NON-PARALYTIC POLIO AND PPS

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INTRODUCTION AND HISTORY

Convincing medical professionals of the reality and appropriate treatment of post-polio syndrome was and often continues to be a long, hard, up-hill struggle. Today there is general consensus in the medical community that there are late effects arising from acute paralytic polio infections of 20 to 40 years ago. An increasing number of medical doctors no longer dismiss symptoms of fatigue, pain, and increasing weakness when presented by a person with a documented history of paralytic polio. This is so even though there is no objective test available to diagnose Post-Polio Syndrome (PPS) nor is there agreement on, or a clear understanding of, the etiology of this disease. However, people with PPS symptoms and a history of non-paralytic polio have great difficulty receiving a diagnosis of PPS.

CATEGORIES OF ACUTE POLIO AND THE DIAGNOSIS OF POST-POLIO SYNDROME

During the acute polio epidemics earlier this century the following categories were used to classify the extent and seriousness of the disease:

Sub-Clinical polio	The person is unaware of infection and gains active (sometimes lifelong) immunity to infection from that strain. Sub-clinical polio usually occurred in infants and very young children.
Abortive Poliomyelitis	In "Current Diagnosis and Treatment" a polio manual for physicians (Brainerd et al. 1968) the symptoms of abortive polio are described as: "Abortive poliomyelitis may simulate acute respiratory infection or gastroenteritis, and is usually not dangerous. The symptoms are fever, headache, vomiting, diarrhea, constipation, and sore throat."
Non-Paralytic Polio	Symptoms, quoting again from Brainerd et al. (1968), are "headache, neck, back, and extremity pain; fever, vomiting, and abdominal pain, lethargy, and irritability are present. Muscle spasm - spontaneous shortening of the muscle or hyperactive stretch reflex with limitation of extension by pain and contraction - is always present in the extensors of the neck and back, usually present in the hamstring muscles, and variably present in other muscles. Resistance to flexion of the neck is noted after a varying range of free flexion. The patient assumes the "tripod" position on sitting up, which he usually does by rolling to avoid flexing the back. Straight leg raising is less than 90

	degrees. Spasm may be observed when the patient is at rest or may be elicited by putting each muscle through the maximum range of motion. The muscles may be tender to palpation."
Paralytic Polio	The symptoms are: "Paralysis may occur at any time during the febrile period. In addition to the symptoms of non-paralytic poliomyelitis, tremors and muscle weakness appear. Paresthesias (tingling) and urinary retention are noted occasionally. Constipation and abdominal distension (ileus) are common. Paralytic poliomyelitis may be divided into two forms that may coexist: (1). Spinal poliomyelitis, with weakness of the muscles supplied by the spinal nerves and (2). Bulbar poliomyelitis, with weakness of the muscles supplied by the cranial nerves, and variable "encephalitis" symptoms. Bulbar symptoms include diplopia (uncommon), weakness of mastication, facial weakness, dysphagia, dysphonia, nasal voice, regurgitation of fluids through the nose, weakness of the sternocleidomastoid and trapezius muscles, difficulty in chewing, inability to swallow or expel saliva and respiratory tract secretions. The most life threatening aspect of bulbar poliomyelitis is respiratory involvement due to pontile (central) involvement. Paralysis of the neck flexors is manifested by "neck drop" on lifting the shoulders from the bed. "…deep tendon reflexes are diminished or lost, often asymmetrically, in areas of involvement." (Brainerd et.al., 1968).

Part of the difficulty getting a diagnosis of PPS, arises from the current practice of strictly categorizing the acute polio illness as paralytic, non-paralytic, abortive and sub-clinical. When polio was all too common, it was generally understood that there was a wide range of damage within every patient, even though the patient was assigned to a specific diagnostic category. However as time passed, much practical and unwritten knowledge was lost. One result is that the diagnostic categories of acute polio infection no longer carry the implication that polio damage occurs as a spectrum within every patient. Now a diagnosis of non-paralytic polio raises doubts in the physician's mind that the person had any neuronal damage and even doubts that the person had polio.

Common sense dictates that it was a rare case of polio that did not blend into the adjoining category to some degree. Many sub-clinical cases probably had gastrointestinal symptoms. An abortive case with fever and headache or neck ache, along with muscle spasms, would argue for at least some involvement of the neuronal system. Autopsies on people who had non-paralytic polio, but who died from other causes, show nerve damage and some degree of neuronal death consistent with paralytic polio (Howe and Bodian, 1942; reviewed by Bruno et al. 1995). From such evidence it appears reasonably certain that there was a degree of neuronal involvement in people with non-paralytic polio (Bruno et al. 1991). The damage may have been sufficient to cause weak muscles but not enough to manifest as paralysis (Sharrard, 1955).

