

# Hirschsprung disease in the U.S. Associated Pacific Islands: more common than expected

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## Abstract

**Introduction:** Tripler Army Medical Center (TAMC) in Honolulu, Hawaii, is uniquely situated to serve patients from the United States Associated Pacific Islands (USAPIs) through the congressionally funded Pacific Island Health Care Project (PIHCP). Because of time differences and distance, a web-based store-and-forward consultation and referral network was established using the internet to more efficiently and economically facilitate patient care. Using both electronic and hard copy records, we sought to establish the incidence of Hirschsprung Disease (HD) in children from the USAPI and contrast it to that of the developed world.

**Methods:** PIHCP website records as well as all the inpatient and outpatient medical records of patients referred to TAMC for treatment of HD from 1994 to 2002 were reviewed. A diagnosis of HD was confirmed in all cases with full thickness biopsy. Incidence figures for HD are based on this review and on the birth rates for these islands from the International Data Base of the US Bureau of the Census.

**Results:** There were 14 cases of short-segment HD referred over a nine year study period. Nine patients came from the Federated States of Micronesia (FSM) with an average annual incidence of 1:3190, which is 1.5 to 2 times the reported incidence in Western nations. Remarkably, seven of these nine were from Pohnpei State, capital of the FSM (annual incidence of 1:1370 or 3-5 times that in the West). Three patients came from the Republic of the Marshall Islands (RMI), and two came from American Samoa (AS). There were no reported consanguineous marriages, associated syndromes, or complications of surgery.

**Conclusion:** HD was found to be up to 2-3 times more common among people from the FSM than has been reported in the developed world. Given the limitations of providing care and obtaining data from all the USAPIs with a population that is spread over a massive expanse of ocean larger than the continental United States, this incidence is likely an underestimation of HD among Pacific Islanders. A secure web-based referral network developed in 1998 has been invaluable in collecting epidemiologic data from these islands as well as in providing health care workers in the USAPI with an efficient and inexpensive means to seek consultation from specialists and sub-specialists at a major tertiary care medical facility.

## Introduction

Hirschsprung disease (HD), a common cause of lower intestinal obstruction in the neonate, results from a failure in the cephalo-caudal migration of neuroblast cells in the alimentary canal between the 5<sup>th</sup> and 12<sup>th</sup> weeks of gestation<sup>1</sup>. The population incidence of HD in the United States and Europe ranges from 1:5000 to 1:7000 live births with a male to female predisposition of approximately 4:1<sup>2-4</sup>. There are no such data available on populations from the Pacific; Micronesia, Polynesia, or Melanesia.

Since Tripler Army Medical Center (TAMC) in Honolulu, Hawaii, opened in 1948 it has provided tertiary medical care to the medically under-served populations of the United States Associated Pacific Islands (USAPIs) (Figure 1). In 1989 special congressional funding was obtained to care for Pacific Islanders under the Pacific Island Health Care Project (PIHCP)<sup>5</sup>. The PIHCP provides care for the underserved indigenous peoples of the Pacific Basin and supplies a wealth of teaching material for the physicians in training at TAMC. The USAPIs, formerly the Trust Territories of the United States, include six jurisdictions spread over a massive expanse of ocean. Three of the island nations are freely associated, independent states: The Republic of the Marshall Islands (RMI), the Federated States of Micronesia (FSM) (including the states of Chuuk, Kosrae, Pohnpei, and Yap), and the Republic of Palau (ROP). The other three jurisdictions are United States Flag Territories: Guam, the Commonwealth of the Northern Mariana Islands (CNMI), and American Samoa (AS). All with the exception of AS are located in the middle and western Pacific in what is termed Micronesia. Each of those jurisdictions is made up of numerous islands extending over more than 1,000,000 square miles of ocean<sup>6</sup>. Medical care on these islands is provided by a variety of practitioners including medical officers, expatriate physicians, nurses, health workers, midwives, health assistants, and traditional healers. With the advances of the Internet and electronic mail, a secure web-based, store-and-forward network was developed and deployed in 1998 to provide a more efficient consultation and referral service for health

care workers in the Pacific Basin attempting to access the PIHCP at TAMC. There are 11 sites throughout these islands that now have this capability. Each is located in a central medical facility (state hospital or ministry of health) that serves as a referral center. All of the cases that have been referred (now numbering nearly 2400) are archived for easy access.

Here we describe our observation of the unexpectedly high incidence of HD in this population by accessing the PIHCP data bank, and discuss the improvements in managing patients referred with this difficult condition using this web-based referral and consultation system.

