Kindergarten Outbreak of an Exanthematous Disease Caused by Echovirus Type 9

By

MARGIT TÓTH, P. OSVÁTH, M. GALAMBOS and B. VOLTAY

László Central Hospital for Infectious Diseases (Director: Dr. J. ROMÁN), Budapest

(Received January 15, 1964)

Several enterovirus types have been found to cause mild illness with rubelliform eruption [1 2, 5, 8, 10, 11, 12, 13, 14, 15, 16, 17]. From such outbreaks echovirus type 9 has most often been isolated. In Hungary the same type of virus caused an outbreak of aseptic meningitis in 1956, as reported by DÖMÖK et al. [4], but in 1960 the virus could not be isolated in the course of screening tests involving faecal samples obtained from 2017 healthy children [3].

The subject of the present report is an outbreak observed in a kindergarten in the 2nd district of Budapest. Similar cases occurred simultaneously in most of the kindergartens in the same district.

MATERIALS AND METHODS

Specimens. Cerebrospinal fluids (CSF) taken under sterile conditions, pharyngeal swabs and faecal samples were examined. Pharyngeal swabs and faecal samples were centrifuged at 8000 r. p. m. for 20 minutes, and 2000 units of penicillin, 2 mg of streptomycin and 100 units of mycostatin were added per ml.

Tissue cultures. Primary monkey-kidney cell cultures pre-incubated for seven days were inoculated with 0.1 of specimen each. As maintenance fluid Parker's No. 199 was used. The tube cultures were re-incubated at 37° C and examined every day microscopically. Cultures showing cytopathic changes were used for passage.

Neutralization tests. The isolates were typed by the neutralization test carried out in monkey-kidney cell cultures. Twenty units of the echovirus 9 rabbit immune serum prepared by the State Institute of Hygiene, Budapest, were used in these tests.

The human sera were inactivated at 56° C for 30 minutes and titrated against 100 CPD_{50} of virus in monkey-kidney cell cultures. The virus-serum mixtures were incubated at +4° C for 12 hours. The inoculated cultures were observed for 10 days.

CASES

Case 1. V. E. a 7 months old infant was admitted on May 23, 1963. She became ill one day before admission, when her temperature rose to 38.5° C. She vomited several times and had little appetite. On the day of admission a rash appeared on her skin. Therapy before admission consisted in aminopyrine suppositories and benzathine penicillin syrup.

At admission the infant is weak but restless, with decreased turgor and a 2×2 inches wide, tightly bulging fontanelle. A papular rash is seen on the face, neck and trunk and on the extensor side of the extremities; it is the densest in the chest. The centre of the papules is bright

red, the borders are paler, pinkish. The colour of the papules hardly fades on pressure. The skin among the papules is intact. The throat is fiery red on both sides, the buccal mucosa is somewhat loose, the tongue furred. The liver is palpable one and a half inches below the costal arch, the spleen can just be felt. There is some nuchal rigidity and a positive Kernig's sign.

Laboratory findings. WBC 3,200,000, with 7 band forms, 47 neutrophile polymorphonuclears, 1 eosinophil, 42 lymphocytes, 3 monocytes, for 100 cells. Haemoglobin, 12.1 g. Urine, negative. ESR, 2.9 mm/h. Platelet count, 95,000 (on the day following admission). Otological finding and X-rays, negative. *Str. haemolyticus* could not be isolated from the throat. Lumbar puncture yielded a water-clear CSF under increased pressure. Pandy's test, negative; cell count, 10; protein, 0.017 per 100 ml; sugar, 87 mg per 100 ml.

Depression lasted for several days, and the patient lost weight but no severe general symptoms were observed. In the following four days the exanthem became more pronounced, and still new papules appeared; then they began to fade. The child had moderate fever for four days, with the peak on the seventh day after admission (this was the only day when temperature rose beyond 38° C). The fontanelle was tight for five days. The patient was discharged on the 13th day fully recovered.

