Clinical Assessment of Self-Reported Acute Flaccid Paralysis in a Population-Based Setting in Guatemala

James J. Sejvar,* Kim A. Lindblade, Wences Arvelo, Norma Padilla, Kimberly Pringle, Emily Zielinski-Gutierrez, Eileen Farnon, Lawrence B. Schonberger, and Erica Dueger

Division of Viral and Rickettsial Diseases, National Center for Zoonotic and Vector-Borne Diseases (NCZVED), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; Division of Vector-Borne Infectious Diseases, NCZVED, CDC, Atlanta, Georgia; Division of Emerging Infections and Surveillance Services, National Center for Prevention, Detection, and Control of Infectious Diseases, CDC, Atlanta, Georgia; CDC–Universidad del Valle de Guatemala Collaboration, Centro de Estudios en Salud, UVG, Guatemala City, Guatemala; Johns Hopkins School of Public Health, Baltimore, Maryland

Abstract. Historically, poliovirus infection has been an important cause of acute flaccid paralysis (AFP) worldwide; however, successful elimination of wild-type poliovirus in much of the world has highlighted the importance of other causes of AFP. Despite the evolving etiology, AFP surveillance in most developing countries still focuses on poliovirus detection and fails to detect many AFP cases, particularly among adults. We assessed 41 subjects self-reporting symptoms suggestive of AFP during a population-based health survey in the Department of Santa Rosa, Guatemala. Thirty-five (85%) of the suspected cases were not hospitalized. Most subjects (37) did not have features consistent with AFP or had other diagnoses explaining weakness. We identified two adults who had not received medical attention for a clinical illness consistent with Guillain-Barré syndrome, the most important cause of non-poliovirus AFP. Usual surveillance methods for AFP, particularly in developing countries, may underestimate the true burden of non-poliovirus AFP.

INTRODUCTION

Acute flaccid paralysis (AFP) is a heterogeneous neurologic condition defined by the onset of acute, areflexic, or hyporeflexic weakness in one or more limbs and/or the cranial nerve-innervated muscles. There are numerous underlying conditions that may lead to AFP, including infectious, toxic, and metabolic causes.¹ Historically, the predominant cause of AFP has been infection with poliovirus, a picornavirus transmitted by the fecal–oral route, and poliovirus infection has led to endemic and epidemic disease that results in AFP. The introduction of an effective poliovirus vaccine in 1955 has led to a dramatic decline in poliovirus infections worldwide; to date, poliovirus-associated AFP has been eliminated from most of the world;² endemic poliovirus infection currently occurs in four developing countries, and epidemics occur in a small number of other countries. Because of the important implications for poliovirus vaccination campaigns, most surveillance for AFP is focused on identification of potential cases of poliovirus-associated AFP. Additionally, surveillance uses the World Health Organization (WHO) AFP case definition, which is intended to be a sensitive but non-specific screen for poliomyelitis cases in the highest-risk age groups for poliovirus-associated AFP. The AFP definition focuses on the presence of acute limb paralysis in children under the age of 15. Although the screening case definition has proved to be a useful and successful tool in poliovirus surveillance, it inherently fails to identify many potential cases of AFP, particularly in persons over 15 years of age.

Since the elimination of poliovirus from much of the world, an inflammatory polyradiculoneuropathy, more commonly referred to as Guillain-Barré syndrome (GBS), has become the most important clinical form of AFP.³ GBS is thought to be an autoimmune condition in which an antecedent event, usually an infection, results in an autoimmune response; then, host antibodies cross-react with epitopes on host peripheral nerves. Although peripheral-nerve myelin is most commonly affected,

several variants of GBS have also been identified, including a predominantly axonal variant (acute motor axonal neuropathy [AMAN]) and a syndrome involving a clinical triad of ophthalmoplegia, areflexia, and ataxia (Fisher syndrome).⁴

Estimates of the incidence of GBS and of other forms of non-poliovirus AFP vary widely. Most estimates have been hospital-based assessments performed in developed countries, and they have suggested an incidence of GBS of between 0.6 and 4.0 cases per 100,000 population, although most well-designed, population-based studies have consistently suggested an annual incidence of 1–2 per 100,000 population.⁴ Studies of AFP, including GBS, have varied greatly in methodologies, case definitions used, and case ascertainment; thus, many estimates have not been directly comparable. Estimates of incidence rates of AFP in developing countries have generally been based on WHO AFP surveillance for poliovirus infection, although a few studies have attempted to assess rates of GBS-associated AFP in the developing world.^{5–12} A hospital-based investigation of the causes of AFP among all age groups has recently been established in Guatemala (E. Dueger, personal communication).