## Methods

We reviewed all the cases of suspected HD referred from the USAPIs to TAMC from 1994-2002. A multi-disciplinary team of consultants including the medical director, pediatric gastroenterologists, pediatric surgeons, and pediatric radiologists reviewed each case. Those patients who had signs and symptoms consistent with HD were accepted under the program and provided round trip airfare from their home jurisdiction to TAMC and back. Definitive care was provided at no cost to the patient or the country of origin. Upon arrival, patients were admitted to TAMC for evaluation and treatment. HD was diagnosed histologically prior to or at the time of definitive surgery. The medical records were reviewed for demographic data, clinical presentation, past medical history, family history, extent of aganglionosis, treatment, complications,

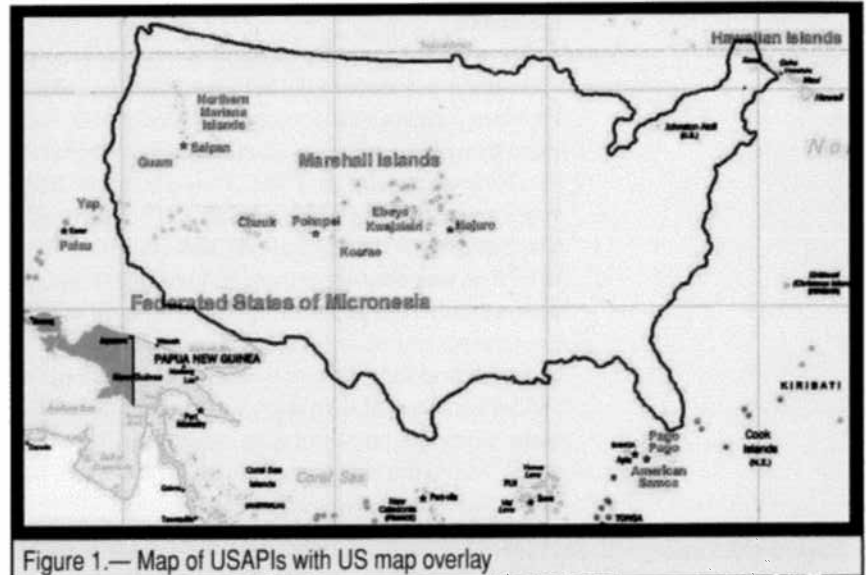


Figure 1.— Map of USAPIs with US map overlay

and any associated conditions. Birth rates on each island nation in the USAPIs were obtained using the International Data Base of the United States Bureau of the Census<sup>7</sup>. The Human Use Committee at TAMC approved the study protocol. Investigators adhered to the policies for protection of human subjects as prescribed in 45 CFR 46. All statistical comparisons were made using Fisher's exact test.

Table 1.— Incidence of Hirschsprung Disease in USAPIs (1994-2002)

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	Average Annual Incidence 94-02
Number of HD cases in FSM*	1	1	3	0	1	1	2	0	0	
Births / year in FSM	3480	3413	3343	3261	3175	3097	3060	3001	2940	
Incidence in FSM	1:3480	1:3413	1:1114	0	1:3175	1:3097	1:1530	0	0	1:3190
Number of HD cases in RMI	0	0	1	0	0	0	0	1	1	
Births / year in RMI	1663	1772	1802	1926	1985	1956	1857	1868	1903	
Incidence in RMI	0	0	1:1802	0	0	0	0	1:1868	1:1903	1:5577
Number of HD cases in AS	0	0	0	0	0	1	0	0	1	
Births / year in AS	1808	1616	1591	1569	1544	1522	1730	1651	1576	
Incidence in AS	0	0	0	0	0	1:1522	0	0	1:1576	1:7304

\*FSM, Federated States of Micronesia; RMI, Republic of the Marshall Islands; AS, American Samoa

## Results

There were 19 patients referred to TAMC via the PIHCP for suspected HD between 1994 and 2002. Fourteen patients had histologically proven HD. They came from three of the six island nations of the USA-PIs. Nine were from the FSM, 3 were from the RMI, and 2 were from AS. Five patients did not have HD. One patient, who was from RMI, had a barium enema (BE) that was consistent with HD but histologically was normal. That patient responded to stool softeners. One patient, who was from Pohnpei in the FSM, had a stenotic anus. That patient underwent anoplasty and was doing well with daily soft bowel movements at the 12 month post operative clinic visit. Three patients, who were also from Pohnpei in the FSM, had constipation that easily responded to stool softeners. There were no cases of HD recorded at TAMC from military dependents for the study period.

