DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
17

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN (EPIDEMIOLOGIC, DIAGNOSTIC AND THERAPEUTIC ASPECTS, LONG TERM OUTCOME)

IRJA LUTSAR

TARTU 1995

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

17

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
17

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN (EPIDEMIOLOGIC, DIAGNOSTIC AND THERAPEUTIC ASPECTS, LONG TERM OUTCOME)

IRJA LUTSAR

TARTU UNIVERSITY
PRESS

Department of Pediatrics, University of Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Medical Science on June 14, 1995 by the Council of the Faculty of Medicine, University of Tartu, Estonia

Opponents: Professor Marika Mikelsaar, M.D., Ph.D., University of Tartu
Professor Rein Zupping, M.D., Ph.D., University of Tartu

Commencement: October 4, 1995

The addresses
of the author: Department of Pediatrics, University of Tartu
6 Lunini Street
EE2400 Tartu

of the distributor: The Library of University of Tartu
1 Struve Street
EE2400 Tartu, Estonia

Publication of this dissertation is granted by the Estonian Science Foundation

Tartu Ülikooli Kirjastuse trükikoda
Tiigi 78, EE2400 Tartu
Tellimus nr. 190.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS 7
ABBREVIATIONS 8
INTRODUCTION 9
AIMS OF THE STUDY 10

PART I: EPIDEMIOLOGY OF THE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN 11
1.1. Review of literature 11
1.1.1. Incidence of ICNS 11
1.1.2. Seasonality of ICNS 13
1.1.3. Age and sex distribution of ICNS 13
1.1.4. Etiology of ICNS in children 14
1.1.5. Outcome of ICNS in children 16
1.2. Patients and methods 18
1.3. Results 19
1.3.1. Incidence of the ICNS 19
1.3.2. Regional distribution of ICNS 21
1.3.3. Sex distribution of ICNS 21
1.3.4. Seasonal distribution 22
1.3.5. Age specific attack rate of ICNS 24
1.3.6. Etiology of ICNS 24
1.3.6.1. Etiology of bacterial meningitis 24
1.3.6.2. Etiology of nonbacterial meningitis 25
1.3.7. Outcome of ICNS 26
1.4. Discussion 30

PART II: ENZYMATIC CHANGES OF THE CEREBROSPINAL FLUID IN PATIENTS WITH THE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM 35
2.1. Review of the literature 35
2.1.1. LDH in the CSF in patients with ICNS 35
2.1.2. AST in the CSF in patients with ICNS 36
2.1.3. CPK activity in the CSF by ICNS 37
2.1.4. GGT in the CSF in patients with ICNS 38
2.1.5. Relationship of CSF enzyme concentration to the prognosis of the patients with ICNS 38
2.2. Patients and methods 39
2.3. Results 41
2.3.1. Activity of AST, LDH, CPK and GGT in the CSF on admission and on the 7–10th day of therapy 41

2.3.2. Prognostic value of intracellular enzyme determinations in the CSF 42
2.3.3. Activity and concentration of intracellular enzymes and ultrasound findings 43
2.4. Discussion 43

PART III: FOLLOW-UP AND LONG-TERM OUTCOME OF CHILDREN AFTER BACTERIAL MENINGITIS 46
3.1. Review of literature 46
3.2. Patients and methods 49
3.2.1. Patients of follow-up examinations 49
3.2.2. Patients of long-term follow-up examinations 50
3.2.3. Study procedures 50
3.3. Results 52
3.3.1. Follow-up of children after BM 52
3.3.2. Long-term outcome of children with BM 54
3.3.3. Prognostic value of clinical symptoms and syndromes 56
3.4. Discussion 58

PART IV: SHORT COURSES OF ANTIBACTERIAL THERAPY FOR BACTERIAL MENINGITIS IN CHILDREN 61
4.1. Review of literature 61
4.2. Patients and methods 62
4.3. Results 64
4.4. Discussion 66
GENERAL DISCUSSION 68
CONCLUSIONS 71
REFERENCES 73
SUMMARY IN ESTONIAN 84
ACKNOWLEDGEMENTS 87
PUBLICATIONS 89
CURRICULUM VITAE 119

LIST OF ORIGINAL PUBLICATIONS

This thesis are based on the following original publications:

I Lutsar I., Põder A., Olesk A., Udras M., Tamm K.
Mädase meningiidi epidemioloogia Lõuna-Eesti lastel aastail 1980–1991.
Eesti Arst 1993, 6, 408–413.

II Lutsar I., Haldre S., Topman M.. Talvik T.
Enzymatic changes in the cerebrospinal fluid in patients with infections of the central nervous system. Acta Pædiatr 1994; 83: 1146–1150

III Lutsar I., Gontmacher A., Närska M., Rüütel V., Topman M., Ilves P., Siirde T., Beilmann A.
Five days of antibacterial therapy for bacterial meningitis in children.
Infection 1995; 23: 113–118.

IV Lutsar I., Siirde T., Soopõld T.
Long term follow-up of Estonian children after bacterial meningitis.
Pediatr Infect Dis J 1995; 14: 624–625.

ABBREVIATIONS

AB	antibacterial therapy
AM	aseptic meningitis
AST	aspartat aminotransferase
BBB	blood brain barrier
BM	bacterial meningitis
CK-BB	creatine phosphokinase isoenzyme BB
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
EC	enzyme committee
GBS	group B streptococcus
GCS	Glasgow coma scale
GGT	gamma-glutamyl transpeptitase
Hib	*Haemophilus influenzae* type b
HSV	Herpes simplex virus
HSVE	Herpes virus encephalitis
ICNS	infections of the central nervous system
ICP	intracranial pressure
IQ	intelligence quotient
LDH	lactic dehydrogenase
MM	meningococcal meningitis
MMR	measles-mumps-rubella vaccine
mo	months
MR	mental retardation
n	number
PICU	pediatric intensive care unit
PMNL	polymorphonuclear leucocytes
SNHI	sensoneural hearing impairment
TBE	tick-borne encephalitis
VZV	varicellae zoster virus
WBC	white blood cells

INTRODUCTION

Infections of the central nervous system (ICNS), especially bacterial meningitis (BM), are still being considered as one of the most important infectious diseases especially among children, still having a lethal outcome or leading to severe sequelae. The incidence rate of ICNS in Finland in the 1970s was 105.2/100 000 children up to 15 years of age whereas occurrence of aseptic and bacterial meningitis was similar (Rantakallio *et al.* 1986). The incidence of ICNS in Estonia today is unknown, while only meningococcal infection, aseptic meningitis (AM) and tick-borne encephalitis (TBE) have been officially reportable diseases and only few studies have described epidemiology of BM, AM and TBE in Estonia thus far. The epidemics of AM in 1950s were first described by Raudam (1967), but due to poor facilities of virological services at that time the etiology of it was not defined. The epidemiology of TBE in whole Estonian population was investigated retrospectively by Raudam (1967) and Vassilenko *et al.* (1990), but there are no data concerning the epidemiology of TBE in children. A retrospective study of BM etiology, morbidity and mortality in Estonia was conducted from 1921 to 1958 by Tulmin (1961).

The epidemiological pattern of BM is different in different countries whereas during the last decades it has changed remarkably over the world. If in the industralised countries BM is a disease of early childhood then in developing world half of the patients are older than five years (Tikhomirov 1990). The studies performed in the area of former Soviet Union expressed that the etiological stucture of BM might be differnt in the East from that in the West. In the USA and in the Nordic countries Hib became the leading cause of community acquired BM (Salwen *et al.* 1987; Wenger *et al.* 1990; Carter *et al.* 1990; Peltola *et al.* 1990), while in the former Soviet Union most cases were still caused by *N. meningitidis* (Cibiras *et al.* 1986; Kostjukova *et al.* 1992). Moreover, better socio-economic conditions and the introduction of newly available and effective conjugate vaccines against Hib infection decreased the incidence of BM especially in the developed world and only single cases of BM were registered during last years (Peltola *et al.* 1992; Adams *et al.* 1993). There are no studies on BM in Estonia, a country that used to be a part of the former Soviet Union and have had no vaccinations against Hib diseases.

Not only incidence but also outcome of BM has changed recently. With the development of intensive care and antibacterial therapy the mortality of BM decreased during the last decades to less than 5% in the developed countries (Salwen *et al.* 1987; Valmari *et al.* 1987; Carter *et al.* 1990). However, a significant number of patients develop permanent sequelae, i.e. an average of 17% of survivors in the developed countries and 26% in the developing world (Baraff *et al.* 1993). It has been shown by Klein *et al.* (1986) that there is a tendency after BM of multiple defects to resolve with time. So far it is not clear whether all children or only some need careful follow up examinations after BM. No data about morbidity, mortality and long term outcome of BM in Estonia in the situation of using new antibiotics and sophisticated methods of intensive care have been published so far.

In spite of numerous diagnostic methods, a differentiation between bacterial and aseptic meningitis sometimes presents a major diagnostic problem (Lindquist *et al.* 1988) and the outcome of patients with ICNS is often difficult to predict (Briem, 1982; Pasaglu *et al.* 1989). The chemical tests most commonly used for the differential diagnosis of meningitis are determination of CSF glucose, CSF protein and CSF/blood glycose ratio, these tests however are not truly specific for BM (Rodewald *et al.* 1991). Estimations of intracellular enzymes such as AST, LDH, GGT, CPK and CK-BB are widely employed as valuable diagnostic aids in diseases involving necrosis or damage of tissues characteristically rich in these enzymes. The activities of these enzymes have been measured in the CSF of patients with a variety of neurological disorders (Riekkinen, 1970; Nelson *et al.* 1975; Landaas *et al.* 1985; Tammpere *et al.* 1987; Talvik, 1992). However, the results obtained in patients with BM and AM are controversial and it is not clear which enzymes will be important in differential diagnosis and in predicting the outcome.