In developing countries such as Guatemala, there may be limitations in the ability of critically ill patients, such as those with AFP, to reach hospitals or come to medical attention. The health-care system in Guatemala is multilayered. Public health care in Guatemala is free and is provided through a system of regional and departmental hospitals, health centers, health posts, outreach centers, and nongovernmental organizations (NGOs). Guatemala is divided into 22 administrative departments; each department roughly corresponds to a “health area” that is responsible for all public health activities within its borders. There is generally at least one regional (referral) or departmental hospital per health area; however, tertiary-care centers, with critical-care capabilities, are located only in several larger regional hospitals and in the capital of Guatemala City. Thus, persons suffering from critical illnesses in rural areas often face long commutes to receive intensive care, and the risk of mortality before reaching even a district-level hospital may be high.

One underlying presumption of AFP assessments is that cases of AFP, regardless of clinical form, would be seen by at least a primary health-care provider or hospital and if clinically

*Address correspondence to James J. Sejvar, CDC, 1600 Clifton Rd., Mailstop A-39, Atlanta, GA 30333. E-mail: zea3@cdc.gov

severe, would be referred to a secondary or one of the main tertiary-care centers; indeed, preliminary questioning of health-care workers at various levels of the Guatemala health-care infrastructure suggested that this might be the situation in Guatemala (E. Duger, personal communication). During a community-based, population-based assessment of health-seeking behaviors for self-reported illnesses, including neurological disease, in one department in Guatemala, 41 persons reported experiencing signs or symptoms compatible with AFP within the 12 months before the interview; only six were admitted to the hospital. The positive response of 35 non-hospitalized persons within one department to questions pertaining to AFP was surprising. If even a small number of these persons did indeed suffer from AFP of any kind and remained non-hospitalized and unseen by health-care workers, this might suggest that the burden of AFP in Guatemala may actually be larger than would be estimated by health facility-based surveillance, and it might suggest that AFP represents a greater public-health problem than is generally recognized in Guatemala.

To better assess the specific underlying conditions prompting the affirmative responses to the AFP questions during the household survey and to estimate the burden of AFP that may not be hospitalized or seen by health workers, we performed a follow-up investigation of these 41 persons.

MATERIALS AND METHODS

From October to December 2006, a population-based assessment of health-seeking behaviors was conducted in the Department of Santa Rosa, Guatemala.¹³ The Department of Santa Rosa has a population of 308,522 individuals (2002 Census) and is located approximately 1 hour southeast of Guatemala City. The department is made up of 14 municipalities. This assessment used a two-stage cluster-sampling procedure to select households and their residents to assess health-care seeking behaviors, health-care use practices, household characteristics, and risk factors for self-reported diarrhea, influenza-like illness (ILI), pneumonia, and neurological illness (acute infectious neurological disease [AIND]; see Figure 1 for case classification questions). The survey was conducted in 60 communities throughout Santa Rosa, and estimates of the incidence of self-reported diarrhea, ILI, pneumonia, and neurological symptoms within the department were made based on subject responses. During this household survey, which collected data on 5,449 persons, 254 reported having neurologic symptoms suggestive of an AIND during the 12 months before the interview. Among these, 41 persons (16%) reported experiencing signs or symptoms compatible with AFP; six were admitted to hospital.

