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NEUROLOGICAL MORBIDITY IN VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS IN BRAZIL

From 1989 up to 1995

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ABSTRACT - We collected 30 cases of vaccine associated paralytic poliomyelitis (VAPP) from 4081 cases of acute flaccid palsies cases notified from 1989 to 1995 to the Brazilian Ministry of Health. There were 30 VAPP cases with 56% of children younger than 1 year old, 56.7% of female. 46% of cases were reported in the Northeast. Ten P2 vaccine virus, 8 P3 and 2 P1 and associations amongst them were isolated. The clinical pattern in 60 days was: monoplegia (16), paraplegia (6), tetraplegia (5), hemiplegia (2) and triplegia (1). There was no strong relationship between fever, before or after the prodrome period, or the use of intramuscular medication to morbidity. *Conclusion:* if the anti-poliomyelitis strategy adopted in Brazil has lead to the eradication of the poliomyelitis with wild virus infection, the existence of a minimum risk of vaccine-associated poliomyelitis is a matter of concern because there will be a permanent neurological deficit.

KEY WORDS: oral polimyelitis vaccine, paralytic poliomyelitis, neurological deficits.

Morbidade neurológica em poliomielite paralítica pós vacinal no Brasil de 1989 a 1995

RESUMO - Trinta casos de poliomielite associada à vacinação oral (Sabin) foram estudados a partir de 4081 notificações de paralisias agudas e flácidas feitas ao Ministério da Saúde no período de 1989 a 1995, com o objetivo de avaliar a gravidade do quadro neurológico. Dezesseis pacientes tiveram monoplegia, 6 paraplegia, 5 tetraplegia , 2 hemiplegia e 1 triplegia. Foram 56% em menores de 1 ano, 56,7% no sexo feminino, 46% dos casos provenientes do nordeste. Em 10 pacientes foi isolado o vírus vacinal P2, em oito o P3 e dois o P1.Os demais tinham associações de mais de um tipo de vírus. Febre antes ou após o período prodrômico e o uso de medicação intramuscular não se relacionaram a maior morbidade. A política antipoliomielite adotada no Brasil levou à erradicação da poliomielite pelo vírus selvagem com um risco mínimo do ponto de vista epidemiológico, porém ainda com custos individuais não desprezíveis.

PALAVRAS-CHAVE: vacina oral, poliomielite paralítica, seqüelas neurológicas.

The introduction of mass vaccination with the live attenuated oral poliovirus vaccine has dramatically modified the epidemic poliomyelitis, causing a sharp decline of the disease worldwide. The oral poliomyelitis vaccine (OPV) was successfully used to control paralytic poliomyelitis in some regions of the world, including China, the former USSR, Japan, the Americas and Oceania, and many smaller European countries, which all together have a population of almost 2 billion. The elimination of wild-virus associated poliomyelitis in the Western Hemisphere in 1991 and the rapid progress in global poliomyelitis eradication efforts changed the risk-benefit ratio associated with the exclusive use of oral poliovirus vaccine[1]. Since 1961, shortly after the introduction of the OPV, cases of paralytic poliomyelitis caused by the vaccine in the United States were reported. Terry cited by Strebel, says that between 1961 and 1984, a total of 229 cases of vaccine-associated paralytic poliomyelitis (VAPP) were reported in the United States, with a range of 14 cases annually after 1965[2] .

In Brazil, the epidemiological surveillance system of the poliomyelitis eradication program of the Ministry of Health, keep in their records a total of 1290 cases of poliomyelitis in the year of 1980.With the beginning of the National Poliomyelitis Eradication campaign, there was a decline in the incidence of the disease and in 1989 the last case of poliomyelitis in Brazil was reported[3]. However, in the last decade a reduction in the notification data recommended by the vaccination eradication campaign in the whole country was noticed. These facts lead to a great concern regarding reintro-

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duction of the wild poliovirus in the population, since the disease is still endemic in some neighboring continents. Moreover, in these days the risk of importing the virus is higher due to the facilities of traveling by airplane as already happened in Canada where there was an outbreak of poliomyelitis originated from the Netherlands[3-5].