Although antibiotics have been used in the therapy of BM for more than 50 years and the number of efficacious antimicrobials has increased, no generally accepted standard for duration of treatment has emerged. A treatment period of 7 days for meningococcal, 10 days for Hib and 14 days for pneumococcal meningitis are the recommendations in most manuals and standard publication (Feigin *et al.* 1992; McCracken *et al.* 1992; Klein *et al.* 1992), but they are not based on controlled clinical trials. Some reports suggest that shorter treatment periods, especially in meningococcal meningitis, are sufficient and safe in uncomplicated cases (Lin *et al.* 1985; Tuncer *et al.* 1988; Pecco *et al.* 1991). A shorter course of antibacterial therapy will result in fewer days of hospitalisation and lower costs.

A better knowledge of the epidemiological situation, an understanding of the prognostically important markers and introduction of treatment regimens based on controlled clinical trials will be important in order to improve the outcome of ICNS in Estonia.

AIMS OF THE STUDY

— to study retrospectively the incidence, the etiologic pattern and the short-term outcome of ICNS in children in South-Estonia during the period of 1980–1989.

— to measure the activity of AST, LDH, GGT, CPK and the concentration of its brain type isoenzyme CK-BB in the CSF in patients with and without the ICNS and to establish whether any of these intracellular enzymes would correlate with brain damage of different etiology and is prognostically important

— to evaluate late sequelae (persisting more than three years) of bacterial meningitis and to establish which features of the acute illness predict long term outcome.

— to determine whether the incidence of early complications of bacterial meningitis in children treated for 5 days with intravenous antibiotics is similar to that seen in children treated longer

PART I

EPIDEMIOLOGY OF THE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN

1.1. REVIEW OF LITERATURE

1.1.1. Incidence of ICNS

Infections of the central nervous system in childhood are still an important problem in pediatrics. There are considerable differences in registration of ICNS in different countries. Therefore it is difficult to compare the data on morbidity and mortality.

Bacterial meningitis: The incidence of BM in Finland in 1978 was 19.0/100 000 children up to 15 years (Valmari *et al.* 1987). Carter *et al.* (1990) comparing the incidence of BM in Scotland in 1946–1961 to that of 1971–1986 found that it was rather similar at 16.9 and 17.8/100 000 children up to 13 years of age respectively. The incidence of meningococcal, *H. influenzae* and pneumococcal meningitis are usually characterised separately. The incidence of MM in some countries is shown in Table 1. The incidence of MM except New Zealand was not higher than 10/100 000 children in the late 1970s and early 1980s. An outbreak of meningococcal infection of group A was registered in New Zealand in 1985–1986 and the attack rate of MM increased almost 10 fold (Lennon *et al.* 1989). A raised number of patients with MM in the middle of the 1980s was also found in European countries — in Russia, in Scotland and in Norway (Voss *et al.* 1989; Devjatkina *et al.* 1989; Carter *et al.* 1990).

Table 1

Incidence of MM in children in different countries

Country (author)	Years	n of patients	Incidence
Sweden (Salwen *et al.* 1987)	1956–1980	201	6.2*
Finland (Valmari *et al.* 1987)	1976–1980	164	2.0**
New Zealand (Lennon *et al.* 1989)	1985–1986	211	30.4*
Scotland (Carter *et al.* 1990)	1971–1986	274	5.3*

* per 100 000 children
** per 100 000 population

The importance of *H. influenzae* meningitis has grown during the last 20–30 years world-wide. The incidence of this disease in Scotland being no higher than 1.5/100 000 children in 1940 to 1950 increased to 6.6/100 000 in 1986 (Carter *et al.* 1990). The attack rate of *H. influenzae* meningitis in Nordic countries in the 1980s was even higher — 31.0 in Sweden; 20.0 in Finland; 19.0 in Norway and 16.0/100 000 children in Denmark (Trollfors, 1987; Peltola *et al.* 1990).

Neonatal meningitis: The occurrence of neonatal meningitis varies in different studies from 0.07 to 0.67 per 1000 live born babies (Bennhagen *et al.* 1987; Bell *et al.* 1989; Zaki *et al.* 1990).

Aseptic meningitis: The epidemiology of AM is not studied frequently. Beghi *et al.* (1984) in a retrospective study of AM in Minnesota through the period of 1950 to 1981 provided the incidence rate of 10.9/100 000 person-years. They found it about six times higher than the rates registered by Centres for Diseases Control. With the introduction of MMR vaccination the incidence of AM caused by those viruses fell dramatically, but post-vaccinal meningitis and encephalitis appeared with the frequency from 1/1000 in Yugoslavia to 1/100 000 vaccination doses in USA (Hayden *et al.* 1978; Cizman *et al.* 1989; McDonald *et al.* 1989; Sugiora *et al.* 1991). The first cases of AM in Estonia were described in the Viljandi district — 412 persons fell ill from June to September 1953. The etiology of AM remain unknown due to poor facilities of virological laboratories at that time, but according to the seasonality, it seems that coxsackieviruses A and B were the main causes of this outbreak (Raudam, 1967). Thereafter only sporadic cases of AM were registered from 1959 to 1962 in Estonia (Raudam, 1967). The attack rate of AM increased in the late of 1960s. In the survey performed by Kutsar (1971) in Pärnu, the incidence rate of that was 200.1 in 1967 and 60.2/100 000 population in 1968.

Encephalitis: Two population based studies of viral encephalitis were performed in North and South Finland during the period from 1973 to 1987. The incidence rate in those areas was rather similar- encephalitis occurred at a rate of 8.6/100 000 in South-Finland and 12.6/100 000 children younger than 15 years of age in North-Finland (Koskiniemi *et al.* 1989; Rantala *et al.* 1989). With the introduction the immunisations against measles and parotitis the incidence of encephalitis declined from 19.8 in 1974 to 2.5/100 000 in 1986 (Koskiniemi *et al.* 1989).

First cases of TBE in Estonia were registered among students of the Agricultural Academy in the area of Lake Peipus in 1950 (Raudam *et al.* 1972). The incidence of TBE at 0.4 to 0.8/100 000 population was rather low up to 1976. A significant rise of the illness was noticed in 1976. The last epidemics of the TBE in Estonia occurred in 1980, 1984 and 1987. The incidence ranges from 3.1–4.4/100 000 population during epidemic outbreaks versus 1.1–1.7/100 000 population in periods of remission (Vassilenko *et al.* 1990).

1.1.2. Seasonality of ICNS

Bacterial meningitis: The number of patients with ICNS increases usually during the cold months of year. MM outbreaks peak from November to March (Goetz *et al.* 1980; Djomina *et al.* 1984; Lennon *et al.* 1989). Cases of *H. influenzae* diseases are registered throughout the year. A spring peak of *H. influenzae* infection was noticed by Rieske *et al.* (1985). In the study performed in Nordic countries most cases of the illness occurred from June to September (Peltola *et al.* 1990). An unexplained biphasic seasonal pattern of the appearance of *H. influenzae* meningitis has been observed in USA (Nesheim *et al.* 1986).

Aseptic meningitis: Seasonality of AM depends on that of enteroviruses. In temperate climates there is a marked peak of viral infections in August, September and October, although some viral activity does occur during the winter months (Ratzan 1985; Kirilenko *et al.* 1990). In a study in Estonia Kutsar (1971) found that single cases of viral meningitis were observed over the year, but the attack rate raised remarkably from August to October.

Encephalitis: The vast majority of encephalitis cases in the areas with existence of arboviral infection occur in the summer. The activity of ticks usually raises in the early spring after a short warm winter (Wood *et al.* 1988). In an epidemiological study in Estonia the highest attack rate of TBE was noticed in April and May (Vassilenko *et al.* 1990).

In countries having no epidemiological activity of arboviruses, sporadic cases of encephalitis occur in any season. However the frequency of it is slightly higher during the winter (Tardieu *et al.* 1986; Klatte–Mayer 1987; Rantala *et al.* 1989).

1.1.3. Age and sex distribution of ICNS

Bacterial meningitis: The age distribution of BM depends largely on the epidemiological and socioeconomical situation of the country. In the developed countries the vast majority of cases are registered among children up to five years, whereas less than 50% of BM patients are under five in the developing world (Tikhomirov 1987). The greatest incidence of pneumococcal meningitis occurs in children between 6 months and four years and in adults over 50 (Djomina *et al.* 1984). The age specific attack rate of *H. influenzae* meningitis is highest at one to three years and it frequency decreases beyond 5 years of age (Peltola *et al.* 1990).

Aseptic meningitis: The data on age distribution of non bacterial meningitis are controversial. It was observed in the study performed by Wildin *et al.* (1987) that of the total cases of viral meningitis 76% were in children up to one year. In another study the rate of children younger than one year was significantly lower and consisted only of 25.3% (Tardieu *et al.* 1986).

The ICNS occur more commonly in male than in female children (Fröber *et al.* 1977; Rantakallio *et al.* 1986; Lennon *et al.* 1989). Only Salwen *et al.*

(1987) noticed a female predominance among children with *H. influenzae* meningitis.

1.1.4. Etiology of ICNS in children

The etiology is related to the age of the patient and a number of factors that may predispose the host to bacterial infections or alter host response to an invading microorganism.