Case 2. V. K., the two-year-old sibling of Case 1. Admission on 24th May, 1963. The child had been ill for two days, a rash appeared on the first day of illness. The patient had not been given any drug.

There were pinhead-sized papules all over the skin. On the face and the neck the exanthem was confluent. Moderately inflamed conjunctivas, injected throat. Bean-sized lymph nodes were palpable on the neck and in the inguinal fossa. The other organs and the laboratory findings were normal.

The exanthem began to fade on the second day after admission and disappeared on the sixth day.

Table I shows the virological and serological findings. These brought evidence of the causal role of echovirus type 9.

The Kindergarten Outbreak

The older sister of the two patients had been ill with similar symptoms five days before the admission of Case 1. Since the two hospitalized children attended no children communities, they must have been infected by her.

The older sister attended a kindergarten where not long before the admission of the two children an outbreak characterized by rubelliform rash had been observed. Out of the 16 children of her group 10 were affected. Most of the cases were diagnosed as rubella. In one case, however, the rash involved only the face and the physician who saw this case was against the diagnosis of rubella. When cases 1 and 2 were admitted, the outbreak had already terminated. For

Table I

Virological data concerning the two hospitalized children

Initials	Age, year	Isolation of echovirus 9 from			Neutralization titre	
		throat	faeces	CSF	acute	convalesc.
V. É.	7/12	+	+	—	1 : 16	1 : 256
V. K.	3	+	+	n. t.	neg.	1 : 64

TABLE II

Distribution by age of the two groups of children

Group	<4 years	4 years	5 years	≧6 years	Total
Kindergarten	2	4	10	—	16
Control	1	5	8	2	16

this reason we could not obtain blood samples from the kindergarten children until two months after the outbreak. These late convalescent sera were tested for neutralizing antibodies to echovirus type 9. The titres were compared with those of 16 children of approximately the same age distribution, treated with dysentery in our hospital (Tables II and III).

The difference in the titre distribution between the two groups of children is highly significant ($p < 0.1$). Out of the 16 kindergarten children 13 had titres of 1 : 64 or higher.

Six of the kindergarten mates showed no symptoms of infection, yet their antibody titres were high. This is not surprising, for echovirus 9 infections often manifest themselves only with fever, headache and nausea; even inapparent infections may occur. The rate of eruptive cases declines with age [13, 17]. The 62 per cent incidence of rash in the children group aged five years on the average is consistent with data published by other authors.

Most of the control children also had antibodies, but their neutralization titres were lower. This finding is not quite consistent with the data of GIBBELS [6] and of HENNIGST [7], who found antibodies to echovirus type 9 in only 30—40 per cent of German children. The difference might be attributed to the fact that in Hungary more children attend children communities and thus meet the virus at a younger age.

According to literary data aseptic meningitis is the commonest illness caused by echovirus type 9. In the course of the present small outbreak the only case showing meningeal symptoms was the only infant affected by the outbreak. The CSF of even this infant showed hardly any pathological changes; the cell count did not surpass the upper limit of the normal

TABLE III

Distribution by neutralizing-antibody titre to echovirus 9 of the two groups of children

Group	Reciprocals of neutralization titres								Total
	<4	4	8	16	32	64	128	256	
Kindergarten	—	—	—	—	3	7	2	4	16
Control	2	1	6	3	1	1	—	2	16

values. The slightly raised sugar concentration pointed to a mild encephalitis. The thrombopenia found at the time of admission in Case 1 is noteworthy. If this is characteristic of echovirus type 9 infections, it might explain the mechanism of the petechial form [13] of this infection and the associated haematuria [11].

* * *

Acknowledgements. The virological examinations were made possible by the Department of Virology, State Institute of Hygiene, Budapest. The authors are indebted to that Institute for providing laboratory facilities and to Dr. I. Dömök for his valuable interest and help.