Between August 21 and 27, 2007, an assessment team, including a board-certified neurologist (J.J.S.), revisited the 41 persons documented as responding affirmatively to ques-

tions relating to AFP during the household survey. Persons were contacted either by telephone or house visit, and they were invited to participate in a follow-up evaluation; for those agreeing, written, informed consent was obtained. Participants were asked several screening questions specifically ascertaining their response to the household survey questions, and those who recalled responding affirmatively to the AFP questions during the household survey were administered a standardized questionnaire to gather information on the temporal profile, pattern, and severity of weakness and the signs and symptoms associated with the illness. These participants also underwent a full neurological examination; additionally, all available medical records and/or neuroimages that were performed in the course of their clinical care were personally reviewed (J.J.S.). Persons were classified, based on responses to the questionnaire and neurologic examination, into categories that included: "not a case of AFP" (either because of an incompatible clinical description or an alternative diagnosis), "suspected case of prior AFP within the 12 months before the survey based on clinical history alone," "suspected case of prior AFP within the 12 months before the survey based on clinical history and persistent static objective neurologic signs," "current case of AFP developing within the 12 months before the survey based on clinical history and ongoing evolving objective neurologic or electrophysiologic signs," or "indeterminate; unable to determine prior history of AFP." Any persons classified as a suspected or current case of AFP were requested to undergo electrodiagnostic testing (electromyography [EMG] and nerve conduction velocity studies [NCS]) at a tertiary-care center in Guatemala City, and they were provided with transport. For persons who had died in the interval period or who were not present in Santa Rosa at the time of the assessment, we obtained as detailed a history as possible from a proxy who was familiar with the illness or episode in question.

The research protocol was reviewed and approved by the institutional review boards of the Universidad del Valle de Guatemala (Guatemala City, Guatemala) and the Centers for Disease Control and Prevention (Atlanta, GA).

RESULTS

We contacted all 41 persons who reported symptoms suggestive of AFP in the 2005 household survey; 35 persons were interviewed directly and for the other 6 persons, history was obtained by proxy. Twenty-one (51%) were female; the median age was 49 years (range = 13–85 years). Twenty-three persons (56%) resided in an area considered urban; 18 (44%) were considered as residing in a rural area.

The nature of the illness reported as AFP and a summary of the classification of these persons is shown in Table 1. Three persons (7%) denied or did not recall having responded affir-

- 1) Fever and confusion or loss of consciousness: "During the past 12 months (may give specific dates), has any member of this household been sick with fever and confusion? Or fever and either loss of consciousness or being difficult to arouse lasting longer than a day?"
- 2) Severe weakness or paralysis of one or more limbs: "During the past 12 months (may give specific dates), has any member of this household been affected by severe muscle weakness or had difficulty moving one or more limbs of their body?"
- 3) Seizures or convulsions: "During the past 12 months (may give specific dates), has any member of this household experienced or been observed to have convulsions with loss of consciousness?"

FIGURE 1. Screening questions were used during the Santa Rosa population-based health-care survey to identify potential cases of AIND.

TABLE 1

Presumptive diagnosis (A) and overall classification (B) of 41 subjects responding affirmatively to questions regarding AFP during a household-based health survey (Department of Santa Rosa, Guatemala)

(A) Diagnosis	N	(B) Classification	N
Pain syndrome	15	"Not a case of AFP"	37
Acute stroke/TIA	6	Likely alternative diagnosis present	19
Clinical history	2	Incompatible clinical description	18
History plus examination findings	2*	"Indeterminate; unable to determine prior history of AFP"	2
History plus radiographic findings	2*	"Suspected case of prior AFP based on clinical history and persistent objective neurologic or electrophysiologic signs"	1
Psychogenic illness	3	"Suspected case of prior AFP based on clinical history alone"	1
Cervical radiculopathy	2		
Bell's palsy	1		
Miscellaneous	7		
Parkinson's Disease	1		
Congenital limb defect	1		
Alcoholic cachexia	1		
Cachexia associated with esophageal cancer	1*		
Meningitis	1*		
Migraine headache	1		
Panic attacks	1		
No recollection of answering yes to AFP question during survey	3		
Unclassifiable	2		
AFP	2		
Total	41		

* Hospitalized subjects.

matively to the AFP question during the household survey and were excluded from further interview. The most common syndrome or condition reported as AFP was limb pain with the subject denying any specific weakness, which was reported by 15 persons (37%). In these circumstances, the person typically described pain in limbs or joints, which was most frequently consistent with degenerative joint disease or arthritis. However, the person specifically denied experiencing any limb weakness or was readily able to discern that the weakness experienced was based on pain. We found that the simple follow-up questions of "did you experience weakness or only pain?" and "was your weakness caused by this pain?" were reliably able to distinguish this group of subjects.

