THIRTEEN-YEAR SURVEILLANCE RESULTS OF ACUTE FLACCID PARALYSIS CASES IN SOUTHEAST TURKEY AND THE EFFECT OF REFUGEE MOVEMENTS ON SURVEILLANCE RESULTS

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SUMMARY

Objective: Acute flaccid paralysis (AFP) is a major neurological problem. Turkey has accepted over 4 million refugees since 2011 due to the wars in neighbouring countries. In the long term, refugees can have adverse effects on the limited resources of health, sanitation, water supply, foodstuff, and shelter services of host countries, precipitating the transmission and spread of enteroviruses causing AFP. This study examines the 13-year surveillance and incidence of AFP cases in southeast Turkey, and questions possible impact of refugee movements on these parameters, comparing the periods before (2007–2010) and after (2011–2019) 2011, when the refugee movements emerged.

Methods: The records of cases reported from southeast part of Turkey with suspected AFP between January 2007 and December 2019 were reviewed retrospectively.

Results: Of the patients, 121 (58.5%) were male. Mean age was 80.36 ± 46.67 months. Eighty-five (41.1%) were aged 60 months or younger. The number of patients under 60 months increased significantly after 2011. Mean incidence was calculated as 0.88 cases/100,000 person years versus 1.58 cases/100,000 person years in the period before and after 2011, respectively. Guillain-Barré syndrome (GBS) was the most common cause of AFP in both periods. As of 2011, however, the incidence of acute transverse myelitis increased approximately 4 times and GBS decreased proportionally. Non-polio enteroviruses were the most frequent isolates, detected from 9.1% of stool samples.

Conclusion: Although refugee movements appear to may have adverse effects on AFP incidence and surveillance outcomes, larger studies involving the whole country, particularly at places where no refugees settled, are needed to achieve more conclusive evidence.

Key words: acute flaccid paralysis, surveillance, refugees, enterovirus, non-polio enterovirus

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INTRODUCTION

Acute flaccid paralysis (AFP) is defined as sudden onset weakness in any part of the body of a child younger than 15 years of age (1). In 1988, the World Health Organization (WHO) founded the Global Polio Eradication Initiative (GPEI) with a view to eradicate poliomyelitis worldwide, which is one of the prevailing and frightening causes of AFP. Poliomyelitis was eradicated in a considerable part of the world within a few years after the GPEI was founded (2). Turkey received the poliomyelitis-free zone certificate in June 2002, by successfully implementing the 4 basic strategies recommended by the GPEI (3). However, AFP remains to be an important neurological issue both in Turkey and in the world, even though the incidence of poliomyelitis decreased by 99.9% (4, 5). In particular, non-polio enteroviruses (NPEV) may lead to AFP outbreaks of transverse myelitis (6–9). Poor hygiene, crowded living environments and low socioeconomic status provide a basis increasing the risk of enterovirus (EV) infections, and children under 5 years of age are at greater risk in particular (10). EVs have a wide antigenic and genotypic diversity, with over 100 serotypes described. They become widespread in both hemispheres, typically from late summer to early autumn. Seasonality of dominant serotypes vary from year to year, some serotypes may reappear after several years (1). EV infections develop in millions of people worldwide each year, particularly in children. Although 75% of infections are asymptomatic, 1% may cause severe AFP-like diseases (1, 6, 10).

Millions of people have had to flee from countries neighbouring Turkey due to wars and other conflicts. Based on humanitarian concerns, Turkey adopted an ‘open door’ policy towards people fleeing from the war to exile and opened their doors to millions of refugees. More than 4 million refugees, mostly from Syria

(3.7 million Syrians, 330 thousand other nationalities), have been admitted to Turkey with increasing numbers since 2011. More than 1.5 million were children aged 0–15, and about one quarter of them migrated to Diyarbakır and surrounding provinces in southeastern Turkey (11, 12). The Diyarbakir province, with three children's hospitals, is a regional centre to which many patients from the surrounding provinces are referred.

Refugees may cause long-term adverse effects on the health, sanitation, water supply, food stuff, and shelter services of host countries with limited resources. Refugee movements may lead to environmental factors promoting circulation and spreading faecal-oral microorganisms such as EVs for all people living in that region (13, 14).