Bacterial meningitis: Most of BM in children between 2 months and 15 years of age are due to *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*, which together account for more than 90% of community acquired BM. The distribution of above noted bacteria differs worldwide (Table 2). In the area of the former Soviet Union 72.6–83.2% of cases of BM in children were caused by meningococci (Djomina *et al.*1985; Cibiras *et al.* 1986; Iljina *et al.* 1990). The rate of pneumococcal meningitis does not exceed 20% in most countries except Israel (Rosenthal *et al.* 1988; Rantakallio *et al.* 1986). Recently *H. influenzae* has become the leading cause of BM in several areas — 62.0% of the cases of BM were caused by this micro-organism in Finland (Valmari *et al.* 1987), 36.8% in Scotland (Carter *et al.* 1990) and 28.6% in Brazil (Bryan *et al.* 1990). A considerable number of cases with unknown etiology is brought about by early onset antibacterial therapy, moreover poor facilities of bacteriological laboratories are also hard to exclude (Giustina *et al.*1985; Kühn *et al.* 1987). A mixed flora was established in no more than one per cent of BM cases. Sferra *et al.* (1988) found combinations of viruses and bacteria in 5 of 276 patients with BM.

Table 2

Etiology of BM in children in different countries

Region (author)	Years	n	Etiologic agents (%)				
			S. pneumoniae	*N. meningitidis*	*H. influenzae*	other	unknown
Moscow (1)	1980–89	2165	7.2	72.6	3.7	2.7	13.6
Moscow (2)	1986–89	4695	6.8	68.7	3.4	3.6	17.5
Lithuania (3)	1970–80	37	10.4	83.2	2.6	—	—
Germany (4)	—	2323	10.6	8.6	8.6	55.5	55.5
Israel (5)	1981–85	142	24.0	20.0	42.0	4.0	4.0
Brazil (6)*	1973–82	4100	15.9	28.9	28.6	17.2	17.2
Scotland (7)	1946–61	285	10.8	46.6	9.1	29.1	29.1
	1971–86	274	6.2	29.9	36.8	25.2	25.5
Italy (8)	1960–80	146	15.1	25.3	0.7	52.1	52.1
West-Australia (9)	1984–88	270	13.3	8.8	68.8	7.0	7.0

* study involved 3186 children and 914 adults; "—" not recorded

1 – Djomina *et al.* 1985; 2 – Iljina 1990; 3 – Cibiras *et al.* 1986; 4 – Kühn *et al.* 1987; 5 – Rosenthal. *et al.* 1988; 6 – Bryan *et al.* 1990; 7 – Carter *et al.* 1990; 8 – Giustina *et al.* 1985; 9 – Hanna *et al.* 1991.

Aseptic meningitis and encephalitis: The etiologic agents in non bacterial ICNS are listed in Table 3. In the prevaccine era, mumps and measles were the agents responsible for the majority of cases of AM and encephalitis (Koskiniemi *et al.* 1989). At present the etiologic factor is not identified in about 10 to 70% of all cases (Wood *et al.* 1988). However, intensive investigations at some centres indicate that enteroviruses account for approximately 80% of all cases of AM; the most common specific types are coxsackieviruses A and B and echoviruses (Tardieu *et al.* 1986; Klatte–Mayer *et al.* 1987).

Table 3

Etiology of non bacterial ICNS in children in different studies

Etiologic agents	Studies/ frequency in %					
	I	II	III	IV	V	VI
1. Arboviruses	—	—	—	—	10.0	—
2. Picornaviruses						
– enterovirus	—	—	7.7	27.0	—	38.2
– coxsackievirus A, B	16.5	—	—	—	—	—
– echovirus	0.9	10.4	—	—	—	—
3. Herpesviruses						
– HSV	—	7.3	6.4	—	5.3	—
– VZV	4.7	25.2	15.4	—	4.0	—
– CMV	—	—	1.3	—	0.1	—
– EBV	—	—	1.0	—	0.2	—
4. Myxo- and paramyxoviruses						
– influenzae	1.7	—	5.4	1.7	—	—
– parainfluenzae	—	—	4.2	8.5	—	—
– measles	1.7	4.2	12.8	—	0.9	—
– mumps	40.9	8.4	16.0	39.0	1.9	22.7
– rubella	—	2.1	1.6	—	—	—
5. Adenoviruses	5.2	2.1	8.7	—	—	—
6. Postvaccinal	—	—	1.0	—	—	—
7. Unknown	29.6	38.9	18.5	23.7	74.3	39.1

Only AM is included in study I, IV, VI.
Only viral encephalitis is included in study II, III, V.

I Rantakallio *et al.* (1986) — Finland 1966–1980
II Rantala *et al.* (1989) — North Finland 1973–1987
III Koskiniemi *et al.* (1989) — South Finland 1968–1987
IV Tardieu *et al.* (1986) — France 1983–1985
V David *et al.* (1985) — USA 1987
VI Klatte–Mayer *et al.* (1987) — Germany 1980s

A study conducted in the Pärnu district in the late 1960s and early 1970s demonstrated a prevalence of coxsackievirus B 5 and B 3 during the epidemic peaks in 1967 and 1968 respectively (Kutsar *et al.* 1968; Kutsar 1971).

The group of herpesviruses, HSV in Germany and VZV in Finland, are the most common cause of viral encephalitis today — (Lietz *et al.* 1986; Rantala *et al.* 1989; Koskiniemi *et al.* 1989).

Neonatal meningitis: Several micro-organisms have been detected to cause neonatal meningitis (Meade 1985). Microorganism accounting for the majority of BM in the older child and infant, are infrequent etiologic agents in the neonatal period, being responsible for only 5.1% of the infections (Abrikossova *et al.* 1991). The three most commonly encountered pathogens are group B streptococci, *E. coli* and *Listeria monocytogenes* accounting for approximately 75% of all neonatal BM cases, whereas *E. coli* K1 is leading at most medical centres (Meade 1985; Abrikossova *et al.* 1991). Since the early 1970s there has been a significant increase in serious infections caused by *Streptococcus agalactiae* (GBS). The reasons for this increase have not been quite understood yet. In a retrospective epidemiological study in Kuwait GBS was found in 7 out of 45 newborns with neonatal meningitis (Zaki *et al.* 1990).

1.1.5. Outcome of ICNS in children

Only few studies investigated outcome of all ICNS, in most other surveys the prognosis of BM and AM are represented separately. The mortality rate of ICNS in the Finnish cohort study in 1966–1980 (Rantakallio *et al.* 1986) was 6.5% and 14.9% of the survivors had some sequalae of their disease. Specific sequelae of meningitis that have been observed include cranial nerve involvement, hemi- or quadriparesis, muscular hypertonia, ataxia, permanent seizure disorders, deafness, cortical blindness, mental retardation and the development of obstructive hydrocephalus (Feigin *et al.* 1992)

Bacterial meningitis: Appropriate antibiotic therapy has altered the outcome of BM remarkably in children who are beyond the neonatal period. A retrospective study of BM epidemiology was conducted in Estonia from 1921 to 1958 (Tulmin 1961). The case fatality rate of MM was 40.4% in the preantibiotic era and dropped to 20.7% with the introducing of prontosil in 1941 and penicillin in 1945. The mortality rate of nonmeningococcal meningitis was even higher — 64 and 43% respectively (Tulmin 1961). The case fatality rate of BM today ranges from 1.8% in Scotland, 3–4% in Sweden and Finland to 12% in Italy and Israel (Giustina *et al.* 1985; Salwen *et al.* 1987; Valmari *et al.* 1987; Rosenthal *et al.* 1988; Carter *et al.* 1990). The outcome of BM in diferent studies according to the etiology is outlined in Table 4.

There are differences in reported mortality and disability rates in various types of BM. The greatest mortality and disability was recorded in patients with pneumococcal meningitis (Fröber *et al.* 1977; Laxer *et al.* 1977; Grubbauer 1982) whereas the case fatality and disability rates of MM are the lowest (Carter *et al.* 1990).

Table 4

Mortality and disability of BM in children in different studies

Region	Mortality (%)			Disability(%)		
	N. meningitidis	*S. pneumoniae*	Hib	*N. meningtidis*	*S. pneumoniae*	Hib
Norway (1)	—	—	6.3	—	—	—
Sweden (2)	2.4	—	—	1.06	—	—
New Zealand (3)	—	—	7.0	—	—	7.8
USA (4)	—	—	10.3	—	—	—
East-Germany (5)	5.0	21.2	0	5.0	42.0	10.0
Brazil (6)	38.0	59.0	14.0	—	—	—
North-Europe (7)	1.0	—	—	3.8	—	—
Scotland (8)	3.0	—	1.2	—	—	—
West Germany (9)	8.3	29.0	1.75	26.9	46.0	3.8
Russia (10)	0	—	—	16.0	—	—
Ukraine (11)	—	—	6.7	—	—	—
Canada (12)	—	10.8	—	—	28.0	—
Georgia (13)	—	12.1	—	—	—	—
UK (14)	—	—	10.6	—	—	—

"—" not recorded

1 – Halstensen *et al.* 1987; 2 – Trollfors 1987; 3 – Lennon *et al.* 1989; 4 – Havens *et al.* 1989; 5 – Fröber *et al.* 1977; 6 – Bryan *et al.* 1990; 7 – Peltola *et al.* 1990; 8 – Carter *et al.* 1990; 9 – Grubbauer 1982; 10 – Pokrovskaja *et al.* 1983; 11 – Kirilenko *et al.* 1990; 12 – Laxer *et al.* 1977; 13 – Botsvadze *et al.* 1983; 14 – Thompson *et al.* 1990.

Neonatal meningitis: The current mortality rate of neonatal meningitis ranges from 22 to 49% in most studies and varies depending on the etiologic agent, the degree of prematurity of the infant, the presence and severity of associated diseases (Apak *et al.* 1983; Bell *et al.* 1989; Zaki *et al.* 1990). Significant neurological sequalae, including hydrocephalus, mental retardation, blindness, deafness and motor disability occur in 40–50% of the survivors of neonatal meningitis (Bell et al. 1989).