Nineteen (46%) persons were found by clinical history, neurological examination, or other diagnostic methods to have a plausible alternative explanation for weakness that prompted the response to the AFP question. In six subjects, acute stroke or transient ischemic attack (TIA), resulting in acute spastic paresis, was the likely etiology of illness. This included two subjects with a clinical history of acute onset of weakness evolving over minutes, unilateral distribution, and associated other signs suggesting stroke/TIA, two subjects for whom stroke sequelae were present on neurological examination, and two subjects for whom neuroradiographic studies conducted during the neurologic event and personally reviewed by the research team clearly showed cerebral infarct or hemorrhage. Two subjects had clinical and neuroradiographic evidence of multiple cervical radiculopathies, producing pain and limb weakness. Three subjects, who did not admit to knowing each other, described a bizarre phenomenon of "involuntary" fist clenching associated with headache, generalized weakness, and inability to conduct daily activities; these episodes were invariably associated with feelings of stress or anxiety and were associated with stressful life events. Neurologic examination in these individuals failed to show any abnormalities; specifically, acute dystonia or other movement disorders were not present. These cases were not clinically compatible with AFP and were thought to be more compatible with psycho-

genic illness. One person whose history was assessed by proxy was described as having observable unilateral facial weakness improving over a period of weeks, which was typical for idiopathic facial palsy (Bell's palsy). An additional seven persons had plausible alternative explanations through clinical history or examination for prompting a response to the AFP question, and they are shown in Table 1. Five subjects had died during the time between the household survey and our assessment; no deaths described by proxy interviewees were suggestive of death from an acute infectious neurologic illness or AFP (death from terminal cancer, acute chest pain followed by collapse and inability to be resuscitated [two subjects], and trauma [two subjects]). In two persons, the clinical history was nonspecific, unable to be conveyed in detail, or otherwise unclassifiable; neurologic examination was normal in both.

We identified two persons for whom clinical history was thought to be compatible with AFP and suggestive of GBS.

The first case was an 18-year-old male with no significant past medical history. In July 2006, he experienced the onset of bilateral hand weakness, noting that he was unable to grip with sufficient strength the bags of bread that he was delivering as part of his work duties. The weakness worsened over several hours, and he developed bilateral paresthesias in his hands, described as a feeling like "... ants crawling on (his) arms." The weakness and paresthesias reached a maximal level within approximately 2–3 days and subsequently plateaued. He also noted a similar sensation of "ants crawling" in his feet, extending to the level of the knees, and noted difficulty with lifting his feet, describing an inability to flex and extend his feet at the ankles. He was able to walk but with great difficulty; lower extremity weakness progressed over a period of 2–3 days, by which point he could ambulate but experienced frequent falls and was unable to run or walk quickly.

Within approximately 2 weeks, he began to experience gradual improvement; by 3 weeks, he was able to use his hands normally, and the upper and lower extremity paresthesias had subsided. By approximately 1 month after onset, he no longer noted leg or foot weakness. The patient felt that he was back

to the baseline level of strength, with absence of paresthesias, by approximately 3–4 months after onset of initial symptoms. He did not seek medical care for his illness.

He specifically denied any facial weakness, dysarthria, or dysphagia. He denied visual problems or bowel/bladder dysfunction. He did not recall any antecedent or concurrent infectious illnesses, fever, or respiratory or gastrointestinal symptoms. During and after the period of weakness, he volunteered that the muscles in his arms and legs would frequently “twitch,” and this twitching was visible to him and others; this continued for several months after onset and into the period of convalescence.

At neurologic examination in August 2007, he showed no detectable weakness, and sensory examination was normal to all modalities. Deep tendon reflexes were diminished throughout, bilaterally and symmetrically. No fasciculations were noted; there was no atrophy or muscle wasting. Electrodiagnostic studies (EMG/NCS) performed in September 2007 were normal.

The distribution of weakness at onset and the onset in the arms before the legs is somewhat atypical for GBS. However, the constellation of distal weakness and paresthesias, the progression of weakness over a period of days with subsequent plateauing, the gradual improvement over months, the description of signs compatible with fasciculations, and the diffuse hyporeflexia on neurologic examination was thought to be clinically suggestive of GBS.