This study examined the surveillance results of the patients who were reported to the Diyarbakır Public Health Directorate with the AFP, to determine the incidence rate of AFP in Diyarbakır province, and to determine whether or not the refugee movements had an impact on these parameters. The periods before (2007–2010) and after (2011–2019) 2011, when the refugee movements started, were compared.

MATERIALS AND METHODS

In this study, the standard surveillance forms of patients with suspected AFP, reported to the Directorate of Public Health at Diyarbakır from January 2007 to December 2019, were reviewed retrospectively. Eligible records were found using the International Classification of Diseases (ICD) code system, where diagnoses are currently recorded. In Turkey, patients are considered to have suspected AFP if they are less than 15 years of age and have at least one of sudden onset weaknesses in at least one extremity; absent or decreased deep tendon reflexes; and respiratory and/or bulbar weakness.

AFP surveillance and laboratory studies are still ongoing to ensure that if poliomyelitis returns, it would be rapidly detected.

Workflow of Surveillance System

Reporting AFP Cases

When a patient is hospitalized due to suspected AFP, the standard surveillance forms, that are prepared by the Ministry of Health and commonly used throughout the country, are completed and the case is reported to the provincial Directorate of Public Health. These forms include patient's identity and address information, date of onset, location and type of the paralysis, other clinical findings accompanying the paralysis, polio vaccination status, contact cases as well as the reporting doctor's identity and address information. These forms also include sampling dates of the two stool specimens that are to be taken 24–48 hours apart in the first 14 days after the onset of the paralysis, and whether any sequelae were present at the end of the 60-day follow-up period.

Collection of Stool Specimens

Stool specimens collected by the healthcare staff of the patient's hospital are handed over to the surveillance teams of the Provincial Directorate of Public Health and then delivered to the National Virology Reference Laboratory of the General Directorate of Public Health in the capital city, in accordance with the cold chain rules. In the reference laboratory, stool specimens are tested for EVs in accordance with the algorithms recommended by the WHO.

Processing Stool Specimens, Virus Isolation and Identification

Centrifuge tubes were labelled with sample numbers and added 10 ml phosphate buffer solution (PBS), 1 g of glass beads and 1 ml chloroform into each tube. Approximately 2 g of faecal sample was transferred to each tube in the biological safety cabinet (BSC), and the tubes were shaken vigorously for 20 minutes by means of a mechanical shaker. Finally, the tubes were spun for 20 minutes at 1,500 g in a refrigerated centrifuge. Working in a BSC, supernatant was transferred from each sample tube into two labelled storage vials. All samples were inoculated onto human rhabdomyosarcoma cells, and mouse cell lines (L20B) as recommended by the WHO for isolation of poliovirus (PV) and other human EV. Cell cultures exhibiting a cytopathic effect were serotyped with antisera pools from the National Institute of Public Health and the Environment (RIVM), the Netherlands, until August 2015 for differentiation of PV and NPEV. Neutralisation assays were performed according to WHO recommendations (15). After 2015, molecular techniques were set up in the laboratory and algorithm for identification of isolates was changed to the real time-based polymerase chain reaction (PCR) assays as intratypic differentiation method developed by CDC (Atlanta, USA). All isolated polioviruses were tested for their wild or vaccine origin by PCR, according to the protocol recommended by the WHO, and sequencing analyses were performed (15).

Calculation of Incidence and Statistical Analysis

Official data of the Turkish Statistical Institute and the Turkish Ministry of Interior, Directorate of Migration Management, were used for Diyarbakır population and refugee numbers, respectively (2, 3). Due to confidentiality laws in our country, we do not know the percentage of residents and refugees among AFP patients. Two patients who were initially considered to have AFP but were eventually diagnosed with arthritis were not included in the incidence calculation.

The data were evaluated by the Statistical Package for the Social Sciences (SPSS 15.0) computer program. Number and percentage values were given for categorical variables, and mean, median, minimum and maximum values were given for continuous variables. Chi-square analysis was used in statistical analysis. $P<0.05$ was considered statistically significant. Since the study design was retrospective, definitive diagnosis and stool culture results of some patients that could not be reached were defined as missing data.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Health Sciences University, Gazi Yaşargil Training and Research Hospital (approval no. 314 of 27 September 2019).