In acute polio, the degree of nerve involvement varies within the entire nervous system. Some areas appear clinically unaffected while, in paralytic polio cases, other regions show flaccid paralysis. In abortive polio the nervous system appears undamaged at the symptomatic level. However the symptoms listed for non-paralytic polio are suggestive of neurological involvement. For nerve damage to be visible as weakness or paralysis a threshold of damage to the neuron population must be involved (Sharrard, 1955). When few neurons are damaged or destroyed, the patient presents with no specific muscle weakness or paralysis but can have undetected neuronal damage (Dalakas (a), 1995). We do not know how this will manifest in later life. There were undoubtedly mistakes in diagnosis and misdiagnosis for many patients. Many people with non-paralytic polio probably were paralytic cases with diffuse weakness that recovered quickly (Dalakas (b), 1995).

THE NON-PARALYTIC POLIO PROBLEM

Reluctance to diagnose PPS in symptomatic people with a history of non-paralytic polio has many reasons. The cause(s) of PPS is not completely understood. Often there is an assumption that neurological damage is the only cause of PPS symptoms. Physicians and clinicians may have unreasonable expectations of the diagnostic accuracy of electromyographic (EMG) studies as well as the accuracy of other tests. Little consideration is given to evidence suggesting that PPS symptoms can arise from damage to areas of the brain during the acute illness, from persistent polio virus RNA, from auto-immune problems, and from neuronal damage which wouldn't necessarily correlate with the expected electromyograph (EMG) readings.

One misplaced criterion for obtaining a diagnosis of PPS is the necessity for a documented case of paralytic polio. Ironically, the reason for this arises out of early research to study PPS. To be certain that test subjects had early polio, and not some other neurological disorder, researchers required that the subjects in the study group have a documented history of paralytic polio with residual weakness or paralysis in at least one limb. Unfortunately, these criteria have spilled over into the clinical area so that many physicians believe you cannot have PPS unless you have a confirmed diagnosis of paralytic polio, *despite the fact that systematic studies have never been done to assess PPS in non-paralytic polio populations.*

A "typical" presentation to a physician of a person with a history of non-paralytic polio and current PPS-like symptoms goes something like this. "As a child, I was very ill with a high fever and a headache. I was hospitalized for a few days (or quarantined and not hospitalized). My mother says I was never paralyzed and I was discharged from the hospital with a diagnosis of 'non-paralytic' polio. I had cramps and pains in my back and legs and I was very weak for some months afterwards but then I recovered completely and forgot all about polio. I wasn't very good at sports, but then, neither were lots of other people. About ten years ago (35 to 45 years after the acute illness), I began tripping on smooth floors and occasionally falling. Now everyday jobs like vacuuming tire me so that I have to lie down for an hour or two before I can do anything else. When I'm this tired, I can't "think", can't focus or remember words. It's difficult to put in a full day of work. My legs ache after I walk only a short distance and at night the muscles in them "jump" or twitch. My feet are always cold. I can no longer climb a flight of stairs and the weakness in my legs is frightening. I saw a neurologist who specializes in PPS and he said that he saw no evidence that I ever had polio although he did not give me a thorough examination or order any tests. He says I don't have PPS and suggested that my problems are caused by arthritis or fibromyalgia."

In one specific case of an individual earlier diagnosed with non-paralytic polio, and now complaining of new problems, the neurologist ordered two EMGs in the area the patient said was weak. According to the neurologist, both EMGs were "normal". From this he concluded that the patient did not have polio and could not have PPS. EMG tests can miss late paralytic polio if the examiner does not find the spot where denervation occurred. With non-paralytic polio EMG positive fiber groups could be difficult to find.

SYMPTOMS, EMGS AND A PPS DIAGNOSIS

Accepted symptoms of PPS include: progressive muscle weakness, fatigue and pain (see general review by Trojan and Cashman, 1997). One of the descriptive criteria today for PPS is progressive weakening in muscles unaffected by the original polio illness. Tests in people who had paralytic polio have shown that limbs, previously designated as unaffected, had some degree of damage (Halstead et al. 1995). Clearly, a person with non-paralytic polio could have had an equal amount of damage during the acute infection but would still be classified as having non-paralytic polio. It therefore is reasonable to assume that new

weakness can occur in *any* muscle of a person diagnosed with non-paralytic polio.

