Lehmann-Horn Questions from Conference

1. Is it possible that a family with juvenile myoclonic epilepsy and Hypo PP for there to be a connection between these 2 diseases?

   In general, it is unlikely for there to be a connection between these two diseases. The genetics behind juvenile myoclonic epilepsy is not worked out; however, given that we do not see the two disorders in a large number of patients, it would lead one to believe that they are unrelated. On the other hand, if indeed one has both, it would warrant research into the possibility of a relationship given that they are both so rare. Sorry to hedge on both sides of the fence!!!

2. Is there anything that helps for chronic cognitive impairment concerns?

   I apologize but would need clarification of this question. I presume you mean “brain fog” associated with attacks of periodic paralysis, and possible continual “brain fog” from an attack that just won’t go away. In this case, proper treatment of the attack with appropriate medication would be the best strategy for alleviating the problem. Also, very strict avoidance of triggers, especially dietary triggers, would probably also help.

3. Does PP cause Peripheral Neuropathy – I have been told I have no muscles to extend toes 2-5 on both feet. Is this the beginning of permanent muscle weakness?

   PP has been associated with nerve conduction defects, but it is not commonly associated with peripheral neuropathy (at least sensory). The lack of muscles more likely could be from permanent muscle weakness due to intrinsic muscle damage from repeated attacks rather than from atrophy due to an injured nerve.

4. Can you better define Paramyotonia - Does paramyotonia only come with Hyper PP?

   Paramyotonia can occur along with hyperPP or by itself. It is characterized by worsening of the muscle stiffness with exercise, in contrast to myotonia congenita, which exhibits the warm-up phenomenon. Hence the name paramyotonia (short for paradoxical myotonia).

5. While our sailboat is in motion I have never had an attack in 6000 nautical miles. Ed sails sometimes day and night for 3-6 days. I have weakness attacks every few days when we are at anchor. Does this mean a mechanical rocking bed may prevent attacks?

   This is an interesting observation, and is an interesting hypothesis. Without proper testing, I could not comment. That said, if it works for you, roll with it!

6. Is it a normal symptom to run out of breath and be tired after sweeping he kitchen floor?

   No, this is not normal. Fatigue can have many causes, from cardiac to endocrine to neuromuscular to poor sleep hygiene to psychiatric. Your doctor should be able to sort it out. It is entirely possible that this is due to periodic paralysis, and one would expect the symptoms to be less with better control of the disease.
7. Will any of these medications trigger an attack? Zetia, Cymbalta, Diclofenac, Amlodipine?
   Any medication can trigger an attack in anyone. That is, it is a case by case, trial and error type of discovery for each individual. That said, physiologically speaking, I would not expect any of these medications to be a significant trigger for periodic paralysis.

8. Can a person be Hypo Pp if their potassium while well (baseline) checked for a full month is in the range of 4.0-4.5?
   Yes. The dip in potassium is seen only during attacks and is normal the other times.

9. Can a person be Hypo PP if attacks occur with potassium at 4.2 in some attacks and 4.6 in other attacks?
   This would be atypical. However, if someone’s normal baseline is say, 4.8 and they get weak at 4.2 and get strong again after ingesting potassium, then one could make a good argument that the person may be hypoPP.

10. Can anything be done to create more awareness among doctors especially Neurologists in Ireland and other countries with this condition does exist and can be real especially if a patient presents as normal at consultation?
   Awareness is a difficult thing to achieve for a rare disease. It is best to make the individual doctor aware of the disease. I wonder if we couldn’t make a program whereby the PPA sends literature or a physician awareness campaign to a specific physician that a member knows s/he is going to see. If literature comes from the PPA rather than from the patient, it may be better received. That said, the physician may become suspicious or skeptical at the coincidence of receiving literature and then seeing a patient the next week.

