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CONVULSIONS IN CHILDHOOD SHIGELLOSIS AND ANTIMICROBIAL RESISTANCE PATTERNS OF SHIGELLA ISOLATES*

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Drug resistance patterns of 68 shigella strains were investigated prospectively in Kayseri during a period of approximately two years. The resistance was highest with ampicillin (58.8%) followed by co-trimoxazole (50%) and ampicillin-sulbactam (13%). Only 2.8 percent of cases were resistant to gentamicin, and all serogroups were sensitive to ceftriaxone. We conclude that in children with severe shigellosis, treatment with ceftriaxone is effective and better than ampicillin and co-trimoxazole for obtaining a clinical cure.

We followed 18 children who experienced convulsions associated with shigellosis. Only one child had a history of febrile convulsions, and two children had histories of convulsive disorders. The majority of the children had generalized, self-limited convulsions which lasted less than ten minutes. Due to the benign and self-limited nature of most of the convulsions, neither diagnostic procedures nor drug therapy are usually necessary. These measures should, however, be considered in complicated cases characterized by focal or prolonged seizures. *Key words: childhood shigellosis, convulsions, antibiotic resistance.*

The shigella species remains a major cause of enteral diarrhea in developing countries. Shigellosis is an acute inflammatory disease of the colon characterized by fever, general toxicity, crampy abdominal pain, and frequent loose stools which contain pus, mucus, and blood. Convulsions occur in 12 to 45 percent of children with shigellosis and are more frequent than in other common febrile infections. Other neurologic findings include headache, lethargy, confusion, nuchal rigidity and hallucination. All of these findings may be present before or after the onset of diarrhea. Although these symptoms have been attributed to the neurotoxicity of shigatoxin in the past, the cause of these neurologic findings has not yet been identified[1,2].

In this study, drug resistance patterns of shigella strains were investigated prospectively in Kayseri between January 1992 and December 1993. Here we reviewed the clinical features of children with shigellosis-associated convulsions and offered guidelines for diagnosis and treatment.

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Material and Methods

We examined the medical records of 68 children who had been admitted to the Department of Pediatrics of the University Hospital in Kayseri with culture-proven shigellosis between January 1992 and December 1993. Each patient's medical and family history as well as clinical and laboratory data were analyzed. All of the 68 isolated serogroups were tested for their susceptibility to ampicillin, ampicillin-sulbactam, co-trimoxazole, gentamicin and ceftriaxone by the agar dilution method[3].

Encephalopathy was defined as a complex of at least two of the following symptoms on admission: severe headache, jitteriness, lethargy, hallucination, confusion, stupor or coma. Convulsions were diagnosed either on the basis of the history taken on admission or if observed during the hospital course. Laboratory investigations included routine hematologic and biochemical examinations, stool cultures, cerebrospinal fluid (CSF) and electroencephalographic (EEG) examination in most of the patients with neurological involvement, and antibiotic treatment was applied according to the antibiogram.

Results

Shigella gastroenteritis was diagnosed by bacteriologic studies in all 68 children. Of the 24 children (35%) who had neurologic symptoms, six (9%) had encephalopathy alone, two (3%) had convulsions and encephalopathy, and 16 (23%) had convulsions alone. EEG tracings were epileptic in three children who did not have a history of convlsive disorders, and lumbar punctures were performed in 14 children. In all of them the CSF chemistry was normal and cultures were negative. Mild lymphocytic pleocytosis, up to 12 cells/mm^3, was noted in only one child.

The mean age was 5.27 years and ranged from one month to 15 years; only two patients were younger than six moths of age, those being one and three months old. Thirty-eight (55.8%) children were between one and five years of age, while 22 (32.3%) children were six to 15 years of age. Forty-seven (69%) of the cases presented during summer and fall. The male to female ratio was 1.22 (41/27).

During clinical follow-up, convulsions were seen in 18 (26.4%) patients and electrolyte imbalances were noted in 14 (20.5%) patients. The distribution of patients according to clinical presentation is summarized in Table I. Mortality was not recorded. The mean hospitalization period was 4.75 days (2-14 days) in 26 children, while the remaining 42 children out of 68 were outpatients.

Table I: Patient Population According to Clinical and Laboratory Presentation

	Patients Without Neurologic Symptoms		Patients with Convulsions Alone		Encephalopathy Alone		Convulsions and Encephalopathy		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total no. of patients	44	66	16	23	6	9	2	3	68	100
History of febrile convulsions	0	0	1	6	1	17	0	0	2	3
History of convulsive disorders	0	0	2	13	0	0	0	0	2	3
Sex										
Male	25	57	13	81	3	50	1	50	42	62
Female	19	43	3	19	3	50	1	50	26	38
Age										
1-11 months	6	14	2	13	0	0	0	0	8	12
1-5 years	26	59	8	50	3	50	1	50	38	56
6-15	12	27	6	37	3	50	1	50	22	32
Fever										
Lower than 38 °C	28	64	4	25	1	17	1	50	34	50
Higher than 38 °C	16	36	12	75	5	83	1	50	34	50
Vomiting	23	52	6	38	4	67	1	50	34	50
Blood/mucus in stool	23	52	10	63	5	83	2	100	40	59
Leukocytosis	9	20	5	31	3	50	1	50	18	26
Leukopenia	4	9	3	19	0	0	0	0	7	10
Shift to the left	8	18	10	63	2	33	1	50	21	31
Hyponatremia	3	7	4	25	2	33	1	50	10	15
Hypernatremia	1	2	0	0	0	0	0	0	1	1.5
Hypokalemia	0	0	2	13	0	0	0	0	2	3
Hyperkalemia	0	0	1	6	0	0	0	0	1	1.5

It was observed that S.sonnei was the most common cause of bacillary dysentery (50%). S.flexneri was second in frequency (44%), three patients had S.boydii (4%) and one patient had S.dysenteriae (1%). Table II summarizes the bacterial serogroups of shigella by neurological status.