The second case was a previously healthy 70-year-old male. In July 2006, he experienced the subacute onset of lower extremity weakness and “walking like a drunk.” As he began to walk back to his house, his legs collapsed on him, and he fell; he noted weakness in his arms as well. He was able to ambulate the approximately 1 kilometer back to his home; however, he developed increasing arm and leg weakness. He specifically denied any facial weakness, dysarthria, or dysphagia. He had no bowel or bladder dysfunction; he had no visual problems. He denied experiencing any pain or paresthesias. He did not recall any antecedent or concurrent illnesses.

By the point of clinical nadir approximately 4 days after onset, he reported the inability to walk and lift his arms to feed himself. He had difficulty describing the distribution of the weakness but felt that his hips and shoulders were weaker than his hands and feet. He subsequently began to slowly improve; by approximately 1 month, he was able to walk slowly around his house with the aid of a stick. By approximately 6 months, he was ambulating and using his arms normally but felt fatigued. He felt back at baseline by approximately 8 months. He did not seek medical care for his illness.

His neurological examination in August 2007 was normal, including limb strength and deep tendon reflexes. Electrodiagnostics were not performed.

Although the rapidity of onset was thought to be somewhat atypical, and the patient was a relatively poor historian, the symptoms described were felt to be possibly consistent with GBS. He did not live in the same or nearby community as the first AFP case.

Presuming that these two cases represent a very small random sample of true AFP, most likely GBS, in the Department of Santa Rosa, we estimated a minimum proportion of such AFP that may go undetected by clinical providers. With these assumptions, we hypothesized that about 20% or less of the true AFP in the Department of Santa Rosa goes undetected by clinical providers. The probability by chance alone of obtaining the observed results based on the validity of such a hypothesis

would be below 5%, a generally accepted level for rejecting hypotheses in scientific studies. Because the observed results are that neither of the two patients with AFP identified in the survey had been seen by a clinical provider, if the true proportion of such unseen cases were as high as 20%, then the chances of the first identified case in the survey having a history of not being seen by a clinical provider would be about 20%. However, the probability of the second case too having a history of not being seen by a clinical provider would be roughly 20% times < 20% or only < 4%. Thus, the study results suggest that with a probability of greater than 95%, the true prevalence of cases of AFP in the Department of Santa Rosa that may go undetected by clinical providers is at least 20%. This could represent a substantial burden of AFP in the Department of Santa Rosa.

DISCUSSION

To our knowledge, this is the first population-based assessment of AFP that used a methodology sensitive enough to identify AFP in people of any age group who neither were hospitalized or seen by a health-care worker for their illness. Our study was strengthened by the standardized nature of the questioning, allowing us to clearly define temporal and clinical progression of the event described as AFP. Additionally, a full neurologic evaluation of persons describing features compatible with AFP allowed for a thorough assessment and a reliable documentation of possible alternative diagnoses; furthermore, it increased the possibility of detecting neurologic signs that may have suggested prior AFP. Finally, unlike the WHO definition of AFP, we included all age groups and were not dependent on identification and reporting of cases by health-care workers. We identified two persons with a clinical history suggestive of post-infectious AFP, or GBS, who were not hospitalized or seen by a health-care worker for their illness. These two persons, an 18-year old male and a 70-year old male, both described clinical events consistent with GBS, including subacute onset of weakness and/or sensory abnormalities in the distal extremities, gradual progression of weakness, and resolution over a period of weeks to months.

“Mild” GBS has been described previously,^{14,15} and the first case, who developed weakness but remained functionally independent and did not seek medical care, suggests that “mild” AFP may occur in the community and not come to medical attention. Electrodiagnostic studies performed on this individual over 1 year after illness were normal; however, reversible electrophysiologic changes have been observed in GBS, and ultimate long-term electrophysiologic improvement in mild illness has not been defined.^{14–16} Additionally, in resource-poor settings such as rural Guatemala, it is possible, and perhaps likely, that persons with AFP may be unable to make it to medical attention or could die of complications of AFP (e.g., neuromuscular respiratory failure) before making it to hospital, which is potentially evidenced by the second case. Thus, AFP rates may be underestimated by usual AFP surveillance studies. This finding may have important ramifications on the estimation of the overall burden of AFP, particularly in developing countries such as Guatemala.

