Elementary, my dear Dr. Allen : The case of barium toxicity and Pa Ping

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Neurology 2010;74;1546
DOI 10.1212/WNL.0b013e3181e222ee

Elementary, my dear Dr. Allen

The case of barium toxicity and Pa Ping

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ABSTRACT

Objective: We aimed to review the English and Chinese literature on Pa Ping and to confirm by personal interview the story of how its pathogenesis was uncovered.

Background: In 1930, Dr. Alexander Stewart Allen noticed a pattern of illness arising in the region of Kiating, China. Area residents began presenting to local hospitals with nausea, vomiting, and diarrhea, and what emerged was a clinical picture of a gradual ascending paralysis that could result in death, termed Pa Ping. All 3 patients observed by Dr. Allen were male, had no family history of the disease, and had recently eaten before the onset of paralysis. Pa Ping developed in Dr. Allen himself, but he survived.

Methods: Medical literature was reviewed for primary sources. Interviews of living descendants and friends of the doctors in China and North America were conducted and information was corroborated by written records.

Results: Dr. Huang, with the National Central University College of Medicine, noticed a striking similarity between Pa Ping and familial periodic paralysis in 12 patients and reported 2 patients with Pa Ping treated with potassium citrate who experienced a reversal of the paralysis. Dr. K.T. Du analyzed meals of patients with Pa Ping seen by Dr. Zhe Tung and found barium in concentrations as high as 25.7%. This finding was confirmed by administering barium chloride to animals, which recapitulated the human syndrome.

Conclusions: Although Dr. Huang had correctly noticed an underlying potassium depletion in patients with Pa Ping, the observations of Dr. Zhe Tung and Dr. K.T. Du ultimately established barium-induced hypokalemia as the underlying cause. *Neurology*® 2010;74:1546–1549

GLOSSARY

AMAN = acute motor axonal neuropathy; **FPP** = familial periodic paralysis; **GBS** = Guillain-Barré syndrome.

In 1930, Canadian medical missionary Dr. A. Stewart Allen[1] (figure) noticed a curious pattern of illness arising in the region approximating the Sichuan city of Kiating (now referred to as Leshan), China. Area residents began presenting to local hospitals with nausea, vomiting, and diarrhea, and what was emerging was a clinical picture of a gradual ascending paralysis that sometimes resulted in their death.[1] The syndrome was a curiosity to visiting foreign medical missionaries; however, native residents were all too familiar with the constellation of symptoms that they called Pa Ping.

METHODS A complete review of the Western literature on Pa Ping was undertaken. Pa Ping was searched in PubMed, HighWire Press, and Google Scholar and yielded A. Stewart Allen's 1943 article and several relevant review articles. All articles and their listed references were reviewed in detail (with relevant references included in e-References on the *Neurology*® Web site at www.neurology.org). Then the Eastern literature was reviewed by members of the research team who were residing in China and they traveled to the region and obtained copies of the original abstracts and articles, translating them from Chinese to English. The story of Pa Ping was also confirmed by personal interview of living relatives of Dr. Allen.

RESULTS Pa Ping, roughly translated, means "soft disease."[1] It was endemic to the region around Kiating, and cases were reported from the Leshan region including Wutungchiao all the way to other parts of Sichuan, China. According to Dr. Allen, the number of patients with Pa Ping was sufficiently infrequent that the

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Disclosure: Author disclosures are provided at the end of the article.

Figure Dr. A. Stewart Allen in Kiating, China

Photograph of Dr. A. Stewart Allen taken in the 1940s at the Canadian Mission Hospital several years after he had recovered from Pa Ping. With him in the photograph is a 3-year-old Chinese toddler whom Dr. Allen had treated for severe malnutrition.

syndrome "caused little concern to area residents . . . often being diagnosed as 'food poisoning,'" and this phenomenon went altogether unnoticed by medical personnel (foreign or otherwise) until the 1930s.[1,2]

For unknown reasons, the numbers of Pa Ping cases increased dramatically after 1932, with Dr. Allen himself falling victim to the syndrome. After feeling unwell while eating his noon meal, Dr. Allen retired to bed without eating dinner and "at four or five o'clock in the morning, [was] unable to draw up the knees, lift the arms, or to raise the body from the bed."[1] This account was corroborated by his daughter, who recalled her father Dr. Allen "eating something . . . and he assumed it was natural table salt and he did suffer [from Pa Ping] and was paralyzed" (Donaghy P, personal communication, 2009). Although Dr. Allen had suffered a severe bout of Pa Ping, within 20 hours, his paralysis had regressed, and he regained full baseline function.[1]

To medical personnel in China, death during the course of Pa Ping seemed to be a matter of fate. In many reported cases, the paralysis spread to the entire body, and the patient ultimately died of respiratory failure.[1,3] Dr. Allen[1] reported a case of rapid progression from vomiting and diarrhea to complete paralysis, including the heart and respiratory muscles, within 48 hours. Dr. Huang[4] reported a case of respiratory failure 24 hours after the onset of paralysis. Other cases followed a similar course to the one experienced by Dr. Allen,[1] where the paralysis regressed and full recovery followed. Interestingly, all patients observed by Dr. Allen[1] were men, had no family history of the disease, and most recalled eating a few hours before the onset of paralysis. For many patients, gastrointestinal disturbances associated with Pa Ping were sometimes assumed to be food poisoning, and were often overlooked.[1,3] Dr. Allen[1] therefore surmised that some cases of Pa Ping might have exhibited a transient paralysis and never presented for formal diagnosis, especially among lower-class women, who were more likely to add salt to meals to compensate for poor nutritional intake.