11. How do you convince Neurologists there is a benefit to do the CMAP EMG while a patient is on treatment?
    The issue is what do you hope to gain from that test? It is typically a diagnostic test rather than a gauge of treatment success. I am sure that if you create a rational case, any reasonable physician would listen.

12. I have Hyper PP – what is the difference between HYPO and HYPER? Are the drugs used the same for both?
    HyperPP gets worse when given potassium. A better term would be “potassium-sensitive PP”. HypoPP gets better when given potassium. A handful of drugs, specifically the carbonic anhydrase inhibitors – acetazolamide and dichlorphenamide – happen to work for both diseases for unclear reasons. Of course, this causes much confusion with patients and physicians, who prefer conceptualizing diseases and treatments as either “black or white”. (Maybe there is some good sense as to why the PPA logo is gray after all!!) 🤔

13. Dr. L-H can you explain how the information you provided on HYPO would apply to HYPER?
In both instances, permanent muscle weakness is characterized by increased sodium content in muscle. By using diuretics to deplete the sodium from the muscle, we hypothesize that muscle strength will improve. In this way, the diuretic strategy would be expected to work for both hypoPP and hyperPP.

14. If Hypo and Hyper present opposite concerns re: potassium why do both respond to Diamox and Daranide?
   This is somewhat of a mystery. There are a variety of theories. One good one is that these diuretics force you to excrete potassium, so this is good for hyperPP. In hypoPP, there are side currents in the calcium and sodium channels that are responsible for the faulty membrane potentials. These drugs appear to block these side currents in hypoPP. All in all, a strange coincidence!

15. Dr. L-H you say that if your K is normal between episodes this is a symptom of something other than PP – what?!
   What I believe I said was that if the potassium is abnormal between episodes, it is likely not periodic paralysis but rather a renal or endocrine problem. That potassium is normal between episodes is a hallmark of periodic paralysis, and it is what makes it so difficult to diagnose.

16. Can permanent weakness be reversed?
   Yes, with appropriate treatment, it can be reversed partially. It really depends on how advanced the permanent weakness is.

17. Do you recommend muscle biopsy and Na MRI as a diagnostic tool for patients? If so where is the NaMRI available? Is this a standard MRI?
   As of now, the Na MRI is an investigational tool that has not made it into mainstream practice. We presented it at PPA to show you “cutting edge” research. One can demonstrate similar phenomena with a regular MRI. Muscle biopsy and MRI can help in the diagnosis or assessment of the extent of fixed weakness, but typically they are tertiary studies that are often not necessary in the diagnosis of periodic paralysis.

18. Is the Na MRI available in the USA?
   Currently, I am unaware of any center that offers this for clinical use in patients.

19. My wife was recently diagnosed with PP. Calcium Channel blockers have stabilized her condition. Why? And does this help explain if she is Hypo or Hyper?
   This is an interesting observation that has been reported infrequently in the literature, most often with hypoPP patients. That said, one cannot rely on this information to render a diagnosis. We don’t know why that would work.
20. What effects do light weight lifting and other exercise have on my long-term prognosis for progressive weakness?

Weight lifting, in theory, tears muscle. As such, it should be avoided in theory. But, not controlled trial has looked at the value or detriment of weight-lifting in periodic paralysis to know for sure if it indeed does any damage at all. There is no reason to believe that patients with periodic paralysis have an impaired muscle repair capability. In general, patients should remain as active as possible. How much exercise they can do depends on what their individual threshold for inducing an attack of periodic paralysis is. If a particular exercise is inducing an attack then they are doing too much. For all patients with muscle disease, it is less desirable to do progressive resistive exercises meant to "bulk up". Rather, patients should do more toning/aerobic types of exercises with less weight/resistance and more repetition. Specifically, eccentric contraction should be avoided.

21. Would a voltage converter help turn a nerve from a P2 to P1 level?

The ion channels do not work that way, but it is a nice thought. Ion channels reverse their states depending on the voltage across the muscle membranes. So, if we could arrange a “micro” voltage converter for each cell, it would be great. But, I believe it would be science fiction today.