Electromyographic (EMG) studies will not show whether or not a person has PPS or is likely to get PPS. EMGs of paretic muscles reveal neuronal damage that occurred during the acute infection and subsequently resulted in the formation of large motor units in muscle (Dalakas (a), 1995). In a person with a history of non-paralytic polio, the presence of an abnormal EMG (one that matches the typical EMG pattern produced by polio affected muscles) is considered proof of previous paralytic polio and usually results in a diagnosis of PPS (Bromberg and Waring, 1991). However a normal EMG can not prove or disprove whether a person had sub-clinical, abortive or non-paralytic polio.

A normal EMG is an indication that the muscle or groups of *muscles which were tested* did not undergo denervation consistent with paralytic polio. However many clinicians maintain "the lack of clear evidence for previous denervation after extensive electrodiagnostic testing is a valid means for excluding the diagnosis of PPS" (Bromberg and Waring, 1991); a view supported by Gawne et al. (1995). This conclusion depends on the certainty that PPS is derived only from motor unit abnormalities and death, and no other metabolic or virological problems within intact neurons play a role - a fact which has not been established. Nonetheless, properly conducted and properly analyzed, EMG tests are valuable for ruling out other neurological conditions and may establish a history of previous *paralytic* polio in people with PPS-like symptoms. They should not be used to 'prove the negative' (an impossible task), that the person does not have a post viral syndrome due to poliomyelitis.

FATIGUE AND NON-PARALYTIC POLIO

Severe, debilitating fatigue is another common denominator of PPS. Many people describe two types of fatigue: one relating to muscles and another relating to cognition and alertness (colloquially called 'brain fatigue'). It is not known if there are two types of fatigue nor if fatigue is generated by more than one mechanism. What is known is that severe fatigue that responds to rest is found in survivors of both non-paralytic and paralytic polio and is a hallmark symptom of PPS (Bruno et al., 1991 and 1995).

A commonly supported idea is that muscle fatigue results from demands on muscles innervated by neurons damaged in the acute illness or demands on muscles innervated by relatively fragile neuronal "sprouts" which developed to replace destroyed neurons (reviewed by Dalakas, (a,b) 1995, Trojan and Cashman, 1997). There is a hypothesis that 'brain fatigue' results from damage to a particular area of the brain involved in maintaining mental alertness, the reticular activating system (Bruno et al. 1991 and 1995). Extensive, post-mortem examinations by Bodian (1949) and others (see Bruno et al. 1995) indicate that some degree of damage to the brain occurred in all polio infections regardless of severity. The 30 to 40 year interval between infection and onset of fatigue could be explained by a combination of damage plus atrophy that occurs with normal aging. However, a counter argument suggests that 'brain fatigue' is not a separate entity but a part of the generalized fatigue resulting from overuse of muscles during everyday living. There also is the possibility that 'brain fatigue' is caused by a combination of the above factors and possibly others.

WHAT PERCENTAGE OF NON-PARALYTIC CASES WILL DEVELOP PPS?

Estimates of the percentage of people who had acute, paralytic polio and now have PPS range from 25% to 70% or higher and there are predictions that eventually all people who had paralytic polio will have PPS to some degree or other. Statistically there is a minimum of 10 non-paralytic polio cases for every documented paralytic case. What percent of people who had non-paralytic, or possibly even abortive polio, will develop PPS? PPS support groups report that between 1 and 10% of their members had non-paralytic polio as children and now have fatigue, new muscle weakness and pain (Falconer, personal

communication). However many non-paralytic cases (and even cases with mild paralysis) were never seen by a doctor and may not know that they had polio. They would not suspect that new muscle weakness, fatigue and pain were due to PPS and would have no reason to join a PPS support group.

A 1951 study of acute polio infection in twins (Herndon and Jennings) and a subsequent follow-up study by Nee et al. (1995) showed that 71% of the twins diagnosed with paralytic polio had PPS symptoms. Interestingly, 42% of twins who had not been diagnosed with paralytic polio also developed PPS-like symptoms approximately 38 years after their affected twin was diagnosed with polio. Herndon and Jennings indicate that most "unaffected" twins actually had sub-clinical or non-paralytic polio. Based on this study it seems that nearly half of the people who had non-paralytic polio may develop PPS.

