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Viral meningitis due to echovirus types 6 and 9: epidemiological data from Western Australia

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SUMMARY

During the autumn of 1992, Western Australia experienced a large viral meningitis outbreak of dual aetiology. Of the 161 cases, 64% were children under 15 years of age, with the highest notification rate being in children less than 5 years of age. Echovirus 9 caused 41% of cases and occurred mainly in the metropolitan areas of Western Australia whereas echovirus 6, which caused 37% of cases, was more widespread. An enterovirus was cultured from 70% of CSF specimens, 88% of faecal specimens and 68% of upper respiratory tract specimens. High CSF white cell counts and neutrophil predominance were common. Seven cases had normal CSF white cell counts even though an enterovirus was isolated from the CSF. Therefore, the CSF findings were of restricted value in excluding viral meningitis, and did not reliably distinguish between bacterial and viral meningitis.

INTRODUCTION

The commonest identified cause of viral meningitis is the enteroviruses [1] which are non-enveloped RNA viruses with 72 recognized serotypes [2], most belonging to the species coxsackie A, coxsackie B and echovirus. The most common echoviruses causing outbreaks or sporadic cases of meningitis are types 4, 6, 9, 11, 14, 16, 25, 30, 31 and 33 [2]. In the northern hemisphere, most cases occur in summer and autumn [3, 4]. Endemic enteroviruses cause meningitis in infants, but epidemic enteroviruses cause meningitis in older children [4].

Outbreaks of enteroviral meningitis usually involve a single serotype. There are very few reports of viral meningitis outbreaks of multiple aetiology and, when they do occur, the number of cases is usually small [5, 6]. The only large outbreak of aseptic meningitis of mixed aetiology to be reported had 136 cases and occurred in Japan in 1986 [7]. In that outbreak, 89% of cases were due to echovirus 7.

An outbreak of meningitis due to echoviruses 6 and 9 was noted in Western Australia (WA) in April 1992. This presented a unique opportunity to study a large outbreak of dual aetiology and to compare the clinical and diagnostic findings for the two viruses involved.

METHODS

In mid April 1992, an increase in viral meningitis cases and isolations of enteroviruses were noted in WA. Data were collected for cases occurring from 28 February until 27 July 1992, when the number of weekly cases had reached a steady state of 3–4 per week.

Data for cases admitted to metropolitan hospitals were extracted directly from their medical records, while data for those cases occurring in rural WA were obtained by telephone or letter. The antibiotic

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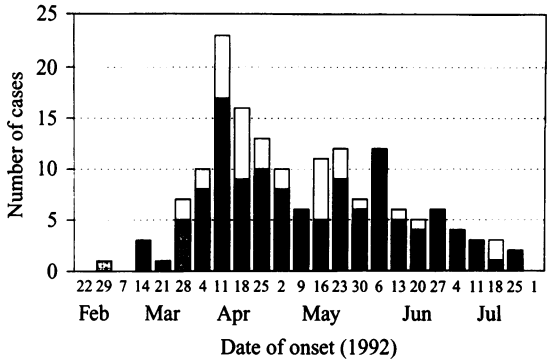

Fig. 1. Date of onset of illness of cases of echovirus 6 (■), echovirus 9 (▨) and other aseptic meningitis (□), Western Australia, 28 February to 27 July 1992.

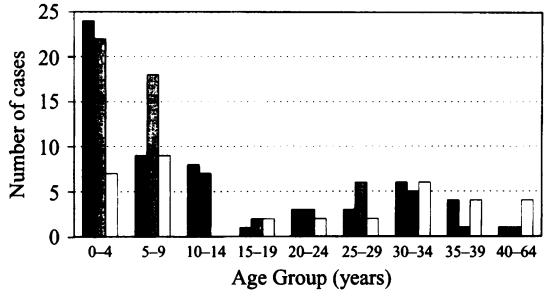

Fig. 2. Age distribution of cases of echovirus 6 (■), echovirus 9 (▨) and other aseptic meningitis (□), Western Australia, 28 February to 27 July 1992.