The aim of the present study is to determine the actual neurological morbidity of vaccine associated paralytic poliomyelitis in the period of 1989 to 1995 in Brazil and their risk factors, to contribute to the discussion about a better way to vaccinate people against poliomyelitis: oral (Sabin) x intramuscular (Salk). It is important to keep in mind that the eradication of the disease in South America through vaccination was a major achievement. Nevertheless, isolated cases of VAPP have been reported in Brazil and other South American countries. After the first enthusiasm, it is timely to study the adverse events and to discuss the vaccines costs/benefit ratio and the ongoing health strategies developed to maintain the eradication of poliomyelitis.

METHOD

The Brazilian poliomyelitis surveillance program data was searched for all cases diagnosed as poliomyelitis from 1989 to 1995. Cases were classified as: a) *vaccine-associated poliomyelitis*: those with acute flaccid paralysis (AFP) who persisted with residual neurological deficit after 60 days and the vaccine poliovirus was identified from the patients stools, collected during the first 15 days of paralysis, or from a sample of the cerebrospinal fluid: b) *compatible poliomyelitis*: AFP with residual neurological deficit after 60 days, or death, or had an unknown follow up, but could not have the stool samples to isolate the poliovirus, c) *not poliomyelitis*: all subjects from whom poliovirus was not isolated in stool or other sample culture. According to the way to acquire the vaccine associated poliomyelitis they were: 1) VAPP *recipients:* cases with paralysis that received the OPV in a period between 4 to 30 days; 2) acquired cases from *contact with vaccinated children* and presented with AFP in the period of 4 to 75 days after the vaccination day; 3) if neither 1 or 2 were identified, it was concluded that the case was acquired from the community.

The patients were studied in relation to some possible risk factors such as: intramuscular injection, previous illness, the type of isolated virus strain (P1, P2, P3), age and gender. The vaccine-associated poliomyelitis cases were distributed according to the Brazilian geographic regions in order to know its frequency and distribution.

All patients had stool samples culture. The isolated virus was classified according to the strains as vaccine poliovirus type 1 (P1), vaccine poliovirus type 2 (P2), and vaccine poliovirus type 3 (P3) or wild poliovirus. The analysis was performed by specialized laboratory reference to the poliomyelitis program, and the stool had to be collected in two samples with an interval of 24 hours until the fourteenth day. If the local condition permitted the patients had their cerebrospinal fluid analyzed and were submitted to an electromyography examination according to the judgement of the assistant physician. The severity of the cases was shown by the intensity of the aggression exemplified by the number of limbs affected: from tetraplegia, the most severe form, to monoplegia, the less severe one.

RESULTS

From a total of 4081 notifications of acute flaccid paralysis, 62 notifications were classified as *compatible with poliomyelitis*, and 30 cases (0.74%) as *vaccine-associated poliomyelitis* (age 2 to 100 months, mean 18.9 months, median 10.5, standard deviation SD = 10.7) there was 13 males (age 3 to 52 months, mean 14.8 months, median 7, SD = 14.8) and 17 females (age 2 to 100 months, mean 22.1, median 16, SD = 22.1).

From these 30 cases, 14 were classified as recipients, as they developed the disease less than 30 days after the vaccination. Ten cases broke up between 31 to 60 days after the vaccine campaign and were considered as acquired from communicants. It was not possible to identify the incubation period in six cases. As long as these people had not been vaccinated in the previous 60 days, the disease was considered as having been acquired in the community.

In 1989 ten cases of vaccine-associated cases were diagnosed. The following years showed that there was decrease in the incidence. Only two cases were registered in 1993 and 1994, raising again in 1995 (Fig 1).

The year of 1989 was studied separately due to the fact that until that year all cases of acute flaccid palsies were investigated independently of the patient's age. Since 1990, only the acute palsies that affects children less than 15 years old were investigated. In 1989, from a total of 917 notifications of acute flaccid paralysis, there were 10 cases of vaccination-associated poliomyelitis. Out of these, three were identified as having received the vaccine. Two cases were acquired from communicants and five cases acquired the infection in the community. There was confirmed participation in the vaccination campaign of all theses cases. From 1990 to 1995, 20 cases of vaccine-associated poliomyelitis were identified; 11 had received the vaccine, one was acquired from communicants and the others from the community.