Co-trimoxazole resistance ranged from 63.3 percent among isolates of S.flexneri to 44.1 percent among S.sonnei strains. Ampicillin-Sulbactam resistances ranged from 26.6-83.3 percent among S.flexneri and 2.9-42.3 percent among isolates

of S.sonnei strains. Gentamicin resistance was found in 5.8 percent of cases with S.sonnei, and no resistance was observed among S.flexneri. All shigella organisms isolated were susceptable to ceftriaxone. Antimicrobial resistance among shigella isolates is summarized in Table III.

Table II: Bacterial Serogroup of Shigella By neurological Status

	Patients Without Neurologic Symptoms		Patients With Convulsions Alone		Patients With Encephalopathy Alone		Patients With Convulsions and Encephalopathy		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total patients	44	65	16	23	6	9	2	3	68	100
Shigella sonnei	25	57	7	44	2	33	0	0	34	50
Shigella flexneri	17	39	8	50	3	50	2	10	30	44
Shigella boydii	1	2	1	6	1	17	0	0	3	4.5
Shigella dysenteriae	1	2	0	0	0	0	0	0	1	1.5

Table III: Antimicrobial Resistance Among Shigella Isolates

Antimicrobial Agent	No. and (%) of Resistant Isolates S.sonnei (n: 34)	S.flexneri (n: 30)	S.boydii (n: 3)	S.dysenteriae (n: 1)	Total (n: 68)
Ampicillin	14 (41)	25 (83.3)	1 (33.3)	None	40 (58.8)
Ampicillin/Sulbactam	1 (2.9)	8 (26.6)	None	None	9 (13)
Co-trimoxazole	15 (44)	19 (63.3)	None	None	34 (50)
Gentamicin	2 (5.8)	None	None	None	2 (2.9)
Ceftriaxone	None	None	None	None	None

Discussion

Convulsions-associated shigellosis has been widely reported in the literature; however, the incidence ranges in different reviews between 12 and 45 percent[4-6]. The overall frequency of convulsions in our study was 26.4 percent, but the frequency of convulsions in hospitalized children was 56.7 percent, not similar to other series. The true incidence of convulsions in shigellosis is probably lower, if children with mild cases who are not hospitalized are included. Among patients with convulsions and encephalopathy only one child was noted to have mild lymphocytic pleocytosis. In all of them CSF chemistry and cultures were found to be normal.

The majority of convulsions were generalized, tonic-clonic and self-limited. The convulsions lasted less than ten minutes, and none of the patients required anticonvulsive therapy.

Shigella sonnei and S.flexneri currently account for most cases of shigella-associated seizures[6], although these species do not usually produce Shiga toxin as demonstrated by toxin neutralization[7]. In fact, in vivo production of shiga toxin in patients with shigella-associated neurologic manifestations or the presence of toxin in their CSF has not been reported, nor has shiga toxin production in vitro by shigella strains been isolated from these patients. In 26 percent of our patients, convulsions were noted. Convulsions have been described in 12-45 percent of hospitalized patients with culture-proven shigellosis, an incidence four times higher than that in other causes of acute gastroenteritis[8]; thus, neurological symptoms are among the most frequent extraintestinal manifestation of shigellosis. However, children may develop seizures during shigellosis even if they do not experience seizures during other febrile infections[9], and shigella-associated convulsions occur in children older than the usual age for febrile seizures[9-10].

The mechanism for the increased frequency of convulsions in shigellosis is unclear. The cell-free neurotoxin secreted by the bacteria Shiga-toxin is not related[7, 11]. Disturbances of electrolyte and glucose blood levels are not usually mentioned as a possible contributing factor in the development of seizures in shigellosis. High fever, hypocalcemia and hypoglycemia, most likely in combination with other factors, may contribute to the occurrence of seizures. Because the convulsions in sihgellosis are usually benign and self-limited, we do not recommend the routine use of diagnostic procedures such as EEG, roentgenography of the skull or computed tomography. In complicated cases, both diagnostic procedures and drug therapy should be considered.

The traditionally used therapeutic agents, ampicillin and co-trimoxazole, have lost much of their effectiveness over the last decade because of increasing multiple antibiotic resistance of shigella due to conjugative resistance to plasmids[12]. These agents are safe for use in children; however, in our study 58.8 percent of shigella organisms were resistant to ampicillin.

Resistance to co-trimoxazole was found in 63.3 percent and 44 percent of S.flexneri and S.sonnei isolates, respectively. A high resistance to streptomycin (80%), co-trimoxazole (53%) and ampicillin (43%) has previously been demonstrated among shigella isolates in Turkey[13]. Resistance to newer quinolones is rare among Shigella species, but their use is not approved in children[10].

All strains isolated from our patients were susceptible to ceftriaxone. Varsano et al.[14] also reported that all shigella organisms isolated were susceptible to ceftriaxone. Shigella remain was almost uniformly susceptible to gentamicin. It is possible that parenterally administered gentamicin might be useful, but it would be appropriate only for seriously ill patients[10].

It is generally accepted that effective antimicrobial therapy for shigellosis shortens the duration of illness. This is particularly important in pediatric populations from less developed countries in its potentially significant positive impact on the growth and nutritional status of the affected children[14]. Ceftriaxone has been shown to be highly active against shigella strains. An important advantage of this cephalosporin is its long serum half-life of 41/2 to 9 hours, which allows once-daily administration[15].

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