Most of the persons who responded positively when asked about acute weakness did not have or describe clinical features consistent with AFP. We found that the most common clinical feature or syndrome that was reported as AFP was generalized limb pain, most often of a musculoskeletal or degenerative joint-disease nature. We found that by asking the subject to

clarify between pain and true weakness, we were able to quickly exclude many such subjects with minimal follow-up questioning; in future population-based surveys of a similar nature, this line of follow-up questioning may serve as a simple but efficient way of excluding cases that are inconsistent with AFP, thus focusing study time and resources. We found that this population-based approach to the assessment of AFP was quite successful in identifying persons who had experienced acute limb weakness. There were six respondents who described clinical features consistent with acute stroke or TIA, including four who had clinical or neuroradiologic evidence to support this diagnosis.

Our study has significant limitations. The original household survey queried about incidents consistent with AFP occurring within the previous 12 months; thus, many answers were subject to significant recall bias. Indeed, some persons attributed their incident of AFP to episodes occurring greater than 12 months before the survey. Accurate clinical histories were difficult to obtain from some persons with limited education and exposure to medical care, and misclassification of some persons is likely. In several cases, persons were either deceased or unavailable at the time of the study, and clinical history was obtained by proxy, which introduces additional bias. Neither of the potential cases that we identified had clear neurologic or electrophysiologic evidence of GBS or AFP at the time that we assessed them. However, we found that in most cases, we were able to reliably elicit clinical histories that strongly suggested alternative etiologies for what was being described as AFP. Additionally, thorough neurologic evaluation of study persons ensured that neurologic signs suggestive of an etiology were detected; alternatively, documentation of an absence of objective neurologic dysfunction in persons with subjective symptoms helped to avoid inclusion of cases without apparent neurologic disease. Review of additional data (head computed tomography (CT) scans, etc.) by a neurologist in the field helped to identify cases with a definitive alternative diagnosis.

Our findings suggest that mild or, in some cases, severe AFP that does not come to direct medical attention may occur in the community setting. Although not directly addressed by our data, it may be hypothesized that the challenges of accessing health care in developing countries may result in such cases more frequently remaining undetected by usual AFP surveillance methodologies. The overall burden of AFP, particularly in developing countries, may be underestimated. As poliovirus continues to be eliminated worldwide, a larger proportion of cases of AFP caused by other etiologies will be recognized and deserving of increased attention. Many infectious, post-infectious, and toxic etiologies of AFP are preventable and in some cases, treatable. Thus, assessment of non-poliovirus AFP will become an increasingly important public health goal. Studies aimed at estimating rates or incidence of AFP, particularly in the developing world, may benefit from a similar strategy of assessing possible incidence and prevalence of non-hospitalized AFP within the community and in all age groups, ideally in a prospective manner with detailed clinical and electrophysiologic evaluation. Such studies may allow for a more reliable estimate of overall disease burden, aid in guiding preventive health measures, and possibly, result in more effective treatment measures at a local level.

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Authors' addresses: James J. Sejvar and Lawrence B. Schonberger, Division of Viral and Rickettsial Diseases (DVRD) and Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, GA, E-mails: JSejvar@cdc.gov and L.Schonberger@cdc.gov. Kim A. Lindblade, Wences Arvelo, Kimberly Pringle, and Norma Padillo, Universidad de Valle de Guatemala, Guatemala City, Guatemala, E-mails: KLindblade@cdc.gov, WArvelo@cdc.gov, kimberly.pringle@gmail.com, and Npadilla@uvg.edu. Erica Dueger, U.S. Naval Medical Research Unit 3 (NAMRU-3), FPO AE 09835-9998, E-mail: erica.dueger@navy.med.mil. Emily Zielinski-Guttierrez, Foothills Campus, Fort Collins, CO, E-mail: EZielinski-Guttierrez@cdc.gov. Eileen Farnon, Division of Healthcare Quality Promotion, CDC, Atlanta, GA, E-mail: EFarnon@cdc.gov.

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