Study of humoral immune mechanisms by passive transfer to mice. N Engl J Med 1977;296:125-31.

[38] **Heininger** K, Liebert UG, Toyka KV, et al. Chronic inflammatory polyneuropathy: reduction of nerve conduction velocities in monkeys by systemic passive transfer of immunoglobulins. J Neurol Sci 1984;66:1-14.

[39] **Yan** WX, Taylor J, Andrias-Kauba S, Pollard JD. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. Ann Neurol 2000;47:765-75.

[40] **Austin** JH. Recurrent polyneuropathies and their corticosteroid treatment. Brain 1958;81:159-92.

[41] **Dyck** PJ, O'Brien P, Swanson C, Low P, Daube J. Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. Neurology 1985;35:1173-6.

[42] **Dyck** PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med 1986;314:461-56.

[43] **Server** AC, Lefkowith J, Braine H, McKhann GM. Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. Ann Neurol 1979;6:258-61.

[44] **van Doorn** PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: A double-blind, placebo-controlled, crosssover study. Neurology 1990;40:209-12.

[45] **Dalakas** MC, Engel WK. Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. Ann Neurol 1981;9 (Suppl):134-45.

[46] **McCombe** PA, Pollard JD, Mcleod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. Brain 1987;110:1617-30.

[47] **Gorson** KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: Clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997;48:321-8.

[48] **Beydoun** SR, Engel WK, Karofsky P, Schwartz MU. Long-term plasmapheresis therapy is effective and safe in children with chronic relapsing dysimmune polyneuropathy. Rev Neurol 1990;126:123–7.

[49] **Uncini** A, Parano E, Lange DJ, De Vivo DC, Lovelace RE. Chronic inflammatory demyelinating polyneuropathy in childhood: Clinical and electrophysiological features. Childs Nerv Syst 1991;7:191-6.

[50] **Hahn** AF. Treatment of chronic inflammatory demyelinating polyneuropathy with intravenous immunoglobulin. Neurology 1998;51 (Suppl 5):S16-21.

[51] **De Luca** G, Lugaresi A, Iarlori C, Marzoli F, Uncini A, Gambi D. Interferon beta normalizes suppressor cell function in dysimmune neuropathies. J Neuroimmunol 1998;82:1-4.

[52] **De Luca** G, Lugaresi A, Iarlori C, et al. Prednisone and plasma exchange improve suppressor cell function in chronic inflammatory demyelinating polyneuropathy. J Neuroimmunol 1999;95:190-4.

[53] **Bouchard** C, Lacroix C, Plante V, et al. Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. Neurology 1999;52:498-503.

[54] **Feasby** T, Brown WF, Gilbert JJ, Hahn AF. The pathological basis of conduction block in human neuropathies. J Neurol Neurosurg Psych 1985;48:239-44.