Acute flaccid paralysis surveillance in southeastern Turkey, 1999-2010

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The aim of the study was to report the results of acute flaccid paralysis (AFP) surveillance and to evaluate the performance of surveillance in the southeastern region of Turkey in the 12 years from 1999 to 2010. We investigated cases in seven provinces of the southeastern region of Turkey. In the evaluation, AFP Case Report Form, Laboratory Investigation Form and 60-Day Case Investigation Form were used; individuals' demographic characteristics, clinical findings, status of vaccination, sample results, and 60-day follow-up were evaluated. Incidence ranged from 0.60/100,000 in 2008 to 1.60/100,000 in 1999. Dysstasia and loss of strength were the most frequently reported prodromal symptoms. Coxsackievirus and echoviruses were the most frequent viruses detected. One-quarter of the AFP cases could not be followed up in the present surveillance system.

Key words: acute flaccid paralysis, surveillance, poliomyelitis, southeastern Turkey.

Polio cases have decreased by over 99% since 1988, from an estimated 350,000 cases then to 650 reported cases in 2011. The reduction is the result of the global effort to eradicate the disease. In 2012, only three countries (Afghanistan, Nigeria and Pakistan) remain polio-endemic, down from more than 125 in 1988. Failure to eradicate polio from these last remaining strongholds could result in as many as 200,000 new cases every year, within 10 years, all over the world. In most countries, the global effort has expanded capacities to tackle other infectious diseases by building effective surveillance and immunization systems[1].

In May 1988, the World Health Organization (WHO) established the goal of global eradication of poliomyelitis by the year 2000[2,3]. Their main strategies were maintaining high immunization coverage with oral polio vaccines (OPV) through the Expanded Immunization Program, conducting National Immunization Days of OPV, and detecting all suspected poliomyelitis cases through the Acute Flaccid Paralysis (AFP) surveillance, which underpins the entire eradication initiative. WHO stresses that all cases of AFP should be reported[4-6].

A country's surveillance system should be sensitive enough to detect at least one case of AFP for every 100,000 children under 15 years. In Turkey, a national polio eradication program was started in 1995, including AFP surveillance to certify the country as free of indigenous wild poliovirus. The last known case of polio in Europe caused by indigenous wild poliovirus transmission occurred in southeast Turkey in November 1998[7,8]. Although wild poliovirus has been eradicated in many countries, thousands of AFP cases occur annually worldwide that are not associated with wild poliovirus[9].

There are many causes and differential diagnoses of AFP (Table I).

With recent changes in Turkey's childhood vaccination calendar, all children in Turkey were to receive three doses of inactivated polio vaccine (IPV) at 2-4-6 months of age, two booster doses of IPV at 18 months of age and primary first-class, two doses of OPV at 6-18 months of age[12]. OPV causes paralytic poliomyelitis in vaccine recipients or their

Table I. Causes and Differential Diagnoses of Acute Flaccid Paralysis10,11

• Infectious	
Viral	
Enteroviruses	Poliomyelitis, Coxsackie A (A7, A9; A4, A5, A10), Coxsackie B (B1-B5), echoviruses (6, 9; 1-4, 7, 11, 14, 16-18, 30), enterovirus 70, enterovirus 71
Other viruses	Myxoviruses (mumps virus), toga and arborviruses, Epstein-Barr virus; human immunodeficiency virus (HIV), Japanese B encephalitis virus, West Nile virus
Bacterial	Campylobacter jejuni (leading cause of Guillain-Barré syndrome)
•*Metabolic- transient and periodic paralysis*	
Hypokalemic	Familial, Sjögren's syndrome, hyperthyroidism, gossypol-induced (toxic phenolic pigment in the cottonseed), association with barium poisoning, association with hyperaldosteronism
Normo- or hyperkalemic hypophosphatemia	Familial, adynamia episodica hereditaria of Gamstorp
•*Drug-induced*	
Antibiotics	Aminoglycosides, polymyxin B, tetracyclines
•*Organic volatile hydrocarbons*	
	Hexane, methyl butyl ketone, carbon disulfide
Tricresyl phosphate	Jamaican ginger tonic, contaminant of cooking oil, mustard oil, or flour
Other	Cantharidin, diethyltoluamide (DEET), dithio biuret (rat poison), triethyl dodecyl-ammonium bromide (mouse poison)
•*Toxins*	
Bacterial	Botulinum, diphtheria, tetanus (cephalic form), Moraxella
Fungal-mycotoxins	Penicillium citrea-viridae, Penicillium islandicum, Penicillium citrinum
Insect	Tick paralysis, spider venom, cockroach, beetle, wasp venom, Lepidoptera larvae
Parasite/protozoa/dinoflagellates	Paralytic shellfish poisoning-saxitoxin, ichthyotoxism (sardines)
Reptiles-snake venom	Cobra, Australian elapid, krait, mamba, sea snake
Plants and plant toxin	Gloriosa superba (daisy) [root], Lathyrus species (sweet pea), Aconitum (monkhood), hemlock (parsley), Karwinskia humboldtiana/coyotillo (buckthorn) [berries], Calliopsis species (daisy), Cassia (bean), Cycas (evergreen), [seeds], Gelsemium [blossoms], Heliotropium (bush tea shrub), Melochia species [stems], Oenanthe species 9parsnips0
•*Metals*	Organic tin compounds, lead
•*Pesticides*	EPN, trichlorfon (Dipterex, dichlorvos (DDVP), DEF, isofenphos (Oftanol), leptophos (Phosel)
•*Inherited/congenital/acquired*	Werdnig-Hoffmann disease, Wohlfart-Kugelberg-Welander disease, porphyric polyneuropathy
	Guillain-Barré syndrome, China paralytic syndrome, Bell's palsy, transverse myelitis, acute motor axonal neuropathy, traumatic neuritis, myasthenia gravis, porphyria,
•*Unknown/multiple causes*	polymyositis, trichinosis
•*Asthma*	Polio-like Hopkins' syndrome