22. Can a channelopathy cause low Co2 levels? Why?

I would not expect a channelopathy to cause low CO2 levels. If it did, I would not understand the mechanism. Acetazolamide and dichlorphenamide cause excretion of bicarbonate, resulting in a metabolic acidosis. The body will blow off more CO2 than usual to accommodate for that change. But this situation applies to treated patients.

23. Can a channelopathy affect ACTH levels? Why?

Probably not. Certainly we have not found that periodic paralysis affects ACTH levels.

24. How do you get DME Monitors? What kind of equipment should I have ready for my 8 year old daughter? I have pulse ox – do we need a defibrillator, O2, Ambu, way to monitor K at home?

I apologize. I am not sure what a DME monitor is.

25. At what point do I call 911? Respiratory difficulty, throwing up, can’t swallow?

This is a personal question with no routine good answers. Anytime you feel your life is in danger, you should call 911. Respiratory difficulty and trouble swallowing are reasonable reasons for calling 911.

26. Why does PP affect only skeletal muscles except when it affects heart and respirations? What other exceptions are there?

The mutant ion channels are primarily found in skeletal muscle in the case of periodic paralysis. Respirations are controlled by skeletal muscle. I am not sure I understand...
what you mean by exceptions. We suspect the GI tract can slow down during a paralysis attack. For Andersen-Tawil Syndrome, the mutant potassium channels can also be found in the heart muscle. Electrical disturbances of the heart can occur due to low or high potassium in the blood without having a mutated ion channel located in the heart muscle itself.

27. What causes the pain with PP?
   One possibility is the swelling of the muscle during a weakness spell that compresses pain-mediating nerve endings in the muscle.

28. What is the correlation between PP and myoclonic and Dystonic Activity?
   Patients with hyperkalemic periodic paralysis can demonstrate paramyotonia. This is not universal.

29. Why does a person react to Diamox?
   Positively or negatively? And in which disease? For some people with hypokalemic periodic paralysis, acetazolamide cause ill-feelings, usually within a day or two of taking the drug. We don’t know why this occurs. In terms of benefit, for hyperkalemic periodic paralysis, causing potassium-diuresis is felt to be the main mechanism of action. In hypokalemic periodic paralysis, correction of alkalosis is felt to play a role. In both disorders, we suspect there is also some direct effect on the abnormal ion channel currents as well.

30. Why does a person also have success with Spironolactone?
   Spironolactone is a potassium-sparing diuretic, so it prevents the kidney from excreting potassium. In doing so, blood potassium levels are kept more elevated than they otherwise would be, and this is thought to prevent attacks of weakness. Spironolactone also excretes sodium, which is felt to collect pathologically in affected muscles.

31. What connection if any is there between PP and arthritis and also juvenile RA?
   We do not believe there is a connection.

32. Would it be possible to be emailed Understanding PP so we can give it to our doctor? She is struggling to understand the disorder and my family is suffering. I would love to have medically sound information to give her.

   Please submit your request to PPA ASK THE EXPERTS and we can go from there.

33. What are ways to increase muscle strength and muscle stamina once it is lost? PT brings on muscle weakness and paralysis. Is there any help for permanent muscle weakness?
   Optimizing therapy is one way of doing so. This entails trial and error with different kinds, doses, and combinations of diuretics, diet, and in the case of hypokalemic periodic paralysis, potassium supplements.
34. Is sleep paralysis connected to this disorder?
   Sleep paralysis is an unrelated disorder, but it often is on the differential diagnosis of periodic paralysis.

35. What meds affect Hypo negatively?
   Potassium-wasting diuretics cause low potassium and thereby trigger attacks. Medications with glucose in them can also be problematic as glucose causes endogenous insulin secretion, which drives potassium into cells causing hypokalemia and thereby inducing an attack. Epinephrine and related adrenergic agonists (like albuterol) can also drive potassium into cells. Asthmatic and insulin-dependent diabetic patients with periodic paralysis are among the most difficult to manage. Periodic paralysis patients can be triggered by any medication unpredictably on a case-by-case basis.