When the cases reported were plotted by regions, the vaccine-associated paralysis predominated in the Northeast region (46%), with a minor frequency in the Midwest and North regions (Fig 2).

Gender and age - There was predominance of females, with 17 cases (56.7%). The great majority of cases were in children less than five years old with 96.6% of VAPP cases, and 17 cases (56.7%) less than one year old, decreasing progressively in frequency according to the age. Between five and nine years old the frequency was only 4% (Table 1).

Risk factors - Eight patients received intramuscular injections previously, but this was not related to a more severe form of the illness. It was not possible to demonstrate any case associated with immune depression since it was not the goal at that time and was not investigated. Twenty-six cases presented with fever, that started during the prodrome or at the same

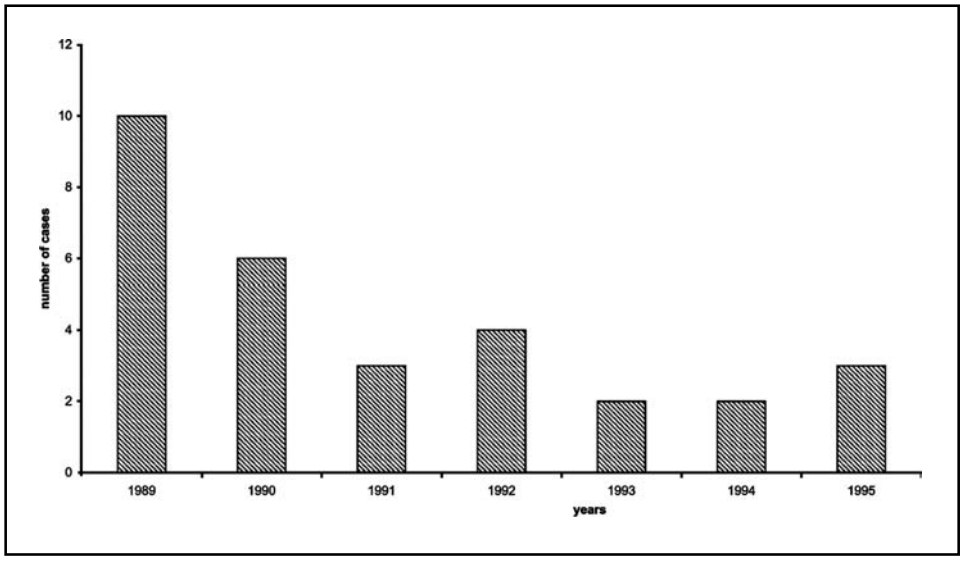

Fig 1. Vaccine-associated poliomyelitis in Brazil from 1989 to 1995.