RESULTS

Of the 207 patients with a diagnosis of AFP 109 (52.6%) came from Diyarbakır city centre and the other 98 from 13 different cities in the neighbourhood, 121 (58.5%) were male. Mean age was 80.36±46.67 months, while 85 (41.1%) were aged 60 months or less.

Patients' age, gender, clinical diagnoses after follow-up and examination, and stool culture results are summarized in Table 1. Guillain-Barré syndrome (GBS) was the most common clinical diagnosis, at the end of the follow-up period with 151 (72.9%) patients. The second most common diagnosis was acute transverse myelitis (ATM), with 15 (7.2%) patients. After 2011, while GBS decreased proportionally, acute transverse myelitis was detected to have increased almost 4 times. No virus was isolated in the stool samples of 173 patients, while virus was detected in 24 (11.6%) patients (data were missing for 10 patients as stool was not collected or data were not reported). Serotyping was not performed in 13 non-polio and EV positive patients, and they were reported as NPEV. Poliovirus was not detected but one patient had vaccine-induced Sabin-like polio. For the remaining 10 patients, Coxsackie A, B was detected in five, echovirus in one, enterovirus in three and human herpesvirus 7 in one patient.

Most of the patients were admitted to hospital in spring (n=61, 29.47%), followed by summer (n=58, 28.02%), winter (n=56, 27.05%), and autumn (n=32, 15.46%) (Fig. 1). Distribution of AFP cases varied markedly by year, in some years, 4–5 times as many patients applied to hospitals when compared to other years. The highest number of admissions occurred in the period 2015–2017.

For the Diyarbakir province and 0–15 aged population, annual incidences were 0.34–1.83 cases/100,000 before 2011, and 0.33–2.43 cases/100,000 in 2011 and after. The mean incidence was 0.88/100,000 before 2011, versus 1.58/100,000 in and after 2011. The 13-year mean incidence was found to be 1.38/100,000 (Table 2).

There was no statistically significant difference in EV isolation rates in stool before and after 2011, whereas a statistically significant increase was found in the incidence of ATM before and after 2011 (p=0.02). The rate of patients aged 60 months and younger was 25% before 2011, and 45.4% in and after 2011 (p=0.015) (Table 3).

DISCUSSION

This is the first study examining the potential impact of refugee movements in southeast Turkey on AFP surveillance results and incidence.

Those who settled in refugee camps isolated from the local inhabitants were small portion of the refugees coming to Turkey; 10% in the highest period and 1.4% in the lowest period. Thus, 90–98% of the refugees settled in cities and towns, using

Table 1. *Clinical characteristics and surveillance results of patients (N = 207)*

Age (months), mean (SD)		80.36 (46.67)
Gender, n (%)	Male	121 (58.5)
	Female	86 (41.5)
Final diagnosis, n (%)	Guillain-Barré syndrome	151 (72.95)
	Acute transverse myelitis	15 (7.25)
	Encephalitis/cerebellitis	8 (3.86)
	Peripheral neuropathies	7 (3.38)
	Acute disseminated encephalomyelitis	5 (2.42)
	Stroke	4 (1.93)
	Myopathies	4 (1.93)
	Myasthenia gravis	2 (0.97)
	Neuroblastoma/adrenal tumour	2 (0.97)
	Arthritis	2 (0.97)
	Acute lymphoblastic leukaemia	1 (0.48)
	Intoxication	1 (0.48)
	Missing data	5 (2.42)
Virus isolation in stool sample, n (%)	No virus isolation	173 (83.57)
	NPEV* (untyped)	13 (6.28)
	Coxsackie A, B*	5 (2.41)
	Echovirus 6*	1 (0.48)
	Sabin-like polioviruses	1 (0.48)
	Human herpesvirus 7	1 (0.48)
	Adenovirus	3 (1.45)
	Missing data	10 (4.83)