Summary

Echovirus type 9 was isolated from throat swabs and faecal samples obtained from two siblings suffering from a disease characterized by rubelliform rash. Paired sera showed significant rises in the neutralizing antibodies to the same type of virus. In one of the cases (a seven-month-old girl) pronounced meningeal symptoms and thrombocytopenia were also observed. The infection had originated in a kindergarten group, where 10 out of the total 16 children had been affected by similar exanthemata. Two months later the kindergarten children had significantly higher neutralization titres to echovirus type 9 than a group of control children of the same age distribution.

References

1. Berglund, A., Böttiger, M., Johnson, T., Westermark, S.: Aseptic Meningitis with Rubella-like Rash. Arch. ges. Virusforsch. **8,** 294 (1958).
2. Constable, F. L., Hewitt, L. F.: Outbreak of ECHO Type 9 Infection in a Children's Home. Brit. Med. J. **1,** 1483 (1961).
3. Dömök, I.: Virological Aspect of Coxsackie Virus Infections. Arch. ges. Virusforsch. **13,** 128 (1963).
4. Dömök, I., Molnár, E., Jancsó, Á., Dániel, M.: Fiatal, egészséges gyermekek enterovirus vizsgálata 1960. évben, az első poliovirustörzsekkel végzett vaccinatiós kampányok után. Orv. Hetil. **103,** 1402 (1962).
5. Garnett, D. G., Burlingham, A., van Zwanenberg, D.: Aseptic Meningitis of Virus Origin. Lancet **1,** 500 (1957).
6. Gibbels, E., Scheid, W.: ECHO-Virusinfektionen und ihr Vorkommen in Westdeutschland. Dtsch. med. Wschr. **88,** 1349 (1963).
7. Hennigst, W.: Beitrag zur Epidemiologie der Echoviren. Dtsch. med. Wschr. **84,** 1022 (1959).
8. Lennartz, H., Maass, G., Kersting, G.: Zur Aetiologie der abakteriellen Menigitis. Klin. Wschr. **35,** 327 (1957).
9. McLean, D. M., Melnick, J. L.: Mouse Pathogenic ECHO 9 Virus and Meningitis. Proc. Soc. exp. Biol. (N. Y.) **94,** 656 (1957).
10. Rotem, C. E.: Meningitis of Virus Origin. Lancet **1,** 502 (1957).
11. Sabin, A. B., Krumbiegel, E. E., Wigand, R.: ECHO Type 9 Virus Disease. Amer. J. Dis. Child. **96,** 197 (1958).
12. Sauthoff, R., Mittelstrass, H. K.: Klinische Symptomatik bei ECHO-Virusinfektion. Mschr. Kinderheilk. **108,** 110 (1960).
13. Solomon, P., Weinstein, L., Chang, T. W., Artenstein, M. S., Ambrose, C. T.: Epidemiologic, Clinical and Laboratory Features of an Epidemic of Type 9 ECHO Virus Meningitis. J. Pediat. **55,** 609 (1959).
14. Takos, M. J., Weil, M., Siegel, M. M.: Outbreak of ECHO 9 Exanthem Traced to a Children's Party. Amer. J. Dis. Child. **100,** 360 (1960).
15. Tyrrell, D. A. J., Clarke, S. K.

HEATH, R. B., CURRAN, R. C., BESWICK, T. S. L., WOLMAN, L.: A Coxsackie Virus Related to ECHO 9 Virus. Brit. J. exp. Path. **39,** 178 (1958).
16. TYRRELL, D. A. J., SNELL, B.: Recovery of a Virus of an Epidemic Exanthem Associated with Meningitis. Lancet **2,** 1028 (1956).
17. WENNER, H. A.: Ein Überblick über die Natur und derzeitige Bedeutung der ECHO 9 Viren in der klinischen Medizin. Klin. Wschr. **14,** 313 (1959).

Dr. M. TÓTH
Gyáli út 7.
Budapest IX. Hungary