Aseptic meningitis: The prognosis of AM is usually good, the mortality and disability rates are almost zero (Etter *et al.* 1991; Rorabaugh *et al.* 1993).

Encephalitis: The prognosis of encephalitis depends to some extent on the etiology and the age of the child. Case fatality rates of encephalitis vary in different surveys from 1.05 to 9.6% (Rantakallio *et al.* 1986; Koskiniemi *et al.* 1989; Rantala *et al.* 1989). The prognosis of encephalitis due to herpesviruses with a mortality of 44–85% is the worst (Lietz *et al.* 1986; Wagner *et al.* 1987). Sequelae involving the central nervous system, visual or auditory functions are being detected in 7 to 25% following encephalitis (Koskiniemi *et al.* 1983; Rantakallio *et al.* 1986). A study conducted in Estonia showed a mortality rate of TBE of 0.28% (Vassilenko *et al.* 1990).

1.2. PATIENTS AND METHODS

The study consisted of a retrospective review of all cases of ICNS in children up to 14 years of age inclusively in South Estonia between January, 1, 1980 and December, 31, 1989. During this period children with ICNS were treated in neurological or intensive care units of Tartu University Hospitals, in the Infectious Diseases Hospital of Tartu and in the Tartu University Children's Hospital, but also in pediatric units of the districts hospitals located in this area. Annual reports and patients records of those hospitals were used. Patients included had diagnoses according to the 9th edition of the International classification of Diseases listed as follows: 036 (meningococcal infection); 047 (enteroviral meningitis); 072 (mumps); 063 (TBE); 320 (BM); 321–322 (meningitis of unknown etiology); 323 (encephalitis). Patients with the above noted diagnoses having no affection of the central nervous system were excluded. Three sudden deaths at home due to BM were traced through pathology records.

Diagnostic criteria: Children were included if a clinical diagnosis of BM, AM or encephalitis was made and one of the following criteriae described by Scheibe *et al.* (1983) and Feigin *et al.*(1992) were fulfilled

1. for *bacterial meningitis*
   — sterile CSF, but more than $200x10^6$/l WBC, predominantly polymorphonuclear leukocytes
   — micro-organism grown from CSF
   — micro-organism grown from blood with more than ten WBC in the CSF
2. for *aseptic meningitis*
   — above mentioned excluded
   — more than ten WBC in 1 ml of CSF
3. for *encephalitis*
   — more than 10 lymphocytes per ml of CSF and typical changes in EEG
   — clinical signs of encephalitis and typical changes in EEG
   — increased protein concentration in CSF and typical changes in EEG
4. for *tick-borne encephalitis*
   — four fold rising of the titre of antibodies in complement fixation reaction test, history of tick bites and above mentioned criteria of encephalitis or aseptic meningitis
5. for *neonatal meningitis*
   — above mentioned criteria of BM
   — age up to one months

Characteristics of the region.

South Estonia is epidemiologically a predominantly rural area, with no big cities. The biggest town is Tartu with the population of 112 000. The other towns located in this area are small with a maximum population of 15 to 20 000. Six districts of Estonia are included in this study: Tartu, Valga, Võru,

Põlva, Viljandi and Jõgeva. The total population of this region is approximately 400 000 representing less than 1/3 of the total population of Estonia. Rural and urban people are almost equal in number to each other. The average childhood population (0 to 14 years incl.) has increased from 85 416 in 1980 to 88177 in 1989. The mean value was 86 593 children during these 10 years. The statistical data used were collected from the year books of the Estonian Health Ministry in 1980 to 1989.

For *statistical analysis* computerised package STATVIEW 512 was used.

1.3. RESULTS

1.3.1. Incidence of the ICNS

A total of 573 cases of ICNS were recorded in a ten year period in children less than 15 years (excl.) of age. Of these 223 had infection of bacterial and 350 of non bacterial etiology. The annual incidence rate of ICNS ranged from 45.3 in 1989 to 119.8 in 1984 per 100 000 children amounting to a mean incidence rate of 66.2/100 000 children (Figure 1).

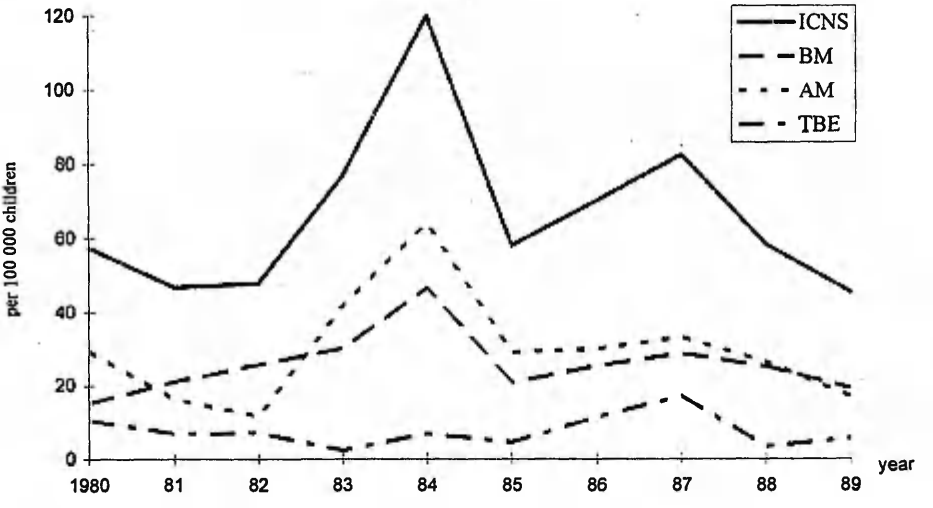


Figure 1. Incidence of ICNS, BM, AM and TBE in children in South-Estonia in 1980–1989

The annual incidence of AM and BM was relatively similar. Figure 1 shows an antagonistic epidemic course of bacterial and non bacterial ICNS in 1980–1982: the AM appear to have declined at the time when BM increased. From 1983 onwards the figures are becoming more similar. The maximum rise of BM as well as AM is to be seen in 1984.

The overall incidence of BM was 25.8/100 000 children including occurrence rates of MM at 9.0, of pneumococcal at 1.15, of *H. influenzae* at 1.03, of meningitis caused by opportunistic bacteria at 1.49 and of meningitis with unknown etiology at 15.0/100 000 children. Our data revealed a slight peak of MM in 1984 to 1986. The mean incidence of AM was 29.8/100 000 children ranging from 11.6 to 64.0.

The course of the estimated rates of TBE was also intermittent: small peaks were registered in 1980; 1986 and 1987 with the incidence rates of 10.5; 11.4; and 17.1/100 000 children respectively, whereas the overall annual rate of TBE was 7.6/100 000 children up to 14 years.

There were 24 newborns with bacterial meningitis in this period, an incidence rate of 0.42/1000 live births. The yearly distribution of incidence of neonatal meningitis is shown in Table 5 and ranges from zero (1980 and 1985) to 1.16/1000 live born babies in 1986.

Table 5

Incidence of neonatal meningitis per 1000 live born babies in South Estonia in 1980–1989

Year	n of patients	incidence
1980	0	0
1981	1	0.16
1982	4	0.66
1983	3	0.5
1984	2	0.33
1985	0	0
1986	7	1.16
1987	2	0.33
1988	1	0.16
1989	4	0.66
Total	24	0.42

1.3.2. Regional distribution of ICNS

The ICNS did not occur of an equal frequency in the whole area studied (Table 6). The highest incidence rate amounted to 105.9/100 000 children in the district of Viljandi, while it was only 40.6/100 000 children in the least affected district of Võru. The high incidence was mainly due to the rise of AM and encephalitis especially in 1985–1986. Cases of TBE were only registered in three districts (Jõgeva, Tartu, Põlva) which correspond geographically to the zone of lake Peipus. The highest attack rate of 17.5/100 000 of TBE was seen in the Jõgeva district.

Table 6

Regional distribution of ICNS in children in South Estonia in 1980–1989 (incidence per 100 000 children)

Region	BM n	Incidence	AM+E n	Incidence	TBE n	Incidence	Total n	Incidence
Tartu town	48	20.4	73	31.0	27	11.5	148	62.8
Tartu distric	24	21.3	30	26.6	11	9.8	65	57.6
Võru	25	24.3	25	24.6	1	1.0	51	49.7
Põlva	33	41.1	25	31.2	6	7.5	64	79.7
Jõgeva	24	24.7	11	11.3	17	17.5	52	53.6
Valga	31	35.5	52	60.1	2	2.3	85	99.4
Viljandi	38	37.0	68	66.2	2	1.9	108	105.2

AM+E included AM and encephalitis except TBE.

The regional distribution of BM in the area studied was relatively constant and varied from 20.8/100 000 in the town of Tartu to 41.5/100 000 in the district of Põlva.

A predominance of rural people among ICNS patients was seen in all forms of ICNS, a overall ratio urban *versus* rural people registered was at 1:1.6 with a maximum of 1:1.9 in AM.

1.3.3. Sex distribution of ICNS

Comparing both sexes, there is a slightly higher prevalence of ICNS as a whole as well as of different forms in males (Table 7). The overall ratio of boys versus girls was 1.7:1.

Table 7

Sex distribution of different forms of ICNS in South Estonia children in 1980–1989

	girls:boys
Bacterial meningitis	1:1.22
Aseptic meningitis	1:1.85
TBE	1:1.46

1.3.4. Seasonal distribution of ICNS

Figure 2 demonstrates the monthly fluctuation of ICNS in South Estonia over a period of ten years. The lowest rate of infection appears to be in January (27.6/100 000) and continues with a slight fluctuation until April. A steep increase in the number of cases is being noticed in May persisting into June and July. The number of cases gradually falls from August. The monthly incidence rate of BM as a whole as of MM in particular is relatively constant demonstrating only a slight not significant increase in February and in March. The strong seasonal variation of ICNS is caused by AM and particularly encephalitis. Single cases of encephalitis (1 to 5 cases) have been registered from August to April, whereas 70.6% of all cases occur during three months of the year — May, June and July. This strictly seasonal distribution of non bacterial infections was mainly caused by TBE occurring only in early summer.