NPEV – non-polio enteroviruses; *viruses classified as NPEV

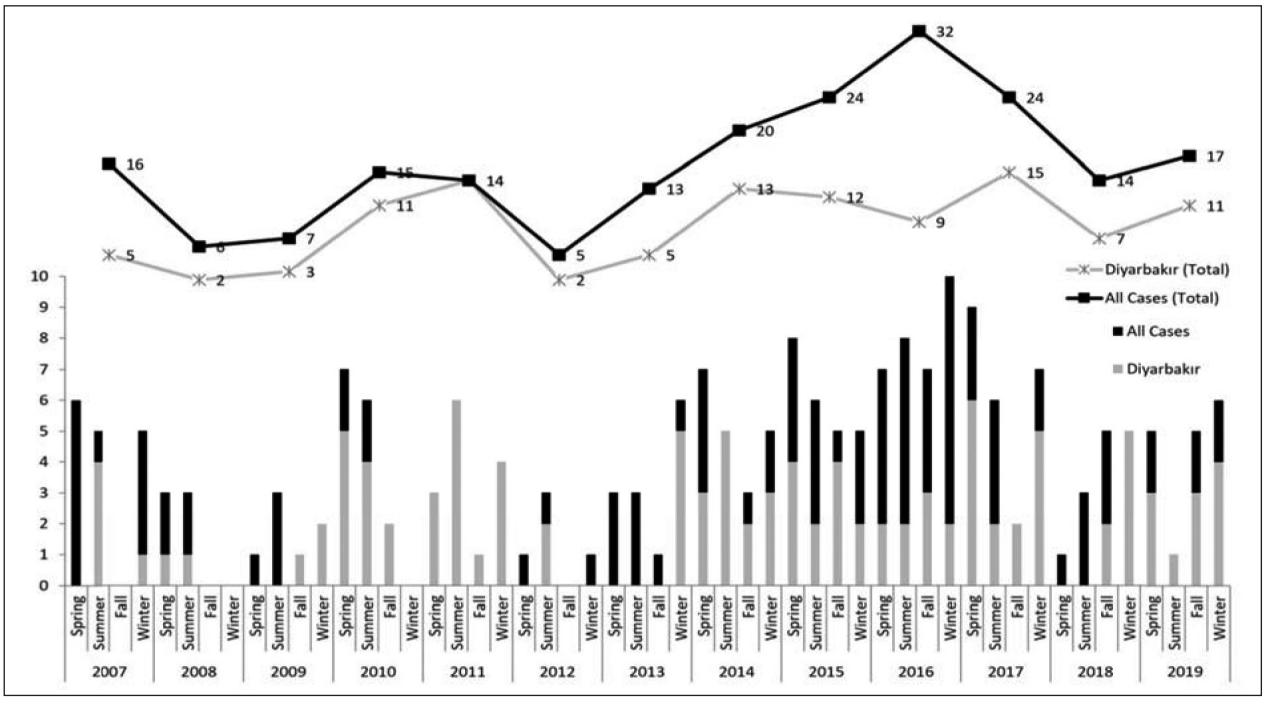

Fig. 1. *Distribution of Diyarbakir cases and all cases according to seasons and years.*

Table 2. *Average incidence of AFP cases by years in Diyarbakir province*[a]

Years	Number of AFP cases	Incidence per 100,000[b]	0–15 years population	Total population
2007	5	0.85	588,909	1,460,714
2008	2	0.34	594,242	1,492,828
2009	3	0.50	600,547	1,515,011
2010	11	1.83	600,567	1,528,958
2007–2010 total cases/mean incidence	21	0.88		
2011	14	2.29	611,684	1,595,161
2012	2	0.33	614,186	1,616,385
2013	5	0.81	614,589	1,631,655
2014	13	2.11	617,000	1,659,266
2015	12	1.95	615,838	1,678,414
2016	9	1.46	614,409	1,697,337
2017	15	2.43	618,214	1,724,119
2018	7	1.12	622,507	1,756,614
2019	11	1.76	624,907	1,780,571
2011–2019 total cases/mean incidence	88	1.58		
2007–2019 total cases/mean incidence	109	1.38		