Table II. The Total Population and Under 15 Years Population of Seven Provinces

	Under 15 years population/Total population				
Provinces	2000	2007	2008	2009	2010
Şanlıurfa	639,118/ 1,443,422	646,665/ 1,523,099	665,270/ 1,574,224	685,027/ 1,613,737	701,191/ 1,663,371
Diyarbakır	591,556/ 1,362,708	553,352/ 1,460,714	558,560/ 1,492,828	564,408/ 1,515,011	565,386/ 1,528,958
Mardin	315,577/ 705,098	297,494/ 745,778	291,913/ 750,697	288,243/ 737,852	288,104/ 744,606
Batman	214,317/ 456,734	200,178/ 472,487	201,996/ 485,616	205,368/ 497,998	206,222/ 510,200
Şırnak	166,259/ 353,197	187,129/ 416,001	188,759/ 429,287	191,285/ 430,424	192,997/ 430,109
Siirt	122,595/ 263,676	124,760/ 291,528	125,485/ 299,819	125,791/ 303,622	124,801/ 300,695
Hakkari	105,653/ 236,581	101,537/ 246,469	101,474/ 258,590	100,431/ 256,761	98,475/ 251,302
Total	2,155,075/ 4,821,416	2,111,115/ 5,156,076	2,133,457/ 5,291,061	2,160,553/ 5,355,405	2,177,176/ 5,429,241

Turkey Statistical Institute

healthy contacts at a rate of approximately one in every 2.5 million doses administered, or 1 in 800,000 first vaccinations[11,13]. Vaccine-derived polioviruses, genetically drifted strains that regain neurovirulence, have caused several outbreaks of paralytic poliomyelitis in different parts of the world[14]. VAPP (Vaccine-Associated Poliomyelitis) is defined by WHO as poliomyelitis that occurs in a vaccinee between 7 and 30 days after a dose or in a person in close contact with a vaccinee between 7 and 60 days after the dose was received. VAPP occurs at a low rate, estimated as one case per million births by WHO, but also reported as approximately one case per 750,000 vaccinees in the United States, one per 400,000 in Norway, England and Wales, and one per 143,000 in India[15,16]. In the United States, all cases of flaccid paralysis with residual deficit after 60 days and that have had contact with vaccinated persons are considered VAPP, but it is not necessary to identify the Sabin-strain virus[17]. The estimated VAPP rate is 0.2 to 0.4 per million doses of OPV[18]. The change from OPV to IPV reduces the risk of disease caused by vaccine-derived poliovirus (VDPV). WHO still considers use of OPV necessary to control polio in countries where the disease is still endemic or circulation is re-established. Encouraging countries to change to IPV when possible will reduce the risk of VAPP for everybody[19].

The aim of this study was to report the results of AFP surveillance and to evaluate the performance of surveillance in the southeastern region of Turkey in the 12 years from 1999 to 2010.