The incidence of HD varied greatly among the island nations (Table 1). The FSM, with an average annual number of births per year of 3190, demonstrated a yearly incidence as high as 1:1114, with an average annual incidence of 1:3190. There were no cases from the FSM referred in 1997, but that was preceded by the highest incidence recorded in 1996 of 1:1114. There was one case referred for each year in 2001 and 2002 (one from Pohnpei and one from Chuuk). For unclear reasons these patients did not travel to TAMC although, it is likely that they were sent to the Philippines. Based on the descriptions on the PIHCP web-site, including BE films, the most likely diagnosis in both those cases was HD. Remarkably, seven of the nine histologically diagnosed cases from the FSM were from the state of Pohnpei, the capital of FSM. Since birth rate figures are not available for individual states throughout the FSM, we can only extrapolate an estimate of the incidence of HD for Pohnpei State. Since approximately 1/3 of the population of the FSM lives in Pohnpei State, and assuming fairly uniform birth rates throughout the FSM, we estimate that the average annual incidence of HD for Pohnpei was as high as 1:1367 during the period 1994-2002. The RMI and AS referred fewer cases. With only 3 cases from 1994-2002 (Table 1), the RMI had an average annual incidence of 1:5577 births. Similarly, with only 2 cases in the same period, AS had an average annual incidence of 1:7304 births. When comparing the incidence rates between island nations, the FSM had a significantly higher incidence ( $p=0.0377$ ) when compared to the combined HD incidence in AS and the RMI.

During the study period there were 9 HD cases per 28,770 births in the FSM (7 cases/9,590 births in Pohnpei State); 3 cases per 16,732 births in the RMI; and 2 cases per 14,607 births in AS. During the same timeframe 25,016 infants were born at TAMC and no cases of HD were identified. As can be seen in Table

2, the marked increased incidence of HD in patients from Pohnpei is highly significant.

Ten patients (71%) presented in the first 2 weeks of life and were diagnosed by one month of age. Three patients (21%) presented within the first year of life, and only one patient (7%) presented late at 2 years of age. The presenting symptoms were typical of HD, with no stool in the first 24 hours of life in 9 patients (64%), constipation in 3 patients (21%), and a distended abdomen in all patients. Other presenting symptoms included vomiting and cachexia in one of the patients who presented late. There was one patient who had a meconium plug at birth treated with gastrografin enema by his primary care physician. He was discharged from the hospital and lost to follow up only to present at 3 months of life with a perforated sigmoid colon and peritonitis. There were no patients with enterocolitis on presentation.

Aganglionosis was limited to the rectum or rectosigmoid colon in all cases. All patients underwent surgical intervention with initial diverting colostomy followed by a rectosigmoidectomy (Swenson procedure) or an endorectal pull-through (Soave procedure). Few patients had minor postoperative complications; one patient had colostomy prolapse, and another had a wound infection. A third patient developed vomiting and constipation 4 months post-operatively. At surgery multiple adhesions were identified and released then the patient recovered uneventfully.

After definitive treatment, the patients were returned home, most within 1 month of surgery. Follow-up was provided locally by their primary provider. Limited resources and difficult access may have precluded detailed long term follow-up in some cases. Considerable experience with the program, however, suggests that, if there were problems, the medical director would be notified, and, if necessary, arrangements would be made to bring the patient back to TAMC for complications. One patient did return for incontinence 16 months post-operatively. Simple dilations were all that was necessary for this patient.

The male to female ratio was 3.7:1 for the total number of cases, which is similar to the 4:1 ratio observed in western societies. FSM had a lower male predominance of 2:1. There were no associated anomalies or congenital syndromes found in any patient. Interestingly, two of the three patients referred from the RMI were paternal cousins. That same family had another child diagnosed with HD prior to this study period. There were no other patients with a family history of HD and no history of consanguinity.

## Discussion

We found that the incidence of HD in the FSM was 2-3 times greater than that reported in the US or Europe. Out of the group of island nations within the PIHCP, the FSM also had a statistically significant

