

Chronobiology of meningitis

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Aim. Our study intended to verify the seasonality of aseptic meningitis.

Methods. We studied 156 patients hospitalized at the Infectious Department of Padua University between 1990 and 1997. Fifty-nine of them (M=40, F=19), mean age 18.9 ± 7.3 , were affected by aseptic meningitis (1 patient was affected by herpes virus meningitis, 31 subjects by mumps virus meningitis and 27 from enterovirus meningitis). The diagnosis was made by studying the patients' clinical history, via physical examination and serological tests. All the patients were submitted to liquor examination and evaluation of its characteristics also for viral and bacterial antigens. For all the patients cultural tests of feces, urine and throat samples were carried out.

Results. The evaluation of seasonality of aseptic meningitis in the cases showed a peak in July. The analysis for gender, showed greater incidence for females in September and for males in June-July. The cases were also subdivided according to the etiology of the meningitis and the result was a peak in July for mumps meningitis and a peak in September for enterovirus meningitis.

Conclusion. In the light of these results we can conclude that aseptic meningitis has greater incidence in summertime. This observation is consistent with the fact that infectious diseases undergo fluctuation depending on the immune activity which is depressed by the exposition to

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sun rays and UVA. The different seasonality of aseptic meningitis as regards gender is attributable to the different etiology of meningitis in the 2 genders.

Key words: Meningitis, chronobiology.

Some diseases, such as stroke ¹ or aortic dissection, ² present a chronobiological rhythm.

Numerous infectious diseases also show a seasonality of epidemics: ³ measles and whooping cough occur more often in spring, ⁴ while diphtheria and scarlet fever occur more often in winter. ⁵ Herpes virus infections also present seasonality. ^{6,7}

Some studies report that meningitis of bacterial or viral etiology also shows seasonality. *Haemophilus Influenzae* and *Neisseria Meningitis* present an incidence peak in winter, ⁸ while the pneumococcal disease has 2 peaks, 1 in autumn and 1 in spring. ⁹

The seasonal variability of viral meningitis is due to the spread of infection from enteroviruses which are the etiologic agents of

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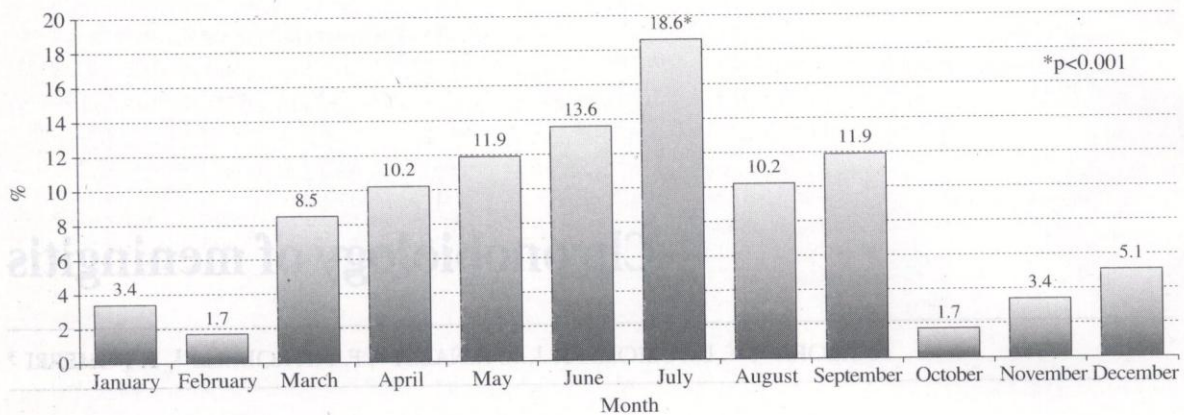


Figure 1.—Seasonal distribution of aseptic meningitis.

80% of aseptic meningitis. Their incidence is in summer.¹⁰

Materials and methods

We have considered all the cases of meningitis observed in the Infectious Diseases Department of the Padua Hospital from 1990 to 1997. Padua is a town in North-East Italy with a population of 300 000 inhabitants. Its climate in summer is warm and humid. Padua has an important University Hospital, which is a reference point for the whole North-Eastern area of Italy. In particular, the Infectious Diseases Department is one of the best centers of diagnosis and cure in Italy.

During the considered 7-year period, we re-examined all the cases of meningitis hospitalized in our clinic and evaluated the presence of seasonal rhythm in the subjects with aseptic meningitis. The diagnosis was made through clinical history and physical examination.