Material and Methods

All cases of AFP including Guillain-Barré syndrome (GBS), transverse myelitis, etc. in children younger than 15 years reported to the Department of Communicable Diseases of Provincial Health Directorates from 1999 to 2010 were included in this study. We investigated cases in seven provinces (Diyarbakır, Urfa, Mardin, Batman, Şırnak, Siirt, and Hakkari) of the southeastern region of Turkey. These provinces had a total population of 5,429,241 in 2010, of which 2,177,176 were children under 15 years[20].

AFP case studies and follow-up system5,13,21-23:

1. All physicians are responsible for notification of cases of AFP.

2. The physicians inform the responsible person of the Provincial Polio Eradication Program about the case as soon as possible by telephone. The Case Report Form is passed to the responsible person of the Provincial Polio

Eradication Program.

3. The responsible person of the Provincial Polio Eradication Program is in charge of the registration of each case, visits the notifying physician, and ensures stool samples of the cases are taken.

4. The Case Report Form is sent to the Turkish Public Health Agency.

5. Two stool samples are taken, 24 hours apart, within 14 days of the onset of paralysis, and are sent to the virology laboratory of the Refik Saydam Institute with the Laboratory Investigation Form. One copy of the Laboratory Examination Form is sent to the Turkish Public Health Agency.

6. Cases are visited in the home, and the stool samples of five contact people (preferably under the age of 5) are taken. The Laboratory Investigation Form is completed and sent with the stool samples of the cases and contacts.

7. The responsible person of the Provincial Polio Eradication Program completes the Case Investigation Form, follows the cases for 60 days, and defines the diagnosis at the end of this period. The Case Investigation Form is sent to the Turkish Public Health Agency.

8. If two stool samples are not taken within 14 days of the onset of paralysis and paralysis is continuous at the 60th day, a copy of the patient's hospital file is sent to the Turkish Public Health Agency.

9. For an active surveillance, health institutions are visited by the responsible person of the Provincial Polio Eradication Program at least once every two weeks. The AFP Active Surveillance Form is completed and faxed to the Turkish Public Health Agency.

Virus isolation and typing are performed in the virology laboratory of the Refik Saydam Institute, Ankara, Turkey, which is accredited by the Global Poliomyelitis Laboratory Network of WHO[24].

In the evaluation, the AFP Case Report Form, Laboratory Investigation Form and 60-Day Case Investigation Form were used; individuals' demographic characteristics, clinical findings, status of vaccination, sample results, and 60-day follow-up were evaluated. A written permission was obtained from the Turkish Ministry of Health for the research.

In the analysis of the collected data, the Statistical Package for the Social Sciences (SPSS) 15.0 statistics package software was used. In the analysis, after error checks, percentage distributions were used.

Results

Two hundred sixty-five cases of AFP in children younger than 15 years reported to the Department of Communicable Diseases of seven (Diyarbakır, Urfa, Mardin, Batman, Şırnak, Siirt, and Hakkari) Provincial Health Directorates from 1999 to 2010 were included in this study. In 265 cases, the male to female ratio was 1.4. Twenty-seven cases (10.2%) were under 1 year of age. Two hundred twenty-four (84.5%) cases were vaccinated with at least one OPV dose; 189 (71.3%) cases were followed up 60 days from onset of symptoms of AFP (Table III). Our surveillance system did not collect information on the clinical diagnosis. However, we did obtain information on the final diagnosis in 162 cases (61.1%). GBS was diagnosed in 67 cases (41.4%), transverse myelitis in 5 (3.1%), encephalopathy and encephalitis/meningitis in 14 (8.6%), and not polio in 71 (43.8%).

In this study, only one case, who had no paralysis 60 days after onset, had a history of polio vaccination within the previous 30 days. We did not consider this case, or the other cases with Sabin-strain polio virus stool specimens, as VAPP, as none had paralysis persisting after 60 days.

Two hundred and sixty-five cases were identified in the 12 years, for a mean annual incidence rate of 1.05/100,000 children aged under 15 years. Incidence ranged from 0.60/100,000 in 2008 to 1.60/100,000 in 1999 (Fig. 1).

Dystasia and loss of strength were the most frequently reported prodromal symptoms (in

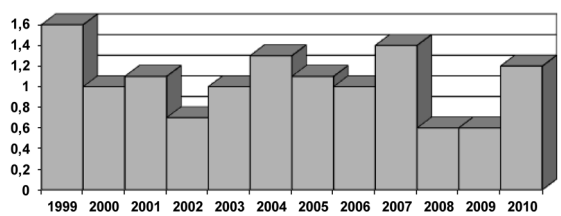

Fig. 1. AFP incidence rate in the southeastern region of Turkey, 1999-2010.