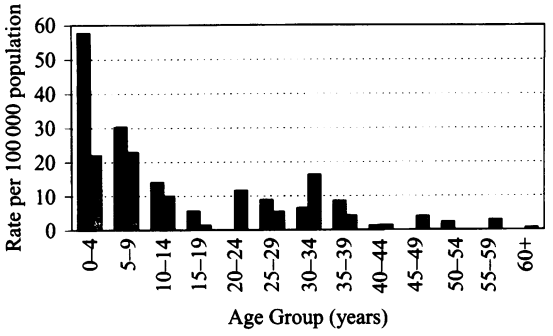

Fig. 3. Age-specific rates for viral meningitis by sex, male (■), female (▨), Western Australia 28 February to 27 July 1992.

treatment for cases was noted but not recorded in sufficient detail for analysis. Early in the outbreak, 52 cases were interviewed to ascertain any contact with similarly infected persons and to estimate the duration of symptoms after leaving hospital.

The laboratory of the admitting hospital performed routine CSF microscopy and bacterial cultures. Enteroviral cultures on specimens were performed either at Princess Margaret Hospital for Children, Royal Perth Hospital or at the Western Australian Centre for Pathology and Medical Research (PathCentre) using standard cell culture techniques. All isolates were identified at PathCentre using pooled antisera [8], then confirmed with type-specific antisera.

Viral meningitis was defined as signs and symptoms of meningitis (such as fever and headache, with or without photophobia or neck stiffness) combined with either a raised CSF white cell count (WCC) in the absence of bacteria, or isolation of an enterovirus from CSF with or without an elevated CSF WCC. The normal CSF WCC was accepted at less than 5×10^6 white cells per litre (< 5 cells/mm^3).

Cases of clinically suspected viral meningitis were further classified as: confirmed cases, cases in whom echovirus 6 or 9 was isolated from the CSF; probable cases, cases in whom echovirus 6 or 9 was isolated from the faeces, pernasal aspirate or throat swab but no virus was isolated from the CSF; compatible cases, cases with an elevated CSF WCC for whom no other organism was isolated from the CSF, and enteroviral cultures were negative or not performed. Two cases without CSF results were included because they had classical clinical illnesses and had siblings with culture proven enteroviral meningitis.

Seven confirmed cases (four echovirus 9, three echovirus 6) and one probable case (echovirus 6) were excluded due to inadequate clinical details.

In order to determine the background enteroviral activity during this period, all enteroviruses isolated by PathCentre between 29 December 1991 and 1 November 1992 were typed as echovirus 6, echovirus 9 or 'other enterovirus'.

Data analysis was undertaken using Epi Info version 5.01a [9]. Rates were calculated using the 1992 estimated population of WA as calculated by staff of the Health Services Statistics and Epidemiology Branch (HSS&EB) of the Health Department of WA. The demographics of hospitalizations during 1990 and 1991 were obtained from the Hospital Morbidity Database System maintained by the HSS & EB.

Rates are per 100000 population; percentages and rates were rounded if more than 10. The 95% confidence intervals (CI), Kruskal–Wallis or χ^2 tests were used for comparisons.

RESULTS

Of the 161 cases of viral meningitis detected during the outbreak, 63% were classified as confirmed, 15% as probable and 22% as compatible. Echovirus 9 was isolated in 66 cases (41%) and echovirus 6 in 59 cases (37%).