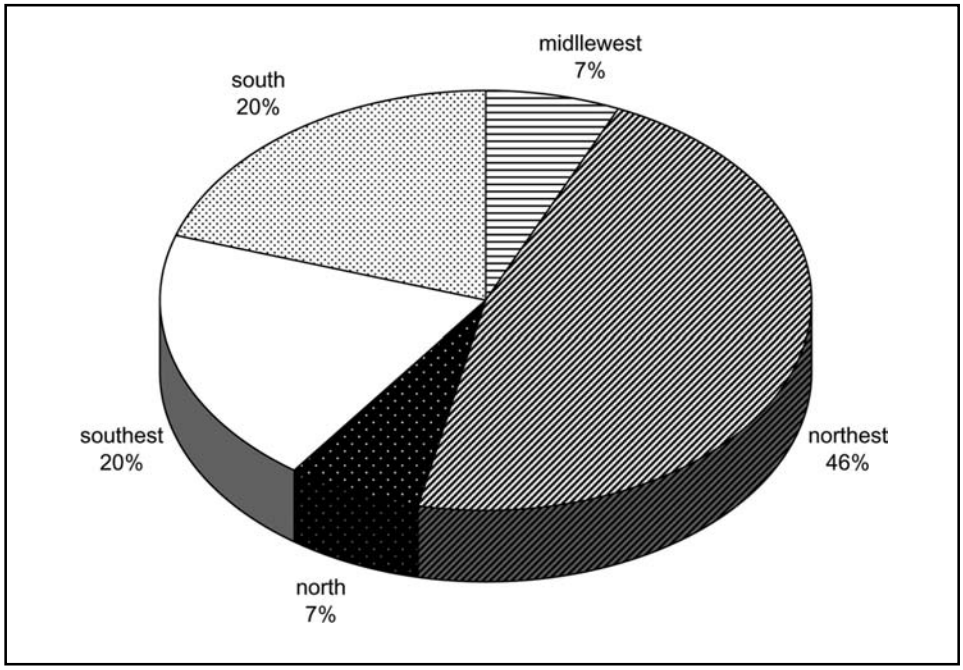

Fig 2. Distribution of vaccine-associated polimyelitis by regions.

time as the paralysis, so they were interpreted as a component of the clinical picture and not as an indicative of immune deficiency or a sign of complication.

Diagnosis and morbidity - Table 2 shows the distribution of all vaccine-associated poliomyelitis cases according to the clinic, type of virus identified and the presence of risk factors. Table 3 correlates the illness severity to the type of virus.

In five cases the disease had affected all four limbs. In only one case it had affected three limbs. In eight cases two limbs were affected. From those, two cases presented hemiplegia and six paraplegia. Finally, the last 16 patients had paralysis in only one limb (Table 2).

In only one case association with cranial nerve palsy was noticed. There were two cases of respiratory tract complications. The inferior limbs were affected more severely and in the whole the predominance was of the less severe forms of the disease. (Table 2).

In the follow-up at 60 days all cases with monoplegia remained as so but some became less severe. One case of

tetraplegia turned to paraplegia and another with residual neurological deficit in the right arm and the left leg. Another case remained with triplegia. Two cases of tetraplegia remained unchanged at the evaluation within 60 days, one of them with tracheotomy. However, in one of those, a later reevaluation in ten months showed only monoplegia.

The cerebrospinal fluid was examined in 10 patients. It showed mononuclear pleocytosis in five cases and in three cases there was high protein content, which was compatible with viral meningitis. There were two cases with dissociation between protein and cytology content, but that proved not to be Guillain-Barré syndrome by the clinical and other laboratory features. The electromyography test was performed in 25 of these 30 cases, being compatible with poliomyelitis in 22 cases.

The isolation of the virus in the stool was possible in 29 cases. In one case (case 12) identification of the virus was possible only in the cerebrospinal fluid. From the three different viruses presented in the oral vaccine, the P2 type was present in 10 cases (representing 33% of the cases), the P3 type in eight cases and the P1 type in two cases. In the other 10 cases there was an association of poliovirus present in the vaccine. In four cases the P1P2P3 were identified, in four cases P2P3 and in one case P1P3 (Table 2).

Table 1. Distribution of vaccine-associated cases by age 1989 to 1995.

Years	Number of cases	%
< 1	17	56.7
1< 2	6	20
2 < 3	2	6.7
3 < 4	3	10
4	1	3.3
8	1	3.3

Source: GT-polio/FNS/ Brazilian Ministry of Health.

DISCUSSION

The definition of VAPP cases differs according to the author[6-8]. In this study, it was considered as vaccine-associated poliomyelitis recipient only those cases in which the disease started between four and thirty days after the vaccination. The cases acquired from communicants were those who presented the disease between 4 and 75 days. Since 1997, the Brazilian Health Ministry changed and adopted the Pan American Health Organization definitions to classify the recipient cases as those cases occurring between 4 up to 40 days and cases acquired from communicants those in which the symptoms began between 4 to 85 days after the vaccine campaign, with the need to still have residual neurological deficit after 60 days of the disease. Other studies may use other criteria or even simplify them as in the United States, where all cases of flaccid palsies with residual deficit after sixty days and that have had contact with vaccinated persons are considered VAPP, but it is not necessary to identify the virus[7].