36. How important is blood pressure variations and blood pressure control to the long-term progression of this disease?
   I am unaware of any correlation between blood pressure control and periodic paralysis. That said, certain blood pressure medications are diuretics (either potassium wasting or potassium sparing) and/or potassium-sparing (i.e., ACE inhibitors). While these medications serve to control blood pressure, they can positively or negatively affect a person’s periodic paralysis depending on which type of disease a person has.

37. Why is alcohol such a trigger for many of us?
   Alcohol is felt to cause electrolyte disturbances and dehydration, especially during recovery from the alcohol in the hours after indulging. Because alcohol is a depressant of inhibitions in small to moderate doses, we may do things we are not aware of during drinking – like dietary indiscretion or physical activity beyond our normal comfort level. This may play a role.

38. Do we have any understanding of how Hypo PP can have initial onset at age 54? Is it possible to have symptoms and a mutation after surgery?
   It is not likely that surgery can cause an ion channel mutation that would mutate all the body’s ion channels in all the muscles cells of the body. This would have to occur in the egg, sperm, or shortly after fertilization. We do not understand why periodic paralysis can become evident in some individuals near birth and in others late in life.

39. What do you consider an aggressive dose of a potassium sparing diuretic such as Amiloride? I take 10mg of Amiloride and 750mg of Diamox. Could I take more Amiloride?
   This is a consideration that must be made with your doctor. In general, Amiloride, when given by itself, is labeled for doses between 5-20mg.

40. Is exon skipping (per MDA magazine) at all applicable to PP?
   In short, probably not. The ion channels involved in periodic paralysis are felt to be necessary for life, such that fully mutated proteins are likely not compatible with life. The mutations we see in periodic paralysis are of one base pair in DNA resulting in one
change in the amino acid sequence of the affected ion channel.

41. Is it common for patients with PP to have a mixed presentation of PP, mitochondrial disease and hemiplegic migraine?
   This would certainly not be common, and, statistically speaking, it borders on impossible.

42. Is it possible to take large doses of K (100-120 daily) if you do not have PP or a kidney K wasting disease?
   It is possible to do so. I would be concerned about elevating serum potassium and causing arrhythmias.

43. I have PP episodes at 4.0-3.8 - is this Hypo? My doctor calls my episodes when hospitalized normokalemic – comments please? What would be recommended K level to prevent episodes?
   This is always a tricky subject. If the diagnosis is indeed periodic paralysis, then one should think about the disease as: 1) potassium administration makes weakness better (hypokalemic periodic paralysis), or 2) potassium administration makes weakness worse (hyperkalemic periodic paralysis, and a better term might be potassium-sensitive paralysis). That said, hyperkalemic periodic paralysis patients sometimes require potassium. The term normokalemic is confusing and antequated. It has referred to patients that have either hyperkalemic or hypokalemic periodic paralysis whose attacks of weakness correspond with serum potassium measurements in the normal range. Indeed, we suspect that in such cases, there is either a relative hyperkalemia or hypokalemia in the individual, whereby the abnormal value is either lower or higher than the non-weak baseline but still within the normal reference range for potassium. It is difficult to recommend a particular target potassium level in such cases. It is not unreasonable to shoot for a level of 4.5 in a hypokalemic periodic paralysis patient that gets attacks of weakness at 4.0.

44. Has a precedent been set for pre-diagnosis of Andersen Tawil in IVF and is embryo selection possible?
   Preterm diagnosis for ATS can be achieved. Embryo selection should be possible if the gene is known.

45. Is there any evidence as to which drug is more effective for Andersons – Diamox or Daranide?
   Right now, I don’t believe there is good evidence for one over another. It would require trial and error by an individual to see which is better.