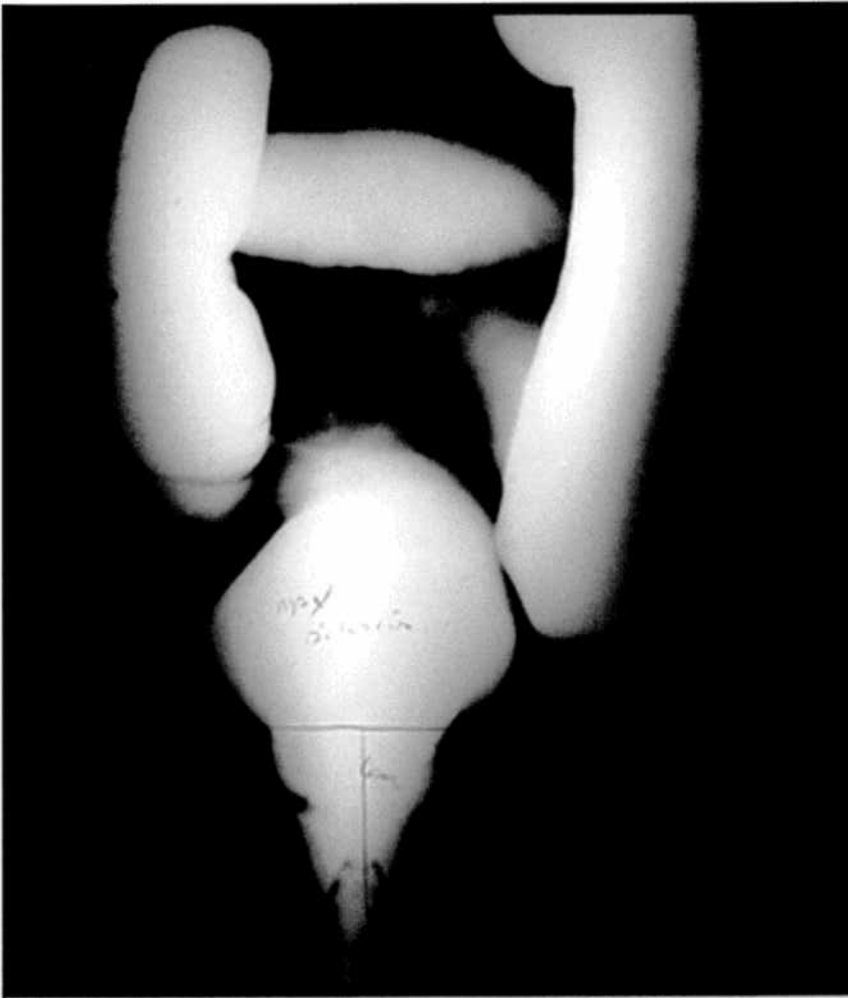


Figure 2.— Barium Enema from PIHCP web site demonstrating transition zone. This is an example of the quality of film that is transmitted by the web-site.

Table 2.— Hirschsprung Disease Cases/Total Births (1994-2002)

Jurisdiction	Cases	Births	p value*
Pohnpei State, FSM**	7	9,590	
RMI	3	16,732	0.043
AS	2	14,607	0.034
TAMC	0	25,016	0.000125

\*As compared to Pohnpei State

\*\*FSM, Federated States of Micronesia; RMI, Republic of the Marshall Islands; AS, American Samoa; TAMC, Tripler Army Medical Center

higher incidence than the other referring island nations. That is despite having very similar migration histories and Western influences. Among these, the state of Pohnpei had by far the most cases with an estimated average annual incidence of 1:1367. In the years 2001-2002 there were another two patients with probable HD referred from FSM, (one from Chuuk and one from Pohnpei) yet for unclear reasons they never traveled to TAMC. The higher incidence of HD in Pohnpei, which approaches an 8-fold increase over the other jurisdictions and TAMC, cannot be explained by greater ease of referral because, although Pohnpei is the capital of the FSM, all states in the FSM have their own PIHCP network facilities. Some of the outer islands of Pohnpei are hundreds of miles from the capital.

There appears to be no ready explanation as to the increased frequency of HD in this population. After an extensive search of the literature through two databases

we have found very little published on the incidence of HD in Asian or Pacific nations. According to Ikeda and Goto, the incidence of HD in Japan is 1:1600<sup>8</sup>, which might suggest a possible genetic influence in the Pacific Islands from Japan. Epidemiologic studies have demonstrated a sex ratio for HD in Asia that, like that seen in our study population, is similar to the US and Europe<sup>9-10</sup>. On the other hand, anthropologic data suggests that the heritage of people from the USPAI is quite distinct from Asians in Japan and China since people in the Pacific Islands appear to have migrated from Southeast Asia at least 5000 years ago.