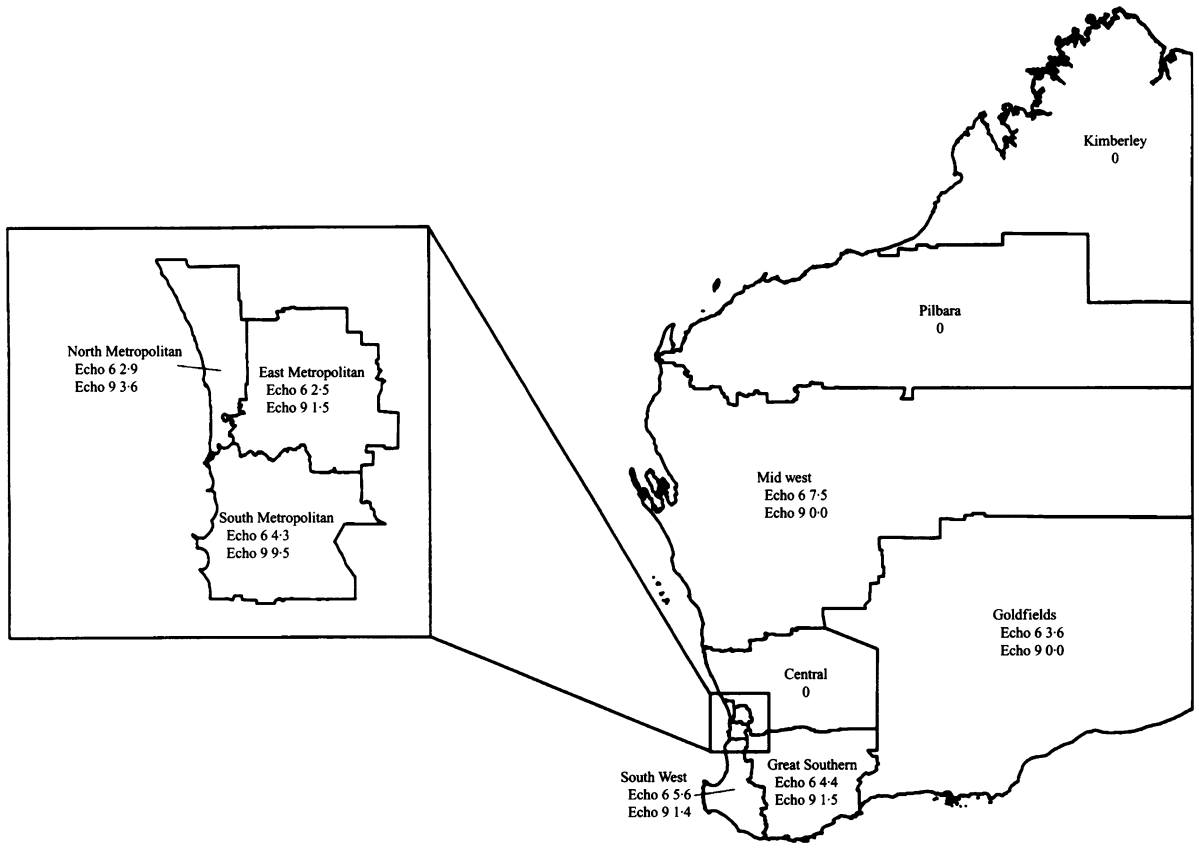

Fig. 4. Notification rates (rates are per 100000 population) of viral meningitis due to echovirus 6 or echovirus 9 by health region, Western Australia, 28 February to 27 July 1992.

The epidemic curve showed autumn/winter peaks in April and May/June (Fig. 1) at levels threefold higher than the previous 2 years. The notification rate (NR) for the whole of Western Australia was 9·4 per 100000 persons, with no significant difference between the male rate of 10 (95% CI = 8·5–12·9) and the female rate of 8·0 (95% CI = 6·1–9·9). Male-to-female ratios were the same for echovirus 6, echovirus 9 and compatible cases and matched the ratio for the Western Australian population ($P > 0·05$).

Cases in this outbreak had a significantly lower mean age (14 years; 95% CI, 12·3–16·6) than patients admitted to hospital for viral meningitis in 1990 and 1991 (23 years; 95% CI, 20·9–24·8). Sixty-five percent of our cases were less than 15 years of age followed by a minor peak in the 25–34 age group (Fig. 2). The mean age for confirmed and probable cases was 12 years (95% CI, 10·0–14·4) and was the same for echovirus 6 and 9, but significantly lower than that of 21 years (95% CI, 15·3–26·1) for the compatible cases.

The highest age-specific notification rates were 58 per 100000 males less than 5 years of age and 30 for males aged 5–9 years (Fig. 3). The rates fell in older children and rose again for young adults, especially for females. Among infants, echovirus 6 predominated, accounting for 69% (18/26) of confirmed and probable cases. Seven infants developed echovirus 6 meningitis within 9 days of birth and in one case echovirus 6 was also isolated from the maternal faeces.

Perth is divided into three metropolitan health regions (north, east and south) and the country area into seven health regions (Fig. 4). Most cases (82%) occurred in the Perth metropolitan area giving a notification rate of 10 per 100000 population compared with 6·3 in the combined country regions. The highest notification rates were in the South Metropolitan Region, (NR = 19) and the adjacent South West Region (NR = 12). However, echovirus 9 predominated in the former and echovirus 6 in the latter. The echovirus 6 cases were evenly distributed across the 3 metropolitan regions and the rural areas as a whole, whereas cases of echovirus 9 occurred more often in the South Metropolitan Region than in the other three areas ($\chi^2 = 20·4$, 3 D.F., $P < 0·001$).