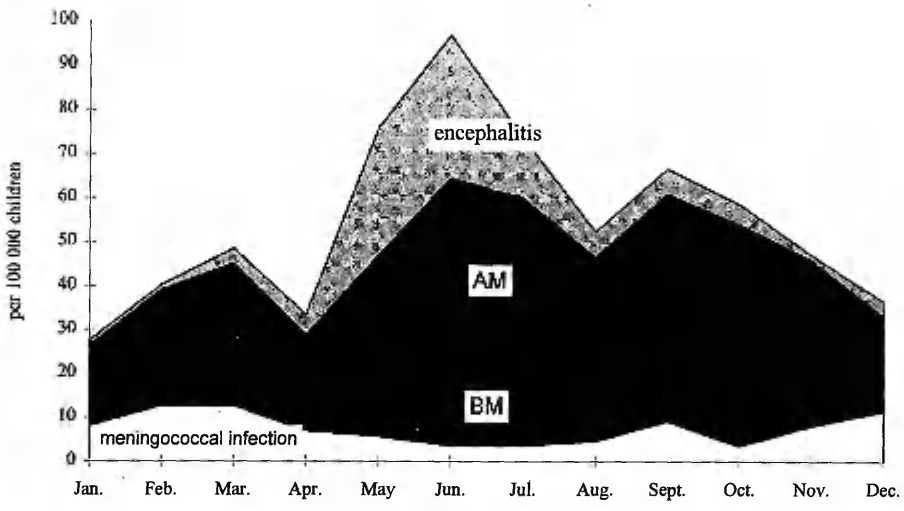


Figure 2. Monthly distribution of encephalitis, aseptic and bacterial meningitis and meningococcal infection in children in South-Estonia in 1980–1989.

1.3.5. Age specific attack rate of ICNS

The distribution pattern of age specific attack rate of children with BM differed considerably from the pattern in non bacterial ICNS. The BM affected mostly younger children (84.3% were up to 5 years of age) while non bacterial ICNS predominantly occurred in those being older (only 19.7% were up to 5 years of age) (Figure 3).

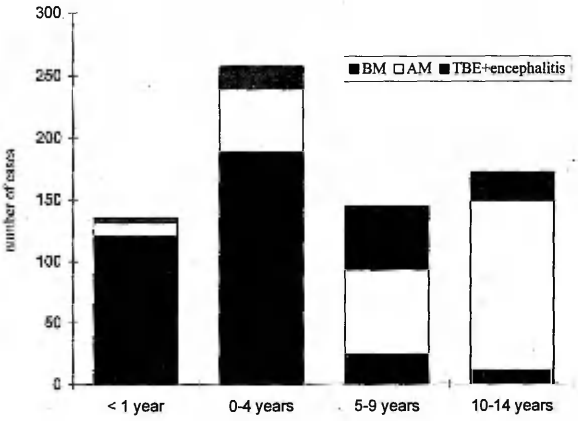


Figure 3. Age distribution of BM, AM and TBE+encephalitis in South-Estonia in 1980–1989.

Table 8 demonstrates the prevalence rates of different forms of ICNS depending on ages. A significantly higher prevalence rate of BM was seen as at the age under one year as well up to five years- 207.9 and 65.5 per 100 000 children of that age respectively ($p<0.005$). The percentage of infants among different forms of BM ranged from 100% of meningitis caused by opportunistic bacteria to 48.9% of MM cases. A similar trend was seen among children under five years of age too: 100% of opportunistic flora meningitis, 90.2% of MM and 77% of *H. influenzae* meningitis occurred at that age.

Table 8

Age specific prevalence of ICNS per 100 000 children in 1980–1989

Diagnosis	<1 year	0–4 years	5–9 years	10–14 years
BM	207.9*	65.5*	8.3	3.8
AM+encephalitis	15.3	23.9	41.6	55.6
ICNS	223.0	89.4	49.9	59.5

*$p<0.005$

The cases of AM were found predominantly in children older than five years of age (207 cases and 86.2% of the total) whereas 138 cases (53.8%) of the total occurred in the age group between 10–14 years.

The predominance of children older than five years was less apparent among encephalitis (except TBE) patients — 11 cases and 43.3% of the total and no cases were diagnosed in the age group between 10–14 years. The cases of TBE occurred preferably in schoolchildren — 63 cases (95.4%) of the total diagnosed were older than five years of age.

1.3.6. Etiology of ICNS

1.3.6.1. Etiology of bacterial meningitis

As shown in Table 9 *N. meningitidis* with 38.1% was the most common microorganism causing non-neonatal BM during the study period. *H. influenzae* and *S. pneumoniae* as causes of nonneonatal BM occurred at similar rates, both in 4.5% of the cases. An increase of *H. influenzae* among the etiologic factors to 12.5% was noticed during the last three years (1987–1989) studied, nevertheless *N. meningitidis* remained a leading microbe in the etiology of BM (30.3%). The microbes responsible for BM were not identified in 101 cases (50.7%) and this number was constant throughout the study period.

Figure 4 demonstrates that the Gram negative enteric bacteria *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae* were the predominant causes of BM in newborns accounting for 29% of all cases. *N. meningitidis*, *S. pneumoniae* and *H. influenzae* were found in three patients (12.4%). Gram positive organisms such as *S. agalactia* and *S. aureus* were detected in one and two cases of neonatal meningitis respectively. The etiology of the neonatal meningitis remained unknown in 11 cases (45%) of the total.

Table 9

Etiology of nonneonatal BM in South Estonia in 1980–1989

Year	Etiologic agents (n of patients)					
	N. meningitidis	*S. pneumoniae*	*H. influenzae*	Other	unknown (%)	Total
1980	5	—	—	—	8 (38.4)	13
1981	8	—	—	—	9 (52.9)	17
1982	9	1	—	1	8 (42.1)	19
1983	12	4	1	1	5 (21.7)	23
1984	10	—	—	—	28 (73.6)	38
1985	6	—	—	—	12 (66.6)	18
1986	9	—	1	—	5 (33.3)	15
1987	4	4	3	—	12 (52.1)	23
1988	4	—	3	2	11 (55.0)	20
1989	9	—	1	—	3 (23.0)	13
Total	76	9	9	4	101 (50.7)	199
% of the total	38.1	4.5	4.5	2.0	50.7	

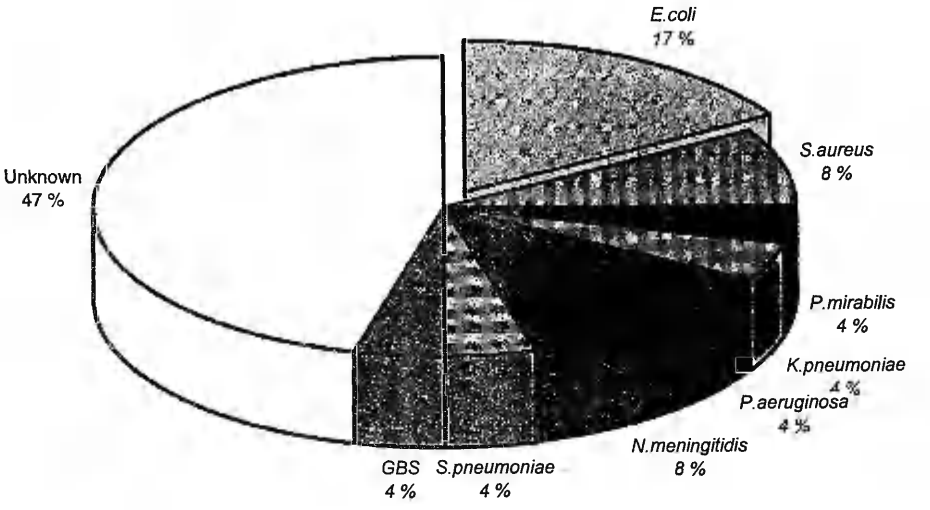


Figure 4. Etiology of neonatal meningitis in South-Estonia in 1980–1989.

1.3.6.2. Etiology of nonbacterial meningitis

Table 10 demonstrates the occurrence of different forms of encephalitis in the survey.

Table 10

Etiology of encephalitis in children in South Estonia

Etiology	n of patients	%
TBE	66	71.7
Mumps	10	10.7
Varicella	2	2.2
Rubella	1	1.1
HSV	1	1.1
Influenzea B	1	1.1
Unknown	11	12.1
Total	92	100.0

TBE comprising 71.7% of the cases was the most frequent cause of encephalitis in this survey. Ten cases of mumps encephalitis (10.7%) of the total were identified in the prevaccine era only, that was before the 1984. The etiology of encephalitis remained unknown in 11 cases.

A significant number of cases of AM was unidentified in this retrospective study. The etiological agent was found in only 12 cases of the total of 252 (4.6%). There were 6 cases of echovirus type 7–14, four of adenovirus, one of coxsackie B and one of influenzae virus infection.

1.3.7. Outcome of ICNS

Among the 573 patients with ICNS 31 children died in the acute period of the disease (case fatality rate 5.4%) and 24 (4.4%) among those who survived had some sequelae at discharge. 29 patients of the 31 who died were BM patients.