TESTS TO DETERMINE PRIOR POLIO INFECTION

Right now there are no tests that prove a person has PPS. However tests which indicate that a person definitely had polio are useful in obtaining a PPS diagnosis. There are tests to measure IgG antibody levels to polio virus strains 1, 2 and 3, as well as antibodies to other viruses including non-polio enteroviruses (Leon-Monzon and Dalakas, 1995). Everyone who was immunized will have some level of antibodies. However people who had an acute polio infection should have higher antibody levels to the infecting strain of the polio virus. Significantly higher levels document previous polio although antibody levels decrease with time, and low levels of antibody to polio virus do not rule out a previous polio infection.

By testing antibodies, a correlation was found between increased levels of a particular kind of antibody, designated as IgM, and people who had acute polio and now have PPS symptoms (Illa et al. 1995, Leon-Monzon and Dalakas, 1955). IgM antibodies are produced as a "first response" to an infection and may indicate new antibody response to a particular condition, raising the possibility of testing IgM levels as a PPS indicator (Sharief et al. 1991, Dalakas (a), 1995). The presence of lymphocytes in muscle biopsy along with elevated levels of antibody to polio virus also is consistent with this theory (Dalakas et al, 1984).

A more sensitive test, using the polymerase chain reaction (PCR) technique on cerebrospinal fluid (CSF) obtained from a spinal tap, showed the presence of RNA, derived from polio virus RNA in people with PPS but not in CSF from people without a history of polio (Leparc-Goffart et al. 1996). While this test demonstrates a history of polio infection, the necessity for a spinal tap precludes use as a general test for PPS. Moreover, using this test to diagnose PPS must be approached with caution. Muir et al. (1995) found evidence of enteroviruses closely resembling Coxsackie B4 in CSF samples from people with PPS-like symptoms but found no correlation of polio virus RNA and post-polio symptoms (Muir et al. 1996).

POLIO VIRUS, VIRUS RNA FRAGMENTS AND PPS

Polio virus is a "lytic" enterovirus that kills the cells it infects, and researchers long believed no virus existed anywhere in the body for more than a short time after the acute infection. However mutations to the polio virus occur readily during infections (reviewed by Blondel et al. 1998). One mutated form of polio virus can persist indefinitely in tissue culture of human neuronal origin (Colbere-Garapin et al. 1989). These infected neuroblastoma cells continuously produce polio virus into the surrounding medium and are not killed by the infecting virus. Another polio virus, with only two mutations in the virus capsid protein, persistently infects cell cultures derived from human fetal brain cells (Pavio et al. 1996). This evidence suggests that the positive PCR samples, in CSF of people with PPS symptoms and described above, represent either a persistent infection in the nervous system or the continuing presence of pieces of RNA derived from polio virus. In either case it is possible that some PPS symptoms are due to the body

mounting an immune reaction to the presence of the polio RNA. This theory is supported by autopsy findings of chronic inflammation with the presence of lymphocytes in the spinal cord of a PPS patient (Miller, 1995).

There is a view that PPS patients could be divided into two groups (Hollman, 1986). "The first group has muscle deterioration from the early disease. The second group has problems in new muscle groups or those thought to be recovered from the disease. Problems in the second group are thought to have a cause other than simple aging, possibly autoimmune (in origin)". It is clear that an RNA explanation for the late problems of non-paralytic polio patients could fit into Holman's second group.

NON-PARALYTIC POLIO - CAUSED BY POLIO VIRUS OR BY A DIFFERENT ENTEROVIRAL INFECTION?

During polio epidemics it was known that "non-paralytic polio symptoms" were not always due to polio virus. Non-polio enteroviral infections, among others, produced the same symptoms. However, if a patient with nonparalytic symptoms had a sibling or other close contact with a paralytic polio case, then the infectious agent usually was polio virus.

Many non-paralytic cases were due to infection with a less neurovirulent variant of polio virus. Sabin and Steigman (1949) studied an epidemic of "summer grippe" in an attempt to isolate a variant of the polio with lower neurovirulence to make a vaccine. Of their "summer grippe" patients, 50% had a non-paralytic polio caused by a less virulent strain of polio, 20% developed paralytic polio, and the infectious agent of the remaining 30% of patients was not established.

To monitor the strains of polio virus causing a Washington, D.C. epidemic, specimens were obtained from 63 paralytic cases, 87 non-paralytic cases with positive spinal taps and 5 non-paralytic cases with negative spinal taps (Shelokov et al. 1955). Of the paralytic cases, 64% had polio virus strain 1 (pv1), 33% had pv2 and 3% had pv3. Of the non-paralytic cases, 25% had pv1, 10% had pv2 and 4% had pv3 while 61% were untypable and presumably had an infection other than polio virus. Interestingly, of the 5 cases with normal spinal taps, one had pv1, one had pv2 and the other 3 were untypable.