Of the 52 cases interviewed, 32 (55%) could identify a possible contact and 25 could give the likely date of infection. The estimated incubation period ranged

Table 1. *Cases of viral meningitis by CSF WCC for each virus type, Western Australia, 28 February to 27 July 1992*

	Number of CSF specimens			
WCC × 10^6/l	Echovirus 6 isolated	Echovirus 9 isolated	No virus isolated	Total
⩽ 499	46	30	17	93
500–999	8	15	6	29
1000–1499	2	10	3	15
⩾ 1500	2	11	9	22
Total	58	66	35	159

Table 2. *Mean and range of CSF WCCs, by virus type, Western Australia, 28 February to 27 July 1992*

	WCC × 10^6/l			
	Echovirus 6 isolated	Echovirus 9 isolated	No virus isolated	Total
Mean (95% CI)	316 (164–468)	853 (580–1125)	890 (582–1198)	665 (517–813)
Range	0–3500	3–6500	15–3200	0–6500

Table 3. *Cases of viral meningitis by proportion of mononuclear cells in CSF specimens and virus type, Western Australia, 28 February to 27 July 1992*

	Number of CSF specimens			
Mononuclear cells (%)	Echovirus 6 isolated	Echovirus 9 isolated	No virus isolated	Total
0–20	14	4	0	18
21–40	9	12	2	23
41–60	5	9	6	20
61–80	7	19	8	34
81–100	18	19	17	55
Total	53	63	33	149

from 2–15 days, with a peak of 2–4 days for echovirus 6 and 9. Cultures were available for 5 sets of cases and contacts, all of which were echovirus 6.

The usual presentation was fever, headache, neck stiffness and vomiting, with photophobia and lethargy in a few cases. Gastrointestinal symptoms occurred in 83% (55/66) of echovirus 9 cases but only 63% (37/59) of echovirus 6 cases (Yates corrected $\chi^2 = 5{\cdot}8$, $P < 0{\cdot}02$). Only four cases of echovirus 6 and one of echovirus 9 developed a rash.

The length of hospital stay was similar for the three main aetiologic groups, with a range of 0–15 days and a median of 3 days. Seventy-eight percent of cases were admitted to hospital for 4 days or less.

The CSF WCC varied widely (Table 1), with lower mean counts for echovirus 6 than echovirus 9 (Table 2). There was a higher proportion of mononuclear cells in cases with echovirus 9 than with echovirus 6 ($\chi^2 = 10{\cdot}0$, 4 D.F., $P = 0{\cdot}041$) and even higher in cases with culture negative meningitis compared with those with culture-proven enteroviral meningitis ($\chi^2 = 10{\cdot}3$, 4 D.F., $P < 0{\cdot}04$) (Table 3). Neutrophil predominance in confirmed cases was unrelated to time since onset of illness. In six cases neutrophil predominance of over 60% persisted for 5–7 days after the onset of illness.

A normal CSF WCC did not exclude viral meningitis, as echovirus 6 was isolated from five CSFs with normal counts, and echovirus 9 from two. All were collected within 2 days of onset, 5 from neonates, 1 from a child and 1 from an adult. In addition, one

echovirus 6 and one echovirus 9 were isolated from the CSF of two adults with WCCs of between 5 and 9×10^6 cells/l, also within 2 days of onset.

Echovirus 6 or echovirus 9 was isolated from 70% (101/145) of CSF specimens, 88% (43/49) of faecal samples and 68% (52/76) of upper respiratory tract specimens.

During the period of this outbreak there was also an increase in non-meningitis illnesses due to echovirus 6 (46 cases), echovirus 9 (24 cases) and other enteroviruses (62 cases). Where clinical details were available, the most common non-meningitis illnesses associated with echovirus 6 and 9 were non-specific febrile illnesses (20), respiratory tract infections (13) and diarrhoea and/or vomiting (seven). There were also two cases of echovirus 6 neonatal sepsis.

DISCUSSION

To our knowledge, this is the only detailed analysis of epidemiological and diagnostic features of a large outbreak of enteroviral meningitis of dual aetiology.