The mortality rate of BM registered was 13.0% varying from 2.5% in 1984 to 27.3% in 1986. The disability rate registered at discharge was 8.9% and ranged from 1.1% in 1985 to 22.3% in 1982. A considerable difference in prognosis was noticed between neonatal meningitis and that in older children. 13 fatal cases of ICNS were found in children beyond the newborn age (case fatality rate 3.6%) and 17 patients had a sequelae at discharge (disability rate 3.2%) whereas 11 newborn died (45.8%) and 7 of 13 survivors (53.8%) developed disabilities.

Figure 5 demonstrates that neither the overall mortality of ICNS nor the disability rate varied significantly in the sequence of the 10 years studied, due to rising numbers of neonatal meningitis. The case fatality rate beyond the neonatal period fell dramatically from 10.1% in the first six years to 2.8% at the end of the study, but failed to change to any extent during the first months of life.

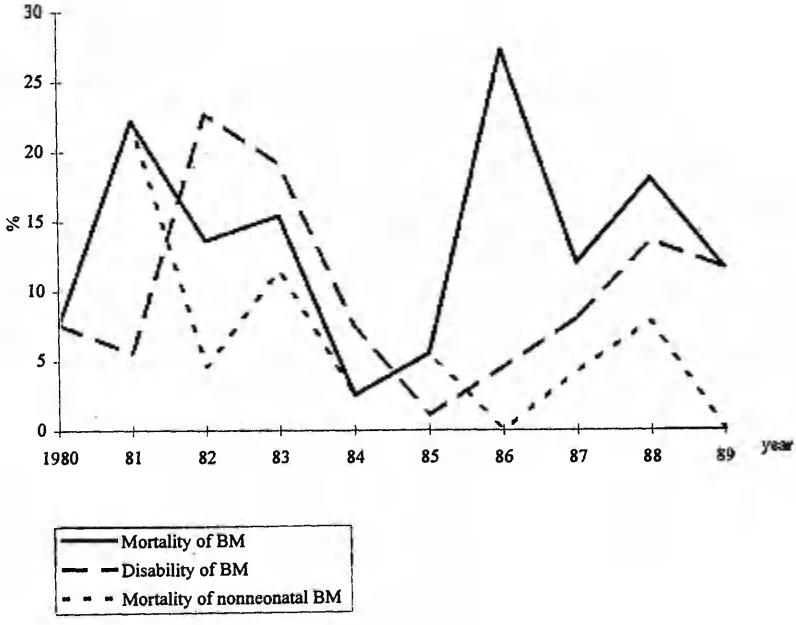


Figure 5. Mortality and disability of BM in children in South-Estonia in 1980–1989.

A detailed analysis of mortality and disability of different forms of ICNS is demonstrated in Tables 11 and 12. The mortality was organism specific and age related with the highest rates of 63.4% for BM caused by opportunistic microbes. On the other hand all those cases were diagnosed in very young children. The case fatality rate of BM beyond the neonatal period was 9.0% (18 cases of death occurred) and 13 (7.1%) of the survivors were discharged with the sequelae (Table 11 and Table 12). *S. pneumoniae* was the most severe of the common causes of BM in infants and older children with a mortality rate of 20% (2/10) and a disability rate of 12.5% (1/8). The lowest case fatality as well as morbidity rates registered were in MM patients — 6.5% and 5.6% respectively. One child died and none had a sequelae of nine — *H. influenzae* meningitis patients. A trend towards decreased mortality and disability rates with increasing age was identified in general as well as in different forms of BM. As an exception the case fatality rate of MM was higher in older children in the age group from 5 to 9 years, but only 8 children included were at that age.

There was no fatal outcome among patients with AM. Two children died (2.1%) and four (4.4%) of survivors developed disability following encephalitis. Younger children were more severely affected than older ones–two died and two developed a disability of those being younger than 5 years of age.

Table 11

Disability of different types of ICNS in different age groups in South-Estonia in 1980–1989

Age		*N. meningitidis* (%)	Hib (%)	*S. pneumoniae* (%)	BM unknown (%)	BM other (%)	BM opport. (%)	BM total (%)	Encephalitis (%)	AM (%)	ICNS (%)
0–1 mo	no pat.	2	–	1	5	1	4	13	–	–	13
	died	1 (50)	–	– (–)	3 (60)	– (–)	3 (75)	7 (53.8)	– (–)	– (–)	7 (53.8)
0–1 y	no pat.	33	5	6	47	1	4	96	4	11	111
	died	5 (15.1)	– (–)	1 (–)	9 (19.1)	– (–)	3 (75)	18 (18.7)	2 (50)	– (–)	20 (18.0)
0–4 y	no pat.	61	6	7	82	1	4	161	16	51	228
	died	5 (8.1)	– (–)	1 (14.2)	11 (13.4)	– (–)	3 (75)	20 (12.4)	2 (12.5)	– (–)	22 (9.6)
5–9 y	no pat.	7	2	1	12	–	–	22	51	69	142
	died	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	2 (3.9)	– (–)	2 (1.4)
10–14 y	no pat.	5	–	–	6	–	–	11	23	138	172
	died	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)
Total	no pat.	73	8	8	100	–	–	194	90	258	542
	died	6 (6.8)	– (–)	1 (12.5)	11 (11)	– (–)	– (–)	20 (10.3)	4 (4.4)	– (–)	24 (4.4)
Nonneonatal meningitis	no pat.	71	8	7	95	–	–	181	90	258	529
	died	4 (5.6)	– (–)	1 (14.2)	8(8.4%)	– (–)	– (–)	13 (7.1)	4 (4.4)	– (–)	17 (3.2)

Table 12

Mortality of different types of ICNS in different age groups

Age		*N.meningitidis* (%)	Hib (%)	*S.pneumoniae* (%)	BM unknown (%)	BM other (%)	BM opport. (%)	BM total (%)	Encephalitis (%)	AM (%)	ICNS total (%)
0–1 mo	no pat.	2	–	1	11	1	9	24	–	–	24
	died	– (–)	– (–)	– (–)	6 (54.5)	– (–)	5 (55.5)	11 (45.8)	– (–)	– (–)	11 (45.8)
0–1 y	no pat.	36	5	8	57	3	11	120	4	11	135
	died	3 (8.3)	– (–)	2 (25)	10 (17.5)	2 (66.6)	7 (63.6)	24(20)	– (–)	– (–)	24 (17.7)
0–4 y	no pat.	65	7	9	93	3	11	188	18	51	257
	died	4 (6.1)	1 (14.2)	2 (22.2)	11 (11.8)	2 (66.6)	7 (63.6)	27 (14.3)	2 (11.1)	– (–)	29 (11.2)
5–9 y	no pat.	8	2	1	13	–	–	24	51	69	144
	died	1 (12.5)	– (–)	– (–)	1 (7.6)	– (–)	– (–)	2 (8.3)	– (–)	– (–)	2 (1.3)
10–14 y	no pat.	5	– (–)	–	6	–	–	11	23	138	172
	died	– (–)	–	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)	– (–)
	no pat.	78	9	10	112	3	11	223	92	258	573
Total	died	5 (6.4)	1 (11.1)	2 (20)	12 (10.7)	2 (66.6)	7 (–)	29 (13)	2 (2.1)	– (–)	31 (5.4)
Nonneonatal meningitis	no pat.	76	9	9	101	2	2	199	92	258	549
	died	5 (6.5)	1 (11.1)	2 (22.2)	6 (5.9)	2 (100)	2 (100)	18 (9.0)	2 (2.1)	– (–)	20 (3.6)

1.4. DISCUSSION

This study programme analysed the epidemiology of the ICNS. using several sources of case ascertaintment for first time in Estonia. Registering only AM, TBE and meningococcal infection, the existing surveillance system has been seriously underestimating the true incidence of the disease in the community.

The epidemiological pattern we observed had the incidence rate of 66.2/100 000 children and is in keeping with comparable data from Spain in 1988 of 60/100 000 children (Roca *et al.* 1992). A considerably higher rate of 105.2/100 000 was demonstrated in a Finnish cohort study covering the period from 1966 to 1988 (Rantakallio *et al.* 1986). The difference from our data might be explained by high frequency of mumps encephalitis, while the Finnish study was conducted in the prevaccine era. A relatively constant incidence of ICNS in South–Estonia during the study-period was revealed by us. The only peak registered was in 1984, whereas both bacterial and aseptic meningitis were identified to rise. We only can speculate that it was caused by meningococcal meningitis, while an increased number of patients with the MM in the middle of the 1980s occurred all over the world (Halsensten *et al.* 1987; Lennon *et al.* 1989; Havens *et al.* 1989; Carter *et al.* 1990). However, a considerable number of unidentified cases of BM in this study does not allow to say that with certainty.

The annual incidence of BM 25.8/100 000 in South Estonia was rather similar to findings from Nordic countries in the 1970s and 1980s — 16.9 – 19.0/100 000 (Carter *et al.* 1990; Peltola *et al.* 1990). With the introduction of immunisation in 1989, using the conjugate vaccine of Hib in Finland, the incidence rate of BM has fallen considerably and the number of cases of BM in the Helsinki area from 66–77 registered yearly in prevaccine era declined to 4 cases in the year (Peltola *et al.* 1992). The decreased number of cases of BM at the end of 1980s was also demonstrated by us whereas no "antimeningitis" vaccinations were performed. Therefore we agree with Michaels *et al.* (1993) that other unexplained factors than Hib vaccinations have a role in the recent decrease in the number of BM cases.