Dr. Keh-Wei Huang,[4] a professor of neurology at the National Central University College of Medicine, formally reported 12 cases encountered in Chengtu between October 1939 and July 1942, and these cases followed Dr. Allen's initial observations. All of Dr. Huang's[4] cases were male, only 1 had a family history, and all developed paralysis following eating and then a period of sleep. Interestingly, 5 of the 12 patients had imbibed specially prepared wine or Ta-chu wine before sleep, and later awoke with paralysis.[4]

Dr. Huang[4] noticed a striking similarity between Pa Ping and a recently described disease, familial periodic paralysis (FPP), a progressive ascending paralysis with intact sensation and pain. Pa Ping was similar to FPP in that patients often experienced paralysis after meals and sleep, with a rapid onset and reversal of paralysis.[1,4] In 1937, Aitken et al.[5] concluded that FPP was likely due to low serum potassium, which was an observation made possible by the advent of serum potassium panels in 1921.[6] This theory of an underlying hypokalemia causing paralysis was bolstered by the successful treatment of FPP with potassium citrate.[5] Dr. Huang,[4] quoting the recent report by Aitken et al, used the connection between FPP and Pa Ping to suggest potassium as a possible treatment for Pa Ping. Although Dr. Huang[4] was not able to definitively rule out FPP, he surmised that due to the lack of a family history of paralysis in 11/12 of his patients, lack of thyroid problems, and the epidemic nature of Pa Ping in salt-producing areas, that this "certainly speaks for a kind of chemical poisoning probably associated with the use of salt."

According to a Chinese colleague of Dr. Huang's: "by noting the similarity between Pa Ping and FPP,

Dr. Huang treated the last four [Pa Ping patients] with potassium iodide and potassium citrate, respectively" (Yoang D, personal communication, 2009; translated from Chinese by Jing Cheng). Of the 2 patients admitted to Chengtu General Hospital who were treated with potassium citrate, the flaccid paralysis abated within a day, although this was not the case with the 2 cases treated with potassium iodide[4] (Yoang D, personal communication, 2009; translated from Chinese by Jing Cheng). This led Dr. Huang to the conclusion that Pa Ping resulted from a disturbed potassium ion imbalance[4] (Yoang D, personal communication, 2009; translated from Chinese by Jing Cheng). Modern-day colleagues of Dr. Huang further assert that "Dr. Huang suggested that a metal associated with the use of salt might disturb the potassium metabolism and consequently cause Pa Ping" (Yoang D, personal communication, 2009; translated from Chinese by Jing Cheng). Regardless, the reason behind this potassium imbalance and subsequent paralysis was yet to be described.

Although Dr. Huang had correctly noticed the underlying potassium depletion common to patients with Pa Ping, it was not until the observations of Dr. Zhe Tung and Dr. K.T. Du of patients with Pa Ping that the root cause of the syndrome was discovered.[3,7,8] One Saturday night, students at Ipin Middle School had soup at a party, and then had symptoms of nausea, vomiting, diarrhea, weakness in muscle strength, paralysis of the extremities, and difficulty breathing in severe cases.[7,8] Dr. Zhe Tung, a doctor and professor at National Tung Chi University, was the first to review this case of mass illness and he noticed that some symptoms were similar to Pa Ping.[7,8] Of interest, Dr. Tung also noticed that the severity of the symptoms correlated with the amount of soup that had been eaten and he had the leftover soup collected for further study.[8] His colleague Dr. K.T. Du, who was a professor of microbiology at the university, and his assistant Dr. Dung analyzed the soup brought in from the group of students at Ipin Middle School.[7] Along with Dr. Dung, Dr. Du found that the meal contained "barium in concentrations as high as 25.67% . . . in salt ingested by cases suffering from Pa Ping."[1,3,7,9] Further work by Drs. Du and Dung revealed that these concentrations of barium salt were indeed toxic to laboratory animals.[1,3]

As most cases of Pa Ping were isolated occurrences, it was a stroke of luck that Dr. Tung and Dr. Du were able to obtain "samples for analysis of all the food eaten by a group of similarly poisoned cases."[1] Barium toxicity therefore emerged as the leading theory underpinning Pa Ping. Using the work of Du and Dung, researchers D.Y. Ku, C.K. Yen, and C.C. Li[10] attempted to establish a solid link between Pa Ping and barium toxicity. Ku et al.[10] confirmed the hypothesis by administering a 10% aqueous barium chloride solution to both dogs and rabbits, which recapitulated the human syndrome, although the team did not measure serum potassium or correlate hypokalemia to barium toxicity. These experimental results clinched barium toxicity as the primary cause of Pa Ping,[1,2,5,7,8,10,11] and finally the mystery was solved.