The meningitis was defined as "aseptic" by studying liquor and serological samples. We evaluated the clinical and physical test of liquor (color, appearance, glucose, presence of proteins, number and type of cells). In the liquor we also searched for the antigen for the following bacteria: *Neisseria Meningitidis*, *Streptococcus Pneumoniae*, *Haemophilus Influenzae*, *Listeria Monocytogenes*, *Streptococcus Agalactiae*, *Escherichia Coli*. The search concerned also the presence of the *Cryptococcus* antigen and the microscopic analysis for micetes. With PCR (polymerase chain re-

action), there was the amplification of viral DNA or RNA in the collected liquor. We searched for positivity of infection caused by DNA (Citomegalovirus, Epstein-Barr, Herpes Zoster) or RNA (Enterovirus: coxsackie, echo and poliovirus) viruses. The serologic tests included antibodies antiviral (Herpes virus 1 and 2, Orthomyxovirus, Paramyxovirus) and if positive, were tested again in another sample after 2-4 weeks to verify the seroconversion. We also tested stools, urine and pharynx for enterovirus. The assessed cases of meningitis were submitted for further evaluation to a team of 3 physicians (an infectiologist, a neurologist and an internist).

The chronobiological analysis was performed using Halberg single cosinor test in which the cosine curve best fitting the data was determined by multiple linear regression. The general equation of the curve is: $Y(t) = M + A \cos(\omega t + \phi)$, where M = mesor, A = amplitude, ϕ = acrophase, t = time. Each value has an estimate of variance. When appropriate, the χ^2 test was utilized to compare grouped data.¹¹

Results

In the 7-year period studied (1990-1997) we examined 156 cases of meningitis. The patients affected by aseptic meningitis were 59 (19 females and 40 males), mean age 18.9 ± 7.3 . The cases of aseptic meningitis were 27 from mumps virus, 31 from enterovirus; only 1 from herpetic virus.

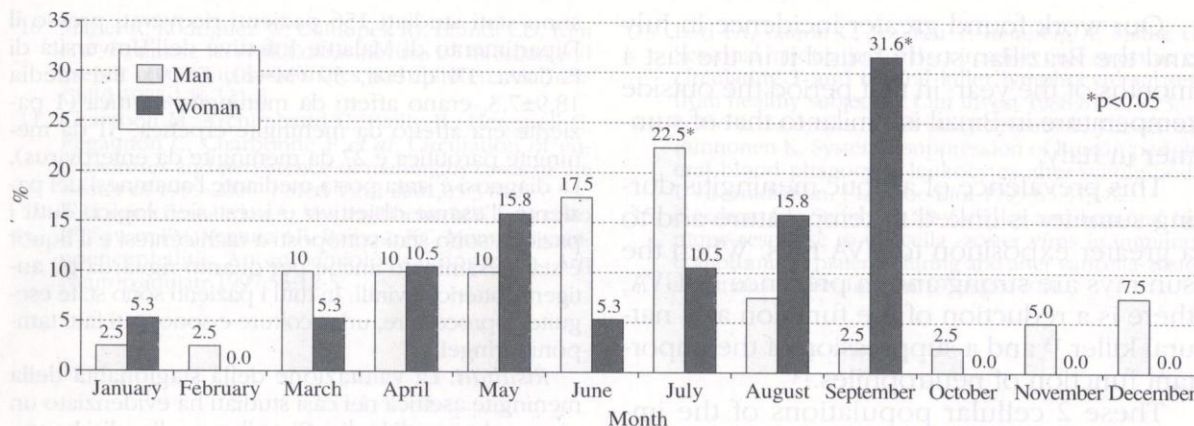


Figure 2.—Sexual distribution of aseptic meningitis globally studied.

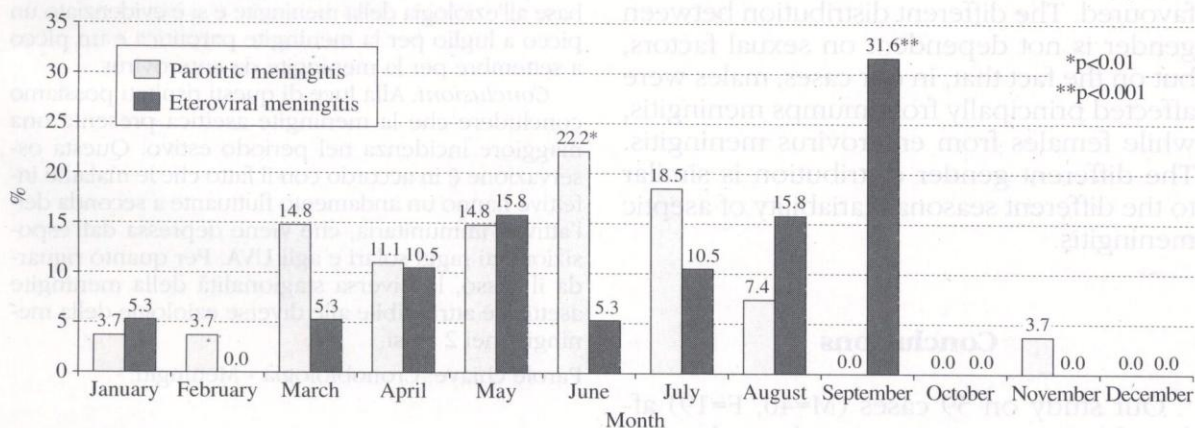


Figure 3.—Seasonal variability of parotitic and enteroviral meningitis.