Our data of the BM etiology are different from those reported in Nordic countries, Australia and USA, where Hib was the leading microorganism in the etiology of BM in children during last decades (Valmari *et al.* 1987; Carter *et al.* 1990; Hanna *et al.* 1991). We, like most investigators from the Central Europe and former Soviet Union (Grubbauer 1982; Giustina *et al.* 1985; Djomina *et al.* 1985; Hensel *et al.* 1992) still found *N. meningitidis* as the most common pathogen in the etiology of BM in children. However, the high number of unidentified cases of BM (50.7%) in this study makes interpretation of these data more difficult. To our opinion the main reason for the low number of bacteriologically proved cases was that children in the area often had to be hospitalised in the district hospitals where the lumbar puncture was performed and antibacterial therapy started, but facilities of bacteriological laboratories were relatively poor. The situation improved in the late 1980s only and this probably contributed to the higher figure for identified microorganisms in the

last years of study, nevertheless the changes in the etiological structure were not in fact significant. It might be that future studies may show a reversal of the current situation. The variation of etiology of BM all over the world is not easily explained. It is possible, that the incidence rate of other than meningococcal meningitis is relatively constant and different etiological structure is associated with epidemic course of meningococcal infection (Kostjukova *et al.* 1992). This view is supported by the study performed by Salih *et al.* (1990) in Sudan. The predominance of Hib among the etiological factors of 57% of patients has been registered during a nonepidemic period whereas in 1988 an epidemic of meningococcus A occurred and a trend towards an increased percentage of *N. meningitidis* of more than 90 was shown. The last epidemic of the meningococcal infection in the former Soviet Union lasted from 1967 to 1986 and that might also explain the predominance of meningococci in this study (Kostjukova *et al.* 1992). Therefore it could be that the incidence rate of Hib meningitis was almost 20 times lower in comparison to the results from Finland or Sweden (Trollfors 1987; Peltola *et al.* 1990). However, at the end of the 1980s, an increase of Hib meningitis cases like by Djomina *et al.* (1985) was observed. There has been much discussion of immunisation against Hib infection in Estonia. In order to provide accurate epidemiological information before introducing vaccination there is an urgent need for prospective studies to be set up to assess accurately the incidence of systemic Hib disease.

The average annual incidence (0.41/1000 live births) of neonatal meningitis was considerably higher than that in Sweden or Australia, but lower than in Kuwait (Bennhagen *et al.* 1987; Zaki *et al.* 1990; Francis *et al.* 1992). The remarkable yearly variation from 0 to 1.16 was mostly caused by the low number of births in the area studied. Contrary to Schattuck *et al.* (1992) showing a decrease of BM cases in newborns during 1974–1988 in USA, our data revealed an increase in cases of neonatal meningitis. This rise is probably associated to the opening of NICU and collecting patients there, using sophisticated methods of intensive care and therefore with the increase of nosocomial infections. Like in the other surveys (Apak *et al.* 1983; Meade *et al.* 1985; Bell *et al.* 1989) Gram–negative facultative flora with the leading role of *E. coli* were the most common causes of neonatal meningitis in South–Estonia. The predominance of *E. coli* K–1 strain in the etiology of neonatal meningitis is obviously associated with its high colonisation rate (40–50%) in pregnant women. Recently in many nurseries over the world *S. agalactiea* has been the essential part of the causes of neonatal meningitis representing over 40% of cases reported in first months of life (Francis *et al.* 1992; Schaad 1992). Only one out of 24 cases of GBS meningitis was registered in this survey. The low number of GBS infection in our study is not explained thus far. Unfortunately there are no data about the carriage of GBS in the genital tract of the pregnant women in Estonia.

In a number of cases (95.4%) as in some other retrospective studies (Hensel *et al.* 1992) the etiology of AM remained unknown. However, with the intensive investigation the etiology might be identified in 60–70% of cases (Tardieu *et al.* 1986; Klatte–Mayer *et al.* 1987). The low confirmation of AM had many

reasons: (1) low interest of practising doctors in the etiology of AM which in most cases has no influence on the therapy, (2) noncomplicated cases of AM are mostly treated in pediatric units of district hospitals having no facilities for virological diagnostics, (3) there is no opportunity of using rapid immunmethods for diagnosing of AM at present. As long as results of virological investigations will become known in 6 weeks, when the patient has been long ago discharged, it is hard to believe, that the interest of practising doctors will increase. On the other hand, without knowledge of epidemiological situation in certain regions prevention of infection would be impossible. However, the strong seasonal variation, with the high incidence of AM in summer months, which corresponds to the maximal activity of enteroviruses, and studies performed in Estonia by Kutsar (1971) in early 1970s allow us to suspect similarly to most others the predominance of enteroviruses in the etiology of AM (Tardieu *et al.* 1986; Klatte–Mayer *et al.* 1987).

All cases of mumps encephalitis registered in this survey were diagnosed up to 1984 — that is the prevaccine period. In a similar way the findings documented by Koskiniemi *et al.* (1989) showed that with the introduction of parotitis vaccination cases of mumps encephalitis have been almost eliminated. Contrary to the studies of Cizman *et al.* (1989) and Fuijnaga *et al.* (1991) of post vaccination encephalitis, no cases of it after mumps vaccination have been registered.

Etiology of encephalitis with the predominance of TBE in 71.7% supports the above investigations, that it is a leading cause of the encephalitis in areas having high activity of ticks (David *et al.* 1989). Like the previous epidemiological studies of TBE in Estonia our also showed the intermittent course of the disease – small outbreaks were registered every three years (Pototski 1988; Vassilenko *et al.* 1990). Contrary to the data of Wood *et al.* (1988), showing that the activity of ticks as well as the incidence of TBE increased following a short warm winter our data revealed the highest incidence in 1986/87, when winter was one of the coldest (unpublished data of meteorology service of Tartu). It is interesting that the occurrence of TBE was registered the areas around Lake Peipus and which is region of simultaneous appearance of two species of ticks — *Ixodes ricinus* and *Ixodes persuculatus*. The data correspond to those published by Pototski (1988).

A predominance (84.3%) of children up to five years in BM patients included in this study is characteristic to developed countries and is similar to studies performed by Halsensten *et al.* (1987) and Peltola *et al.* (1990). A significantly increased incidence of BM in comparison to the other age groups was found in the age up to one year. The reasons of high attack rate of young children are obviously connected to the functionally immature host defence mechanisms in infants and young children (Feigin *et al.* 1992). In contrast, the frequency of nonbacterial ICNS similarly to Tardieu *et al.* (1986) and Hensel *et al.* (1992) was higher among older children constituting 80.8% of the total. The reasons are not clear, but they seem to be social rather than connected to the immunity systems. Older children visiting schools and kindergartens, have closer contact to each other and are therefore more affected than younger.

However, in some studies the high occurrence of enteroviral meningitis among infants and newborns is documented (Schattuck *et al.* 1992; Yamashita *et al.* 1992) and even outbreaks in neonatal nurseries have been reported (Helin *et al.* 1987; Gilbert *et al.* 1988).

The ICNS mortality of 3.6% and disability rate of 3.2% beyond neonatal period reported by us were lower than that in the Finnish cohort study in 1966–1980 (6.5% and 14.9% respectively) (Rantakallio *et al.* 1986) but case fatality rate was higher than that in Spain — 1.4% in 1988 (Roca *et al.* 1992).

The mortality rate of BM in comparison to a previous study performed in Estonia in 1945–1958 has been dropped remarkably (Tulmin 1961) from of 43% to 9%. Nevertheless, it is considerably higher than that in Finland, Sweden or Scotland (Salwen *et al.* 1987; Valmari *et al.* 1987; Carter *et al.* 1990). The case fatality rate was especially high at the beginning of the 1980s, where no pediatric intensive care unit existed in this area and single cases of BM were treated in several hospitals. With the improving facilities of bacteriological laboratories, opening of PICU in Tartu University Children's Hospital and concentrating patients with BM to that, mortality of this disease beyond neonatal period declined considerably from 10.1% to 2.8%.

Like previous studies, we found most favourable outcome of MM — 5% of patients died and 5.6% of survivors developed disability at the discharge in our series. An even lower mortality rate (0–2.4%) has been reported in some other studies (Salwen *et al.* 1987; Peltola *et al.* 1990; Thompson *et al.* 1990). Due to the low number of pneumococcal meningitis in this study our data with the mortality of 20% and disability of 12.5% may have bias towards worse outcome. However, the fact that similar data have been documented by others also lends support to this view (Laxer *et al.* 1977; Grubbauer 1982; Bryan *et al.* 1990).

Case fatality and disability rates of neonatal meningitis have been as high as 45.8% and of 53.8% respectively in South-Estonia and correspond to some other studies (Apak *et al.* 1983; Bell *et al.* 1989). However, there are studies with considerably lower mortality rate. Bennhagen *et al.* (1987) in the study in Sweden in 1983 reported a mortality rate of 3.5% but 50% of the cases were caused by GBS and no cases of *E. coli* meningitis have been registered. Relatively low mortality rate of 7.3% has been documented in another study performed in Moscow (Samsõgina *et al.* 1986), but this study constituted preferably full-term babies and most common microorganisms documented were *S. aureus* and other Gram-positive microbes. A relatively good prognosis of neonatal meningitis caused by Gram-positive microbes in comparison to that caused by Gram-negative enteric bacteria is well documented in previous studies (Unhand *et al.* 1993). Not all reasons of high mortality and morbidity of neonatal meningitis in this study are clear. The high rate of Gram-negative bacteria being prognostically worse and the high ratio of premature babies (14/24) among patients apparent the late diagnosis particularly of ventriculitis and therefore the late onset of appropriate antibacterial therapy as well as intensive care cannot be excluded. Due to difficulties of therapy of neonatal meningitis more attention should be paid to the prevention of neonatal meningitis. It can

be effective only in hospitals where the epidemiological data are correctly documented, that is why a correct registration of neonatal infection in Estonia will be necessary.

The disability rate of BM of 7.1% was registered in similar rates as above noted series (Giustina *et al.* 1985; Valmari *et al.* 1987) and will be discussed in more detail in part III.