Data were limited to that available in case records or by patient recall. Also, as the outbreak progressed and doctors became more confident of their diagnoses, the rates of hospitalization and lumber puncture declined. Therefore many cases were never identified. A number of patients had received antibacterial therapy prior to hospital admission, raising the possibility of masked bacterial meningitis. However, this is unlikely and the clinical course of cases receiving antibiotics did not differ from cases of proven enteroviral meningitis (data not shown). Despite these limitations, analysis of this outbreak has provided valuable information about viral meningitis.

In previous years, enteroviral isolations in WA peaked in winter/spring (data not shown), but this viral meningitis outbreak extended over autumn/winter. It occurred over a background of non-meningitis echovirus 6 and 9 illnesses which continued into spring. Both patterns differ from the summer/autumn seasonality of the northern hemisphere [3, 4].

Most cases occurred in children under 15 years of age, with the highest notification rates in young children. This age distribution may reflect the higher rates of faecal-oral transmission among children [10] and absence of pre-existing immunity, but could reflect increased ascertainment from higher hospitalization and/or lumbar puncture rates in children compared with adults. The relatively high notification rates in young adult women compared to men probably represents acquisition from their children. Conversely, the isolation of echovirus 6 from a neonate's CSF and its maternal faeces indicates that neonatal infections are likely to have a maternal source.

Similarly, although the numbers were small, recent contact with proven or likely cases and occasional isolation of the same virus from both case and contact, supports person-to-person transmission. Presumably the other cases had unrecognized contact with infected individuals, including asymptomatic excretors; infected individuals may shed enteroviruses in the faeces for a month or more after acute infection [2].

There was no clear pattern of spread throughout WA, though both viruses appeared simultaneously in the south of the state while only echovirus 6 was found elsewhere in the state. Echovirus 6 activity was virtually restricted to WA, but echovirus 9 activity was high in other parts of Australia during the same period [14]. In the South-West Region, echovirus 6 predominated despite being adjacent to the South Metropolitan Region where echovirus 9 dominated. Local cycles of transmission among children in these regions are the most likely explanation for this. The high rates in these two adjacent regions may be related to the development of new suburbs with high paediatric populations.

Although both viruses caused a similar range of illnesses, echovirus 9 was the most common isolate in meningitis cases, while echovirus 6 was the most common in non-meningitis cases. The exception to this was the neonates, in whom the majority (16/21) of meningitis cases were due to echovirus 6. This may indicate that infants were more likely to encounter echovirus 6 in the family setting or at birth, as it was more common than echovirus 9 in the community, and/or they were more likely to develop meningitis with this virus than were older children or adults. Rash has been reported to be associated with echovirus 9 infection [10] but was an uncommon finding in our cases.

As reported elsewhere [11], the total and differential CSF WCC varied widely and discriminated poorly between bacterial and viral meningitis. Neutrophil leucocytosis in viral meningitis has been attributed to early responses which are subsequently replaced by a mononuclear cell response [1], but we found that neutrophil predominance in confirmed cases was just as common in late samples as in early samples. As a result many of these cases with high counts or

neutrophil leucocytosis had to be managed as bacterial meningitis at least until the initial bacterial cultures were negative.

The detection of virus in CSF with a normal WCC was noted in 17 cases during an outbreak in Kansas [5]. In our study, all 9 culture positive CSF samples with a low or normal WCC were collected within 2 days of onset suggesting a poor white cell response early in infection. This was influenced by age as 5 of the 7 neonates with positive CSFs had normal cell counts. Hence, a normal CSF WCC does not exclude enteroviral meningitis [1] and viral cultures should be performed if viral meningitis is clinically suspected.

Positive viral cultures from sites other than the CSF are often helpful in making a diagnosis and in patient management [13]. Isolation of an enterovirus from faeces or upper respiratory tract specimens must be interpreted cautiously as enteroviral excretion may be coincidental with another disease process [12]. Such cases can justifiably be included in analyses of outbreaks such as this one provided that there is an associated CSF pleocytosis.

Anecdotally, many cases of possible meningitis in this outbreak did not have a lumbar puncture performed, particularly in the later stages of the epidemic. This approach requires a high degree of confidence that the condition is benign viral meningitis. If there is any doubt, then a lumber puncture is indicated.

Health care practitioners should be aware that outbreaks of enteroviral infection may be due to the co-circulation of more than one serotype. This co-circulation may lead to apparently confusing patterns of spread and occurrence of sequential outbreaks of disease within communities.

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