DISCUSSION It is interesting to note the similarities between the paralysis associated with Pa Ping and that of the classic Landry-Guillain-Barré syndrome, also an ascending paralysis. In 1916, French neurologists Guillain, Barré, and Strohl described a condition in which patients with acute paralysis (previously remarked upon by Landry in 1859) and areflexia spontaneously recovered; this constellation of symptoms is now referred to as Guillain-Barré syndrome (GBS).[12] Classically the syndrome is postinfectious and has been distinguished from other disorders by the hallmarks of rapidly progressive ascending weakness of the muscles and hyporeflexia/areflexia.[12]

Pa Ping is distinguished by a rapid onset, often within hours of a meal and a period of sleep, although the course varies greatly among individuals.[1,4] Similar to GBS, cases of Pa Ping paralysis were found to "[occur] with alarming suddenness . . . from below upward,"[1] although paralysis was asymmetric at times, differing from classic GBS. In Huang's[4] report of 12 patients with Pa Ping, muscle aching was noted up to 2 weeks and gastrointestinal distress up to 12 hours before a paralytic attack[4]; hemiparesis to quadriparesis could then follow within as little as 6 hours and generally abated no longer than 3 days later if the patient recovered. Mortality was estimated to be between 5% and 10%.[3] In contrast, GBS has been reported to reach a nadir in 9.7 ($\pm$6.9) days,[13] with the mean onset of weakness in 1 study reported at 6.1 days.[14] Recovery is longer in classic GBS cases, often with residual symptoms, unlike in Pa Ping, which returns the recovered patient to full baseline functioning.

In both Pa Ping and GBS, cognition is preserved and weakness of the respiratory muscles ultimately leads to death as a potential endpoint. Interestingly, acute motor axonal neuropathy (AMAN), a form of GBS limited to motor pathology, is strikingly similar to Pa Ping and was first localized to China.[15] While there is a wide age range in Pa Ping, AMAN was mostly limited to children and young adults.[15,16] Unlike in classic GBS, AMAN has a more rapid onset, reported as soon as within 1 day.[16] A similar variant

of GBS without sensory loss, but not limited to younger age groups, reported a mean onset of weakness in 3.9 days and a nadir at 6.3 days.[14] There is also a reported 10%–30% prevalence of diarrhea with AMAN.[16] As in Pa Ping, the pure motor paralysis in AMAN is ascending and flaccid with areflexia and retains normal sensory reactions and sensations of pain and touch.[1,4,16] Ultimately respiratory assistance is required in 30% of AMAN cases.[16]

The reasons behind the increasing number of Pa Ping cases in the years following 1932 remain unknown, although it was speculated that "cases had occurred for many years . . . but not much attention had been paid to it until the 1930s"[7-9] (Yoang D, personal communication, 2009; translated from Chinese by Jing Cheng). One possible reason for the cases becoming known was the rising amount of trust among the native Chinese residents for Western medical missionaries and hospitals (Donaghy P, personal communication, 2009). Another potential explanation was that Wutungchiao, always a major contributor to salt production in Szechuan, had "an old and crude [salt] production system, the salt from Wutungchiao contained metals . . . and salt from some . . . [was] barium chloride."[9] Regardless of the reasons why Pa Ping cases increased, this fundamental discovery stimulated further interest into barium toxicity, and subsequently led to the development of a barium-induced mammalian skeletal muscle paralysis (in the 1970s and 1980s), which allowed for a laboratory model for FPP research.[17-19]

DISCLOSURE

L.N. Bowen reports no disclosures. Dr. Subramony has received funding for travel from and served on a speakers' bureau for Athena Diagnostics, Inc.; and has received research support from the NIH (NINDS 1RC1NS068897-01 [Co-I]) and from the National Ataxia Foundation. Dr. Cheng reports no disclosures. Dr. Wu serves as a consultant for Bioness and receives research support from the NIH (NIMH R34 MH080764 [Co-I], NINDS 1R01AR055899 [Co-I], and NINDS R01 NS050506 [Co-I]), the US Department of Veterans Affairs (VA248P0926 [PI]), and the US Army, Department of Defense (W81XWH-06-1-0564, [Co-I]). Dr. Okun serves on scientific advisory boards for the Dystonia Medical Research Foundation and the National Parkinson Foundation; has received funding for travel and speaker honoraria from Medtronic, Inc.; has served/serves on the editorial boards of *Neurology*® and *Parkinsonism and Related Disorders*; is a founder of the COMPRESS software used for deep brain stimulation (DBS) screening and has filed patents regarding double lead DBS, DBS targeting, and COMPRESS; receives royalties from the publication of *Ultimate Neurology Review* (DEMOS, 2007); serves as Medical Director of the National Parkinson Foundation and as a member of the Ask the Expert Forum; and has received research support from Medtronic, Inc. (devices and fellowship grants), the NIH, the University of Florida Foundation, the Parkinson Alliance, the Michael J. Fox Foundation, and the National Parkinson Foundation.

Received November 13, 2009. Accepted in final form February 3, 2010.

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