Extent of disease was fairly uniform in our study population. All the patients in this study had either short segment (involving only anus and rectum) or classic type (involving anus, rectum, and a portion of sigmoid colon) HD as defined by Spouge in 1985<sup>1</sup>. Most of the patients presented in the neonatal period. Both of the characteristics of HD in the Pacific Island population would appear to render protection against enterocolitis, as enterocolitis is more common when HD is diagnosed beyond the first month of life and when it involves long segments of bowel<sup>11</sup>. Hence, in this study, we observed no episodes of enterocolitis. Nevertheless we may not be seeing the more severe cases with the morbidity and mortality of enterocolitis because of the difficulty in access to care for many of these patients. Certainly those infants with multiple associated anomalies or those from distant islands or atolls would not survive long enough to reach definitive medical care.

There were no reports of consanguineous marriages among the patients' parents. Consanguineous unions are culturally unacceptable in Micronesia and Polynesia. These populations keep careful genealogy records to prevent consanguinity, and most have converted to Christianity and are further discouraged from such practices<sup>12</sup>. Therefore, theories of chromosomal abnormalities from consanguineous marriages are not supported by cultural practices.

Down syndrome, which occurs in 3% to 16% of HD patients, is the most common associated chromosomal abnormality<sup>13-14</sup>. Despite the high incidence of HD reported in this study, there were no associated anomalies or syndromes observed, and no patient with Down syndrome has ever been referred in the history of the PIHCP.

Chromosomal analysis of our patients was not possible due to the inherent limitations of a retrospective case review. We only had one example of a familial association in which HD was seen in two paternal first cousins. Interestingly this family produced 2 of the 3 cases seen in the RMI. Studies of complex segregation analysis have demonstrated that the inheritance pattern in cases of HD extending proximal to the sigmoid colon is compatible with a dominant gene with incomplete penetrance, whereas cases in

which aganglionosis extends no further than the sigmoid colon can either be due to a recessive gene with very low penetrance or be due to multifactorial causes<sup>15</sup>. The high frequency of HD that we have seen in Pohnpei raises the question that, at least in this population, HD confined to the sigmoid colon is either due to a dominant gene with incomplete penetrance or a strong environmental trigger. We plan in the future to conduct genetic testing looking particularly at previously identified genes associated with HD such as the RET proto-oncogene<sup>13</sup>.

Archaeological data suggest that the USAPIs might have been inhabited as early as 3000 B.C. Western contact occurred in 1521 when Magellan landed in the Marianas. Since then the islands have been occupied successively by the Spanish, Germans, Japanese, and, since World War II, Americans<sup>16-17</sup>. The Pacific Islands are divided into Polynesia (many islands), which includes the Hawaiian Islands and AS; Micronesia (small islands) including the RMI, the FSM, the ROP, Guam and the CNMI; and Melanesia (black islands) such as Papua New Guinea and the Solomon Islands. The indigenous peoples of Micronesia are thought to have migrated from Southeast Asia.

While there are medical facilities throughout the USAPIs that have access to the PIHCP, there are many Pacific islanders who live too far away (up to hundreds of miles) to have easy access to these facilities. A patient may have to travel hundreds of miles by canoe in order to be seen by a health care worker with access to the web-based referral network. The boat trip may be delayed up to 6 months because unfavorable ocean currents prevent hazardous travel. Those families who are determined to seek medical care might have to travel for days by foot and then canoe with a very sick child who might not be able to survive the travel. That geographic barrier then acts as a filter allowing only the less complicated HD patients to be referred. Some of the inhabited islands of Micronesia are among the most remote in the world. A number are still without electricity. Therefore, our incidence data of HD in these islands is probably a gross underestimate.

Prior to the development of the web-based system, patients were referred to the PIHCP by letter, facsimile, or telephone. The problems of telephonic consultation are obvious and in the Pacific even more of a problem because the International-Date-Line and five time zones separate Hawaii from the Western Pacific. Long distance telephone service costs \$5 to \$10 per minute. Fax seemed to work somewhat more efficiently, but, before official government travel orders were issued, the patient's name, date of birth, and passport number were essential, or the patient was not allowed to travel. Now the process is streamlined greatly. The appropriate specialists and subspecialists are notified of a referral by email. They can then access the appropriate case by the secure web-based page and read the details of the case including history, physical exam, laboratory results, photographs of the patient and view radiographs (Figure 2). The consultant can then make immediate recommendations for stabilization and transport. In this way the patients are cared for more expeditiously. Despite those improvements there are still obvious difficulties in arranging travel for these patients and their parents who may be reluctant to fly thousands of miles to a completely foreign country and culture.

In conclusion, the incidence of HD is higher among certain island nations of the USAPIs than had previously been described in Western nations. This is particularly true of Pohnpei State in the FSM. We

will continue to provide definitive medical care to the underserved peoples of the USAPIs and to study disease processes such as HD unique to this population as long as we have congressional support and are able.

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