The risk rate and incidence of VAPP has already been calculated by Oliveira and Struchiner[6], when discussing the same cases presented here, finding a lower risk rate and incidence of VAPP than those found in other studies. This data differs from Andrus and col.[7] that found fifty four cases in a period between 1989 and 1991, but in this study all patients that had received the vaccine between 4 and 40 days before the palsies manifestation were considered as recipients cases and they not included the virus isolation in stools as a criterion for the case definition. To be more precise, the present study combined the isolation of the virus with the clinical and laboratorial data.

Our data agree with the literature concerning the age incidence and the monoplegia as the prevalent clinical pattern. Authors in Romania that reported poliomyelitis palsies related to vaccine and wild poliovirus did the same observation[9]. In that paper, it was observed a greater risk of VAPP than the usual, which was attributed by the authors to elevated risk factors in the region, pointing the intramuscular injections as risk factor, similar to what occurs in paralytic poliomyelitis. But further studies did not confirm this hypothesis[8,10]. The present study has found that 8 of the 30 cases (26.6%) were exposed to intramuscular injections in the period from oral vaccine exposition to the beginning of the poliomyelitis. Nevertheless, before taking any definite conclusion about this possible risk factor, we agree with other authors that it is necessary to carry out more specific analysis[11].

It was not clear that the severity of infection was related to a special virus strain either alone or in combination, probably due to the great predominance of monoplegia, but the odds rates showed that the more severe forms had 1.67 more probability to be related to P3 than to P1, failling to demonstrate differences between P1 and P2 or P1 and those with more than one virus.

Fever has been present in 24 cases, but only in two cases there was a febrile illness before the beginning of the prodrome period and these cases were not related to any clinical evidence of a congenital or acquired immunodeficiency. Although the immunology and nutritional aspects of these patients were not studied, the higher concentration of VAPP cases in the states with less favorable social and economic situation is notorious. The Northeast region of Brazil was responsible for 46% of the reported vaccine-associated poliomyelitis in contrast to the North and the Midwest regions, each one representing only 7%. As long as there was no report of problems concerning the cold chain and the vaccines are distributed in the same day and from the same source, we cannot explain those diversities. Further studies are demanded.

Table 2. Distribution of the vaccine-associated poliomyelitis Brazilian cases according to age, risk factors and etiologic agent. Period 1989 to 1995.

Case	Age	Risk factors		Isolated virus		Morbidity
		Presence of feverish illness	intramuscular injection	from patient	from communicants	
3a	1y 6m	Prodrome	-	P2	P2	Tetraplegia
1	2y	-	-	P3	P3	Tetraplegia
9	2m	-	-	P3	P3	Tetraplegia
15	4y4m	Prodrome	-	P2	P2	Tetraplegia
20	7m	Prodrome	-	P3	P3	Tetraplegia
6	4m	Before and prodrome	-	P3	-	Triplegia
4	2y	-	-	P2 * P1,P2,P3 **	P2	Paraplegia
5	1y4m	-	-	P3 * P1,P2,P3 **	-	Paraplegia
10	2y5m	Prodrome	-	P1,P2,P3	-	Paraplegia
16	3y9m	Prodrome	-	P1,P2,P3	-	Paraplegia
17	3y11m	Prodrome	Same day OPV	P1	-	Paraplegia
18	3m	Prodrome	-	P2,P3	-	Paraplegia
8	7m	Varicella-Zoster #	-	P3	-	Hemiplegia
14	8m	Prodrome	Gentamicine	P2	P2	Hemiplegia
2	2y	Prodrome	-	P3	-	Monoplegia
3	1y10m	Prodrome	-	P2	-	Monoplegia
7	8m	Prodrome	Peniciline	P1	-	Monoplegia
11	10m	Prodrome	-	P1, P3	No polio	Monoplegia
12	8y4m	Prodrome	Measle vaccine	P3	P3	Monoplegia
13	6m	Prodrome	TDW	P2	-	Monoplegia
19	4m	Prodrome	TDW	P2, P3 * P2 **	-	Monoplegia
1 a	8m	Paralysis	-	P2,P3	-	Monoplegia
2 a	6m	Prodrome	-	P2	P2	Monoplegia
4 a	11m	Paralysis	-	P2	-	Monoplegia
5 a	3y	Prodrome	-	P2,P3	-	Monoplegia
6 a	8m	Prodrome	-	P1,P2,P3	-	Monoplegia
7 a	3m	Prodrome	-	P3	-	Monoplegia
8 a	4m	Prodrome	-	P2,P3	-	Monoplegia
9 a	1y 8m	Prodrome	First day prodrome	P2	-	Monoplegia
10 a	1y	Prodrome	-	P2	P2	Monoplegia