Table III. Age and Sex Distribution, Vaccination Status and Follow-Up 60 Days After Onset of Symptoms of AFP Cases, 1999-2010

	N	%
Age groups		
<1 yr	27	10.2
1-2 yrs	69	26.0
3-4 yrs	62	23.4
5-6 yrs	26	9.8
>6 yrs	81	30.6
Mean±SD: 4.58±3.73	Median: 3.00	Min-Max: 0-15
Sex		
Male	155	58.5
Female	110	41.5
Vaccination status		
At least one OPV doses	224	84.5
Unvaccinated	25	9.4
Unknown	16	6.1
Follow-up 60 days after onset of symptoms		
Yes	189	71.3
No	6	2.3
Unknown	70	26.4

123 cases, 59.1%). Lower extremity paralysis was the most frequently reported feature of paralysis (in 246 cases, 95.7%). In 227 cases (88.7%), AFP started with sudden paralysis. One hundred forty-one cases (74.7%) had no residual paralysis 60 days after the onset of AFP (Table IV).

The viruses isolated from stool specimens are presented in Table V. In most stool specimens (138 stools, 52.1%), no viruses were detected. Coxsackievirus and echoviruses were detected (12 stools, 50.0%, respectively). Sabin-strain polio viruses were detected in 10 cases (3.8%): type 2 in 5 cases, type 3 in 3 cases, and type 1 in 2 cases. All samples of the 10 cases were taken within the first 14 days from paralysis onset. Seven of these cases were vaccinated against poliomyelitis.

Figure 2 shows the monthly distribution of AFP cases; 32 and 13 AFP cases were reported in May and November, respectively.

In this study, AFP surveillance criteria were also evaluated. It was seen that two samples were taken in the same day as well as 14 days. Although the time interval between samples is required to be 24 hours in all cases according to the evaluation criteria, only 70.0% of the cases met these criteria. In all cases, the time that elapses until the samples are sent to the laboratory is required to be 3 days. However, mean±SD was calculated as 5.4±4.9, and the conformity percentage was calculated as 42.7. The time that elapses from paralysis onset to sampling is required to be 14 days, and this time should be met in at least 80.0% of the cases. The mean±SD was found to be 7.8±7.7, and the conformity percentage was found to be 91.3. Reporting is required to be made within 7 days following the onset of paralysis, and the conformity percentage should be met in

Fig. 2. Monthly distribution of AFP cases in the southeastern region of Turkey, 1999-2010.

Table IV. Clinical Features of AFP Cases, 1999-2010

	N	%
Prodromal symptoms		
Dysstasia, Loss of strength	123	59.1
Abasia	88	42.3
Fever	29	13.9
Nausea-vomiting	12	5.8
Malaise, anorexia	7	3.4
Diarrhea	6	2.9
Headache, vertigo	5	2.4
Others*	30	14.4
Unrecorded	57	21.5
Feature of paralysis		
Lower extremity	246	95.7
Upper extremity	102	40.0
Face	16	6.3
Bulbar	13	5.2
Clinical symptoms		
Sudden paralysis	227	88.7
Fever	89	34.4
Asymmetry	71	27.5
Loss of sense	59	23.0
Neck stiffness	22	8.5
Residual paralysis 60 days after onset of AFP		
No	141	74.7
Yes	46	24.2
Death	5	2.6
Unknown	2	1.1

N=265
*Back pain, arm pain, loss of sense, formication, pins and needles, speech disorder, perspiration, urinary incontinence, cough

at least 90.0% of the cases. However, it was seen that this period of time was prolonged up to 90 days, and the conformity percentage was calculated as 67.5%. Even though AFP is not included in surveillance criteria, it was seen that the mean±SD that elapsed from hospitalization to sampling was 3.7±4.4 and was prolonged up to 28 days (Table VI).

Discussion

We found no cases of poliomyelitis between 1999 and 2004 in the southeastern region of Turkey, where the last case was reported in 1998. As this period is more than three years since the last case, this result may be accepted as evidence of poliomyelitis eradication[25]. The annual rate of AFP was over 1/100,000 in children aged less than 15 years, a recognized threshold for sensitivity of AFP surveillance[26]. Incidence ranged from 0.60/100,000 in 2008 to 1.60/100,000 in 1999. In the region, non-polio AFP rate per 100,000 children aged less than 15 years was 0.9 in 1997 and 2.8 in 1998. Twenty-two poliomyelitis cases were confirmed in 1998[27]. There is considerable variation in the rates of AFP reported internationally[28]. The male to female ratio and age range of cases in our study were similar to those reports[29,30].