The percentage of non-paralytic cases caused by polio virus or another virus varied enormously. During a polio epidemic in Hawaii in 1957, specimens were obtained from 38 people with paralytic polio and from 39 cases of non-paralytic polio. "Of the 38 cases of paralytic disease, type 1 polio virus was implicated in 33, Coxsackie B2 virus was isolated…in 2 and no diagnosis was established in 3. Of the 39 cases of nonparalytic poliomyelitis, only 4 were related to type 1 polio virus. There were 16 cases of echovirus 9, 7 cases of Coxsackie A9, and 4 to 5 other enteroviruses." (Johnson 1995).

Depending upon the epidemic, 70%, 39% or 10% of non-paralytic cases were caused by infection with polio virus. It is not prudent, therefore, for an examining physician automatically to conclude that a patient with a history of non-paralytic polio actually did not have polio.

PPS-LIKE SYMPTOMS AND ENTEROVIRAL INFECTIONS

Polio virus is one of more than 70 enteroviruses. A number of enteroviruses (Coxsackie A9 [Gromeier et al. 1997], enterovirus 70 [Gromeier et al. 1997], enterovirus 71 [Melnick, 1984]), as well as a flavivirus, Japanese encephalitis virus [Solomon et al. 1998], among others, can cause polio-like paralysis. These non-polio enteroviral infections may cause PPS-like symptoms as well. Coxsackie virus RNA has been isolated from people with PPS symptoms (Muir et al. 1995), although it is not known if this is a common event. If PPS arises from neuronal damage, then intuitively, enteroviruses causing symptoms that are

clinically identical to polio could cause similar neurological damage during the acute illness which in turn would give rise to PPS-like symptoms in later life. If PPS arises from an immune response to continuous presence of viral RNA, then finding enteroviral RNA (other than polio) in people with PPS symptoms, as was shown by several researchers, also indicates PPS-like symptoms could occur from non-polio virus infections.

NON-PARALYTIC POLIO AND PPS

With respect to a diagnosis of PPS for people with a history of non-paralytic polio and PPS symptoms, there are at least four separate possibilities:

1. The person had non-paralytic (or abortive) polio. At the time of the acute illness there was no obvious damage to the nervous system although unobserved damage was likely. There are no established figures for the minimum amount of neuronal damage which can result in PPS symptoms. Exclusion of a diagnosis of PPS on the basis of a history of non-paralytic polio is not merited.
2. The person actually had paralytic polio but was misdiagnosed. Symptoms of paralysis and/or weakness were missed or the symptoms manifested only for a short time. The patient recovered (apparently) fully within a matter of weeks. This type of polio often was labeled as "non-paralytic". PPS will occur with the same frequency as in paralytic polio cases. Diagnosis of PPS on the same basis as for a patient with a history of paralytic polio is merited.
3. The person did not have polio but had another disease with clinical symptoms similar or identical to polio and currently presents with PPS symptoms. Some evidence supports the hypothesis that non-polio enteroviruses can have late, post-viral effects. If these people have post-viral symptoms identical to PPS, require the same management and have the same prognosis, should they be included under the PPS heading?
4. The person presents with PPS-like symptoms but the cause is not post-viral in origin. More medical examinations are required for the patient and a diagnosis of PPS is not merited.

It is vitally important that people with PPS-like symptoms see a physician since other neurological diseases can have similar symptoms. However, when these diseases have been ruled out then the doctor should consider PPS, especially if the person has an oral history of having had polio. Moreover a documented history of paralytic polio should not be the exclusive criterion obtaining a diagnosis of PPS.

CONCLUSIONS

A history, either oral or documented, of non-paralytic polio is not sufficient reason, by itself, to exclude a diagnosis of PPS. PPS symptoms may have both physical and molecular origins including neuronal damage, persistent viral RNA and immune response. In the case of non-paralytic polio, some amount of damage to neurons almost certainly took place and this may be sufficient to cause PPS symptoms of new muscle weakness, fatigue and pain. If the presence of persistent viral RNA and/or the immune response or other molecular events can precipitate PPS, then even the absence of neuronal damage does not preclude developing PPS. A history of any kind of polio indicates the disease was severe enough to cause damage. However with only 2 years to the 21st Century we still have no objective test for Post Polio Syndrome. Considering the number of people affected and the morbidity and cost to our population, the cause of PPS should be a priority for clinical research in the next few years.

Reprint/Publication Requests

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Top of Article

Content Catalogue | Source Catalogue

Reception | Library | Networking | Directory | What's New?

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