46. What are the most important side effects of long-term Diamox treatment? My son has taken it since age 3.
   Long-term side effects of Diamox are mainly kidney stones. There is some question as to whether or not it also affects calcium metabolism, but my understanding is that this concern is largely theoretical.
47. Is there a way to get an ATS patient out of a full body attack quicker than 4-5 days?  This is a patient-dependent situation. It depends on the nature of the attack.

48. Without a cardi-meter can you tell a difference between Hypo and Hyper attack in ATS patient?  Doing a blood draw during an attack should clarify the situation in most cases.

49. Can a channelopathy give you brisk reflexes and/or upper motor neuron signs? Why?  Conventional dogma would say that we shouldn’t see these things in periodic paralysis. I would not be able to explain the exceptions to this rule readily.

50. Are kidney stones a risk of PP?  Kidney stones are a risk only if one takes carbonic anhydrase inhibitors for the PP.

51. What risk does PP have on shingles?  There is no increased risk for shingles with periodic paralysis.

52. Can a channelopathy affect your antibodies? Example: Low IgA High IgG. Why?????  I would not expect an ion channelopathy to affect levels of immunoglobulins.

53. My family shows signs of PP. Can they get blood test done without a clinical diagnosis?  Yes.

54. How will PP affect my long-term muscle control?  Insofar as muscle weakness occurs (either transiently or permanently), muscle control can be adversely affected.

55. I am moving to Romania to live. Can my Dr. there get information to help me?  Yes. We would be happy to provide your doctor with what information we have. If translation is an issue, consider contacting the U.S. Embassy for translation services.

56. What are other tests that doctors can perform for diagnosis while waiting for gene testing? What treatments can they give?  This is a very involved question. Firstly, for which disease? For periodic paralysis, a number of tests can be done – some recommended, some not:
   a. Genetic testing
   b. Muscle biopsy
   c. Nerve conduction study – McMannis protocol
   d. Blood levels of potassium during and between attacks
   e. Reflex testing and strength testing during and between attacks
   f. Provocative testing – either with potassium, carbohydrates, exercise, and/or insulin – often in a monitored setting
   g. Hormone work-up for thyroid and adrenal gland disorders
   h. Renal work up for potassium-wasting disorders
   i. MRI of muscle to see fat and water content
   Therapies depend on the situation. As it stands, that part of the question is too broad to
57. If I need to have gall bladder surgery what are my options with anesthesia? Is it safe?
This discussion would best be had with an expert in periodic paralysis and your
anesthesiologist and surgeon. It will depend on what type of periodic paralysis you have.
Where possible, depolarizing muscle relaxants should be avoided as well as inhaled
anesthetics. Depolarizing muscle relaxants such as succinylcholine are myotoxic. In
addition, the membrane might not recover from depolarization and cause or a long-lasting
weakness. It is unclear whether or not inhaled anesthetics have to be avoided. As a
malignant hyperthermia (MH) crisis has been reported in the literature for a single
HypoPP patient (diagnosis genetically never confirmed), we recommend avoidance just
to be on the safe side. In a 1990 paper, we have reported equivocal in-vitro contracture
test (IVCT) results for HypoPP patients (the IVCT is the gold standard for MH
diagnosis); the halothane response was pathologic, the caffeine response normal.

58. We sent blood to Ulm about 9 years ago and never heard anything. We need SCN4A
gene sequencing 1 year ago with our doctor and it was negative. Is there another test we
can do to get a more definitive diagnosis?
The specifics of your genetic testing is best addressed directly with Dr. Lehmann-Horn
and his associates privately.

59. Is Daranide something that will be available to try with young children again? I believe it
is only used for over 18 now.
Currently, use in children is experimental.