The distribution of the cases during the year showed a peak of incidence in July (from May to September); (Figure 1).

Subdividing the incidence by gender (Figure 2) we observed that males (n=40) showed a peak incidence in July (n=9) and females (n=19) in September (n=6).

Evaluating the etiology of meningitis from mumps virus and enterovirus, we can observe that the First has an incidence peak during the period June-July, the second in September (Figure 3).

Discussion

The collected data are consistent with the literature, although some epidemiological

studies about seasonality of enterovirus infections are in disagreement. Some authors maintain that enterovirus meningitis (coxsackie and echo) has a peak incidence in summer.¹⁰

A recent study carried out in France in winter, showed greater incidence of enterovirus infection during the 1999-2000 winter.¹¹ Our study revealed greater incidence during the July-September period. This is in agreement with evidence that infections transmitted *via* orofecal way have greater incidence in summer; on the contrary, infections transmitted via aerial way have greater incidence in winter.³

As to mumps meningitis there is only one study carried out in Brazil which agrees with our results.¹²

Our work found greater incidence in July and the Brazilian study found it in the last 4 months of the year: in that period the outside temperature in Brazil is similar to that of summer in Italy.

This prevalence of aseptic meningitis during summer is linked to temperature and to a greater exposition to UVA rays. When the sun rays are strong and in presence of UVA, there is a reduction of the function as a natural killer¹³ and a suppression of the important function of neutrophils.¹⁴

These 2 cellular populations of the immune system are responsible for the control of viral replication.¹⁵ From this observation we concluded that viral infection will be favoured. The different distribution between gender is not dependent on sexual factors, but on the fact that, in our cases, males were affected principally from mumps meningitis, while females from enterovirus meningitis. The different gender distribution is similar to the different seasonal variability of aseptic meningitis.

Conclusions

Our study on 59 cases (M=40, F=19) affected by aseptic meningitis showed a seasonal variability; the cases had greater incidence between May and September with a peak in July.

The cases presented mumps and enterovirus meningitis.

The first was more present during June-July and the second in September. The different seasonality according to gender, that is to say a greater incidence in July for males and in September for females is due to the different etiology of meningitis in the 2 genders. The males' meningitis was due to mumps, the females' to enterovirus.

Riassunto

Stagionalità della meningite

Obiettivo. Il nostro studio ha inteso verificare la stagionalità della meningite asettica.

Metodi. Nel periodo compreso tra il 1990 e il 1997

sono stati studiati 156 pazienti ricoverati presso il Dipartimento di Malattie Infettive dell'Università di Padova. Di questi, 59 (M=40, F=19), età media 18,9±7,3, erano affetti da meningite asettica (1 paziente era affetto da meningite erpetica, 31 da meningite parotitica e 27 da meningite da enterovirus). La diagnosi è stata posta mediante l'anamnesi del paziente, l'esame obiettivo e i test sierologici. Tutti i pazienti sono stati sottoposti a rachicentesi e il liquor è stato esaminato anche per quanto riguarda gli antigeni batterici e virali. In tutti i pazienti sono state eseguite coproculture, urinoculture e sono stati fatti tamponi faringei.

Risultati. La valutazione della stagionalità della meningite asettica nei casi studiati ha evidenziato un picco nel mese di luglio. Circa il sesso, l'analisi ha evidenziato un'incidenza maggiore nel mese di settembre per le femmine e nei mesi di giugno-luglio per i maschi. I casi studiati sono anche stati suddivisi in base all'eziologia della meningite e si è evidenziato un picco a luglio per la meningite parotitica e un picco a settembre per la meningite da enterovirus.

Conclusioni. Alla luce di questi risultati possiamo concludere che la meningite asettica presenta una maggiore incidenza nel periodo estivo. Questa osservazione è in accordo con il fatto che le malattie infettive hanno un andamento fluttuante a seconda dell'attività immunitaria, che viene depressa dall'esposizione ai raggi solari e agli UVA. Per quanto riguarda il sesso, la diversa stagionalità della meningite asettica è attribuibile alle diverse eziologie della meningite nei 2 sessi.

Parole chiave: Cronobiologia - Meningiti.

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