Table V. Viruses Isolated from Stool Specimens of 265 AFP Cases, 1999-2010

	N	%
No virus isolated	138	52.1
Adenovirus	10	3.8
Sabin-strain polio virus	10	3.8
Enterovirus	24	9.1
Coxsackievirus	12	50.0
Echovirus	12	50.0
Unknown	83	31.2

We surveyed prodromal symptoms like fever, respiratory symptoms, diarrhea, and muscle pain, and 78.5% of our cases had at least one prodromal symptom, particularly fever (15.0%). However, this proportion was lower than that reported by Dietz et al.[31], who found that 37% of cases with non-polio AFP had prodromal fever and 21.0% had prodromal respiratory symptoms. Some other studies also found a higher proportion of cases with prodromal fever[29,32]. In patients with non-polio AFP, 30.0% had fever at onset of paralysis and 39.0% had muscle pain[31]. Our cases indicated similar symptoms with similar ratios; however, 27.0% of them had no additional symptoms. Children with non-polio AFP are less likely than those with wild poliovirus isolates to have residual paralysis[27,31].

Different factors can lead to AFP, among which non-polio enteroviruses (NPEVs) are of great importance[33]. In Albania, out of 82 AFP cases not ascribed to polio, enteroviruses other than polio were isolated from eight subjects (7 Coxsackie, and 1 echovirus), and in 65 cases, none of the viruses was isolated[19]. In 17.8% of our AFP cases, enteroviruses like Echovirus and Coxsackie A and B viruses were isolated, a proportion similar to that of Dietz et al[31]. but higher than in Albania[31]. Tang et al.[34] reported that non-polio enteroviruses were isolated from 20.0% of stool specimens in 105 AFP cases. In our study, virus isolation was detected in most of the cases, and a good number of them were connected to GBS.

In a previous report from the Americas, there was no significant increase or decrease by the month of onset of AFP cases[31]. In June, a small increase was seen both in the cases of this study and in a previous report mentioning the same region's cases[27]. However, we may say that in every season, AFP cases can appear, and there is no significant difference between seasons in terms of appearance of AFP. Contrary to this, the temporal distribution of cases is rather characteristic, as most cases were concentrated in the period of May-October, and this situation could be related to the epidemiological progress of enterovirus infections, in which infections in temperate climate countries spread mainly during summer and autumn[35].

Table VI. Quality Surveillance Indicators of the AFP (1999-2010)

	Mean±SD (days)	Min-max (days)	Conformity time	Conformity percentage/ Required percentage
The time lapse until the samples are sent to the laboratory	5.4±4.9	0-27	3 days	42.7/100.0
The time lapse from paralysis onset to sampling	7.8±7.7	0-60	14 days	91.3/80.0
The time lapse from paralysis onset to notification	7.8±10.2	0-90	7 days	67.5/90.0
The time lapse between two samples	1.7±1.8	0-14	24 hours	70.0/100.0
The time lapse from hospitalization to sampling	3.7±4.4	0-28		

The limitations of our study were that we did not establish the exact diagnosis of AFP cases with negative stool specimens or the final diagnosis in a substantial minority of cases. However, most cases with a final diagnosis had GBS (41.4%), and secondly encephalopathy and encephalitis/meningitis. The proportion of GBS in other studies ranged between 30-45%[29,30,36].

It was seen that the time that elapsed from paralysis onset to paralysis reporting, the time that elapsed between acquiring the two samples, and the time that elapsed until the samples were sent to the laboratory do not conform adequately to the evaluation criteria[13,22,23,37]. A successful AFP surveillance program depends mainly on the reporting of cases. There is clearly a need to increase pediatricians' and neurologists' awareness of the importance of AFP surveillance and reporting. Except in 2002, the annual AFP was over 1 per 100,000 children aged less than 15 years. This may be the result of deficiencies in AFP surveillance and has prompted our research into the standard of the current surveillance program in Turkey and the awareness amongst clinicians to report all AFP cases, as required by the WHO guidelines[38].

In conclusion, the surveillance of AFP cases in the southeastern region of Turkey succeeded in establishing the absence of wild poliovirus transmission in this region where the last poliomyelitis cases of the European Region of WHO had been reported. Adequate detection rates were reached in each year except 2002, 2008 and 2009. One-quarter of AFP cases could not be followed up in the present surveillance system. The reasons for this situation should be examined, and the necessary measures should be taken. There is a need to understand the clinical decision-making processes leading to the failure to notify or obtain stool samples from children presenting with AFP39.

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