60. I have 2 boys with possible PP age 7 and 11. Both need to have surgery soon for eyes and
teeth extractions. What are the risks????
The risks depend on the type of periodic paralysis the boys have. Surgical risks and
considerations are outlined for each disease in the following powerpoint presentations:
http://www.periodicparalysis.org/english/View.asp?x=582 – click on:
Jacob Levitt - Hypokalemic Periodic Paralysis 101

61. My Hypo PP started in my late 40’s as exercise intolerance. Please explain how this is
different that early onset. My docs first thought I had Myasthenia Gravis but then I
started with regular episodes of paralysis.
We cannot explain why some people show symptoms later in life and others early in life.
If the mutation is known (and by definition has been present since birth), I don’t expect
“late-onset” disease to be different from “early-onset”.

62. A few years ago my doctor told me that during Pp episodes I do not produce a special
enzyme in my blood and that this would lead to permanent muscle weakness. Is there
such an enzyme? Can he make this abatement?
I am unaware of such an enzyme. He should clarify with specifics. I would be happy to discuss this theory with him.

63. Is a GI-diet good for people with PP?
   Unfortunately, I am unfamiliar with this diet. A diet low in carbohydrates and low in sodium is typically best for hypokalemic periodic paralysis. A diet that avoids high potassium foods is typically best for hyperkalemic periodic paralysis.

64. What is the difference between stiffness and myotonia?
   Stiffness is a sensation of inability to relax muscles, or of muscle tension. Myotonia is a specific type of stiffness defined by a characteristic reading on an electromyogram (EMG).

65. I have twitching during my attacks – why?
   We cannot explain twitching and jerks during attacks of periodic paralysis.

66. If you have 528H genetic defect and no attacks and no weakness How do you titrate medications?
   This is an excellent question. This would depend on the individual case and the person’s response to medications. Monitoring of muscle strength over time (say, each 6 months to one year) would be one way to gauge whether strength is deteriorating and if medication needs to be adjusted.

67. If a woman with AS28H never had attacks but a history in family of muscle weakness is there anything we should be doing to prevent the muscle weakness? Also, same for a man who had one bad attack and now attacks prevented with Diamox – how can one prevent permanent muscle weakness?
   While there is little evidence to support preventing permanent weakness by treating attacks, the current thinking is that people with the gene defect should be on some prophylactic medication and that this medication has a better chance at preventing permanent muscle weakness. Avoiding dietary triggers is also helpful – that is, avoid high quantities of carbohydrates and salt even if they don’t appear to be causing attacks of weakness.

68. Is non-specific elevated sed rate to be expected in this disease?
   No.

69. Are there other connective tissue diseases that are commonly associated with Hypo PP or that are confused with Hypo PP?
   No.

70. Hormones and PP – Progesterone or other hormone to keep me from getting so sick during my periods? Is there a way to measure these hormones during the month?
   I don’t understand this question. If you feel hormonal fluctuations are causing attacks, it would be possible to work with your endocrinologist to measure levels of hormones at
different times during the month and during and between attacks. Perhaps you will find a trend.

71. Diet Coke - does it work for everyone with Hypo PP?
Diet Coke is merely one alternative to a low-sugar drink. It is not meant as a therapy for hypokalemic periodic paralysis. Whether or not it causes attacks in an individual is dependent on the individual. Trial and error is worthwhile if Diet Coke is your fancy.

72. Doctor found soft, squishy muscle tendon during a knee surgery. Doctor is not sure what/why could this be part of damage from HYPO?
It is possible that the muscle was paralyzed during surgery or that it has permanent muscle weakness. Muscle biopsy would be one way to determine this, or possibly MRI. Neither may be necessary.

73. If someone is taking Spironolactone and potassium 3-6 times a day as 25 mEq, where does potassium go? Nephrologist claims test did not show excretion in the kidneys.
Potassium can be stored in muscle, and it does not necessarily have to be absorbed. It depends on a person’s total body potassium stores. If the muscles are relatively potassium-depleted, then they can absorb large quantities of potassium.