[a]Only refugees settled in Diyarbakır are included in the calculation (2 patients diagnosed with arthritis were not included).
[b]Incidence was calculated according to the population aged 0–15 years.

the same neighbourhood, streets, markets, and social areas with the residents (11, 16, 17). This situation, right from the onset of refugee influx, might lead to a competition between the natives and refugees for sharing scarce resources, including water, food, shelter, and medical services, and this presents various challenges in accessing services, deterioration in quality of some services, besides environmental impacts. Refugees, generally on the disadvantageous side in this competition, try to maintain their lives in unfavourable environments, in overcrowded housing conditions with inadequate hygiene. As a result, it is likely to observe deterioration in conditions of health, education, housing, and socioeconomic welfare as well as environmental parameters in those regions, where the lives of both residents and refugees are adversely affected (12–14).

Table 3. *Comparison of virus isolation rates, final diagnoses and rates of patients under 5 years of age before and after 2011*

		2007–2010	2011–2019	Total	p-value*
		n (%)	n (%)	n (%)	
Virus isolation	Negative	39 (88.6)	134 (87.6)	173 (87.8)	**0.085**
	Positive	5 (11.4)	19 (12.4)	24 (12.2)	
	Total	44 (100.0)	153 (100.0)	197 (100.0)	
Final diagnosis	GBS	38 (88.4)	113 (71.1)	151 (74.8)	**0.02**[b] $\chi^2 = 5.369$
	ATM	1 (2.3)	14 (8.8)	15 (7.4)	
	Other[a]	4 (9.3)	32 (20.1)	36 (17.8)	
	Total	43 (100.0)	159 (100.0)	202 (100.0)	
Age (months)	0–60	11 (25.0)	74 (45.4)	85 (41.1)	**0.015** $\chi^2 = 5.957$
	61 and up	33 (75.0)	89 (54.6)	122 (58.9)	
	Total	44 (100.0)	163 (100.0)	207 (100.0)	

[a]All diagnoses except GBS and ATM were grouped as 'other'.
[b]ATM and other diagnoses were combined while performing statistical analysis.
*Chi-square test

Table 4. *Causes of acute flaccid paralysis*

Infectious • Poliomyelitis • Vaccine-associated paralytic polio • Vaccine-derived poliomyelitis • Non-polio enteroviruses • West Nile virus • Diphtheria • Flaviviruses • Adenoviruses • Other viruses (Japanese encephalitis virus, European tick-borne encephalitis virus, etc.)	**Disorders of neuromuscular transmission** • Myasthenia gravis • Lambert-Eaton myasthenic syndrome • Botulism • Tick paralysis • Tetanus toxin • Animal toxins (snake venom, dart poison frog, puffer fish tetrodotoxin) • Organophosphate poisoning
Myelopathic • Postinfectious transverse myelitis • Anti-MOG associated myelitis • Anti-AQP4 associated myelitis • Arterial or venous spinal cord infarction • Compression from spinal abscess, haemorrhage, or tumor	**Myopathic** • Inflammatory myopathy • Rhabdomyolysis • Carnitine deficiency • Periodic paralysis • Weakness associated with critical illness
Neuropathic • Guillain-Barré syndrome • Acquired motor axonal neuropathy • Acquired motor sensory axonal neuropathy • Mononeuritis multiplex • Multifocal motor neuropathy • Acute intermittent porphyria • Toxic neuropathies	

Most of the patients in previous AFP surveillance studies were male and under 60 months of age (18–22). There are also studies that reported a majority of female patients, although rare (23). In our study too, male patients were in majority, however, most of our patients were over 5 years of age with 41% being 60 months or younger. As for the age distribution in the periods before and after 2011, the rate of patients under 5 years of age was 25% before 2011, while it increased to 45% after 2011, yielding a statistically significant difference. The increase in AFP cases younger than 5 years may be attributed to the fact that this age group is more vulnerable to malnutrition, inadequate sanitation, and problems in receiving health and other public services that is likely to occur in the conditions of war and refugee life (14, 24, 25). Furthermore, their immune system which is not fully developed yet at this age and their dependence on parental help for maintaining personal hygiene might be the other factors increasing the risk in this age group.