OPV, oral poliomyelitis vaccine; TDW, (tetanus, diphtheria, whooping-cough); * stool first sample; ** stool second sample; # There were fever was associated to varicella infection but the exact time it happened it was not documented; Case 12 – in this case was not isolated any virus in stool, but in the CSF; Source: GT Polio/CNDI/FNS/MS.

Table 3. Association between virus strains and illness severity.

	Less severe	More severe
P1	1	1
P2	6	3
P3	3	5
Px	6	5

Px, Association of two or three virus strains in the same patient; Less severe, monoplegia; More severe, more then one limb afected.Source: GT-polio/FNS/Brazilian Ministry of Health.

The electromyography performed in 25 cases showed denervation signals pointing to lesion in the anterior spinal cord. But it is not possible to distinguish between all the peripheral neuropathies presenting as AFP with such test. The cerebrospinal fluid turns out to be very important in the differential diagnosis as it shows septic meningitis and in one case permitted the isolation of virus. There was one case in the present study in which no virus was isolated in the stool, only in the cerebrospinal fluid, and the same virus was isolated in one communicant. This child began with a paralysis that persisted after 60 days, fulfilling the diagnostic criterion of a vaccine-associated poliomyelitis case. This is rarely reported in the literature[12].

The importance of the virus virulence versus the patient immunological condition has been discussed in the literature. The presence of the same frequency of P2 and P3 strains is in agreement with other authors[8] and it is suggested that the P2 and P3 strains have a great probability of reversing the virulence compared to the P1 strain. The virulence attenuation and in the same way the virulence reversion can be attributed to genetic mutations and is probably one of the factors that is needed to development of VAPP, in combination with some other host factors[13-15]. De Filipps and cols.[16] published the poliovirus differentiation types in acute flaccid paralysis in Brazil from 1990 to 1993, pointing out the predominance of P3 (45%), followed by the P1 (30%) and the P2 (24%). The predominance of P3 and P2 is also observed when studied in relation to VAPP, confirming their major probability of virulence reversion[16].

Another factor that could be implicated as a major risk to VAPP could be the vaccine utilized in the immunization program. In Brazil the oral vaccine composed with a combination of three alive poliovirus (P1P2P3), has been used. The poliovirus type 1 (P1) is present in greater proportion, followed by the P3 and P2. In the United States the same oral vaccine (Sabin) and the intramuscular vaccine (Salk) composed by three inactive virus in equal doses are used[5,17].

Comparing the capacity of inducing a protective immunologic response, both vaccines have proved to be equally efficient, but some authors consider that the oral vaccine has the advantage of protection against the intestinal infection caused by the wild poliovirus[3,18] and the immunity induced appears to last longer compared to the inactivated intramuscular virus vaccine[19]. Therefore, the oral vaccine has a greater impact in developing countries[3,18]. Furthermore, the oral vaccine by selective pressure elevates the circulation of vaccine poliovirus, increasing the chance of infection by a vaccine poliovirus and reducing the wild poliovirus circulation[19].

If one considers the oral vaccine's great contribution to lower the incidence of paralytic poliomyelitis, the number of cases of VAPP here reported is of minor significance when compared to the risk of introducing the wild virus in the country. This affirmation is valid even comparing with data of other countries where the estimated risk is more elevated.

CONCLUDING REMARKS

Although the anti poliomyelitis strategies adopted in Brazil have lead to the eradication of the poliomyelitis wild virus infection with a minimum risk of complication, the existence of morbidity of the vaccine associated paralytic disease is here reported. From the epidemiological view the low risk of VAPP has been proved, but in an individual basis it is a matter of concern because the injured person presents a great individual, familial and social problem. Therefore, the risk of vaccine-associated poliomyelitis must be subject to further reflection and studies in search of safer solutions.

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