AFP is a clinical picture with a broad spectrum of differential diagnosis to be considered, and it can develop due to an abnormality in any part of the neuraxis. Although the causes of AFP vary regionally and ethnically, Guillain-Barré syndrome is the most common cause in industrialized countries as well as in developing countries. The rate of GBS was reported in the range of 17.8–83.2% in AFP surveillance studies (26, 27). In our series too,

GBS was the most common cause with a rate of 72.9%. ATM was the second most common cause with a rate of 7.25%. When these two periods were compared in terms of diagnoses, GBS decreased proportionally in 2011 and after, while ATM increased almost 4 times. Normally, ATM is a rare disease with an estimated incidence of 1/1,000,000. However, in recent years, NPEV-associated ATM outbreaks, particularly due to Enterovirus A71 (EV-A71) and Enterovirus D68 (EV-D68), were reported in the United States of America and in many other countries (6, 7, 10, 28). In the USA, an increasing number of ATM cases were reported as 120, 153 and 236 in late summer/early fall of 2014, 2016, and 2018, respectively. It is postulated that the outbreak expected for 2020 did not occur due to the COVID-19 restrictions, including widespread use of masks, hygiene rules and limited number of students at schools (28). The increased ATM cases in our study in 2011 and after may be related to refugee movements as well as NPEV-related ATM outbreaks as seen in other parts of the world.

NPEVs became the focus of aetiological research, since they were considered as the predominant cause of AFP in the post-polio eradication period (26, 28). In our patient series, significant fluctuations were determined varying with periods, but with no significant seasonal dominance. Most of the patients applied in spring. Annual number of cases generally increased after 2011, but seasonal distribution of the cases displayed no significant difference. The reason that a higher number of cases were observed in spring in our country might be attributed to the consideration that the incidence depends on the climate and the seasonal differences in average temperatures in each country.

NPEV isolation rates were in the range of 6.1–33.4% in AFP surveillance studies. The WHO set the standard for reference laboratories to isolate 5–25% NPEV in all stool samples, as the competence criterion (15, 28, 29). NPEV could be isolated in 9.1% of stool samples in our study (combining untyped-NPEVs Coxsackie A, B, and echovirus) with no differences in the two-time period studied. Our lower rate of virus isolation from stool than in some other studies may be due to the fact that EV-D68, one of the most common serotypes causing AFP, can be detected best in respiratory tract specimens, but rarely detected in stool and cerebrospinal fluid samples (10, 28, 30). In our country, respiratory tract specimens are not collected for AFP surveillance as the primary goal is to detect polio which is readily detected from stool. Establishing a new standard study protocol for the isolation of NPEVs and collecting respiratory tract specimens in addition to stool specimens may improve the effectiveness of AFP surveillance systems.

AFP annual incidence rates range from 0.43 to 7.3/100,000, where the lowest rates were observed in industrialized countries and the highest rates in Africa, in general (28, 29). In our study, mean incidence of AFP was 0.88/100,000 in the period before 2011, while it was 1.58/100,000 in the period after 2011.

When all the findings are evaluated together, a significant increase was observed from 2011 on, with respect to AFM incidence rates, the proportion of ATM cases and the proportion of children under 5 years of age. However, we do not have conclusive evidence linking these changes to refugee movements. Unfortunately, as mentioned previously, we do not know the resident versus refugee status of AFP cases. A comparison of changes in AFP rates in parts of Turkey that accepted none or few refugees would be informative.

Retrospective design, some missing data, inability to differentiate between cases in refugees and residents, and taking into account only registered regular refugees but not unregistered refugees coming by irregular migration are limitations of the study.

CONCLUSION

Although refugee movements seem to have negative impacts on AFP incidence and surveillance outcomes, larger studies are needed to obtain more conclusive evidence, covering the whole country, particularly the regions where refugees do not intensively settle.

Conflicts of Interest
None declared

Authors' Contributions
NÖ, GK, BT and MÖ – material preparation, data collection and analysis; NÖ, İT – statistical analysis; GK – microbiological analysis. All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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