The good prognosis like in most previous studies (Beghi *et al.* 1984; Etter *et al.* 1991) was characteristic to AM and TBE. The relatively good prognosis of encephalitis in contrast to Rantala *et al.* (1989) with the mortality of 2.1% and disability of 4.4% is most of all associated with high number of TBE cases, which is known as a mild disease and does not leave permanent sequelae (Wahlberg *et al.* 1989). Despite the introduction of antiviral therapy the outcome of HSVE with the mortality rate of 44–85% (Lietz *et al.* 1986; Wagner *et al.* 1987) and disability rate up to 100% (Cameron et al. 1992) is still worse. Only one case of HSVE was registered in this study and the outcome was also poor.

In summary: Approximately 50 cases of ICNS were yearly diagnosed in children in South-Estonia in the 1980s, whereas each year three of them died and two had permanent disabilities. It was characteristic of this area that BM occurred preferably in younger children whereas AM and TBE were most often seen in schoolchildren. The most common microorganism causing BM was *N. meningitidis* but in almost half of the cases the etiology remained unknown. The etiology of AM was unidentified in more than 90% of the cases and according to the seasonality we can only speculate that enteroviruses could be the most common causes of it. To improve the outcome of ICNS (in addition to the concentration of patients with serious form of ICNS to the tertiary care hospitals), the facilities of virological and bacteriological laboratories have to be improved and a surveillance system for the registration of all the cases of ICNS should be introduced.

PART II

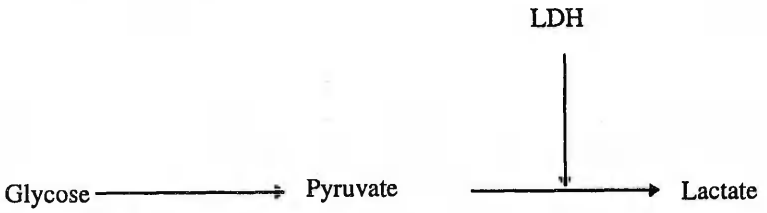
ENZYMATIC CHANGES OF THE CEREBROSPINAL FLUID IN PATIENTS WITH THE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

2.1. REVIEW OF THE LITERATURE

Damage within the central nervous system causes a leakage of certain intracellular enzymes into the CSF. Estimations of AST, LDH, GGT and CPK are widely employed as valuable diagnostic aids in diseases involving necrosis or damage of tissues characteristically rich in these enzymes (Riekkinen *et al.* 1970; Nelson *et al.* 1975; Landaas *et al.* 1985; Tammpere *et al.* 1987; Koskiniemi *et al.* 1988). The results obtained, however, are controversial.

2.1.1. Lactate dehydrogenase in the CSF in patients with ICNS

LDH (E.C. 1.1.1.27) is one out of four main enzyme systems in the human body through which the pyruvate is metabolised to lactate. The active form of the enzyme is a tetramer such that in most tissues including brain a spectrum of five isoenzymic form appear.



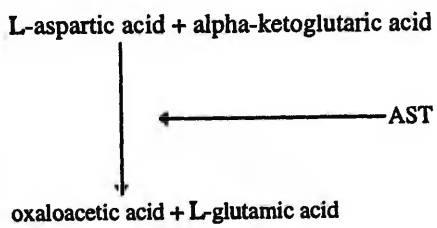
Brain and heart contain mainly LDH 1 and 2 activity (Popovitch *et al.* 1986; Chatterley *et al.* 1991), while granulocytes predominantly exhibit the fraction LDH 5 (Beaty *et al.*1968). No significant regional differences could be observed for LDH in the human brain (Delanghe *et al.* 1990). The activity of the LDH in the CSF fluid is normally lower than in the blood serum (Maas 1977; Pasaglu *et al.* 1989; Chatterley *et al.* 1991).

An elevation of activity of the LDH is shown by several illnesses where a brain hypoxia is present — in patients with BM (Riekkinen *et al.* 1970; Nelson *et al.* 1975; Landaas *et al.* 1985; Pasaglu *et al.* 1989), with malignant brain tumours (Koskiniemi *et al.* 1988; Lampl *et al.* 1990) and with hypoxic-ishaemic brain damage (Talvik 1992). Among the patients with viral meningitis the raised activity of LDH in the CSF was not demonstrated (Nelson *et al.* 1975; Landaas *et al.* 1985).

The question arises whether the raised enzyme activities demonstrated in the CSF after brain injury are the results of brain tissue destruction or whether they may be caused by seepage of blood enzymes through a severely damaged BBB or are granulocytes the main sources of the LDH activity. By comparing the characteristic LDH isoenzyme patterns of the tissues in contact with the CSF isoenzyme patterns of children with neurological disorders, it has been possible to demonstrate more clearly the sources of LDH in the CSF (Nelson *et al.* 1975; Radzavil *et al.* 1986). Where leucocytosis of the CSF occurs as by BM the cells appear to be the source of LDH activity, but in all other cases it seems possible that brain cell damage releases the enzyme into the CSF (Riekkinen *et al.* 1970; Nelson *et al.* 1975; Roslõi *et al.* 1991).

2.1.2. Aspartate aminotransferase in the CSF in patients with ICNS

AST catalyses the transfer of the alpha-amino groups of aspartate to alpha-keto group of ketoglutaric acid, resulting in the formation of oxaloacetic acid (Zakim *et al.* 1982). AST is present in wide variety of tissues including the brain (Awapara *et al.* 1989). It is present in both mitochondria and cytosol of the brain. Large increases in mitochondrial AST are found early in diseases associated with massive tissue necrosis, perhaps reflecting a sudden release of intracellular contents into the circulation (Boyde *et al.* 1968). The regional distribution of the AST in the brain is equal (Delanghe *et al.* 1990) and the normal value does not exceed of 12 U/L (Sirkis 1982; Radzavil *et al.* 1986; Agrawal *et al.* 1989).

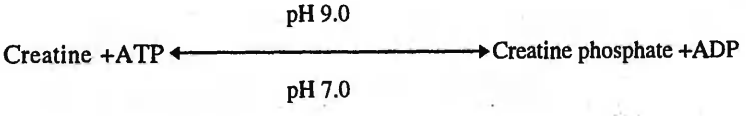


Most authors suggest that the origin of the AST activity in the CSF is most probably the brain tissue destruction (Sirkis 1982; Radzavil *et al.* 1986). An elevation of AST in the CSF during the first hours of illness was found by vari-

ous neurological diseases — in patients with acute stroke (Haldre 1988), with hypoxic-ishaemic encephalopathy in newborns (Tammpere *et al.* 1987) and with ICNS (Sirkis 1982; Agrawal *et al.* 1989). There are differences in AST activity among patients with bacterial and viral meningitis. Sirkis (1982) studied 512 patients with ICNS and found 2.2 – 2.6 fold raised enzyme activity in those with viral meningitis whereas in patients with BM the 3.3 fold increasing of AST activity was documented. Roslõi (1991) described an increase of CSF AST in 75% of BM patients and found normal enzyme values in those with AM.

2.1.3. Creatine phosphokinase activity in the CSF by ICNS

CKP (E.C. 2.7.3.2.) is an energy – transfer enzyme that reversible catalyses the phosphorylation of creatine by adenosine triphosphate. CPK is present in many body tissues and exists in three isoenzyme form; MB in cardiac muscle; MM, in striated muscle and BB, found predominantly in brain (Wiedemann *et al.* 1989).



The concentration of CK-BB is different in various regions of the human brain. Highest tissular CK-BB content was found in the brain cortex and capsula interna while only limited amounts were measured in the pons, cerebellum and medulla oblongata (Delanghe *et al.* 1990). The cellular distribution of the CK-BB in human brain is controversial: Worley *et al.* (1985) and Pfeiffer *et al.* (1983) found it in both neurones and astrocytes but Thompson *et al.* (1980) found CK-BB in astrocytes only. Due to the fact that the CK-BB is not found in white cells and is present only in minimal quantities in red cells it seems to be a good indicator of cellular damage of the brain (Cho *et al.* 1977; Thompson *et al.* 1980). Its normal value in the CSF is low and is equal to 2.5 U/L (Radzavil *et al.* 1986; Pasaglu *et al.* 1989). An elevated concentration of CPK has been shown in patients who suffered subarachnoidal haemorrhage (Maiuri *et al.* 1989), malignant brain tumours (Bach *et al.* 1989), prenatal asphyxia (Praeter *et al.* 1991; Talvik 1992) and also BM and AM (Katz *et al.* 1970; Bach *et al.* 1989; Smirnov *et al.* 1989). However some previous studies indicated that CSF CPK activity is not reliable in differation between bacterial and nonbacterial CNS infections (Katz *et al.* 1970; Briem 1982; Smirnov *et al.* 1989).

2.1.4. Gamma-glutamyl Transpeptitase in the CSF in patients with ICNS

GGT (E.C. 2.3.2.2.) catalyzes the transfer of gamma-glutamyl groups from peptides such as glutatione to other amino acids. Characteristic to GGT is widespread distribution of the enzyme in the cell membranes of the kidney, seminal vesicles, pancreas, liver, spleen, heart, and brain (Zakim *et al.* 1982). The concentration of GGT in the CSF is usually almost zero (Radzavil *et al.* 1986). The CSF GGT is elevated in association with BM, especially within the first days of the illness (Radzavil *et al.* 1986; Nand *et al.* 1992). Roslõi *et al.* (1991) determined an elevated activity of GGT in all meningococcal infection patients with increased ICP and he suggests, that this is connected to the increased permeability of BBB.

2.1.5. Relationship of CSF enzyme concentration to the prognosis of patients with ICNS

The amount of enzymes released from damaged tissue into extracellular fluid (Go *et al.* 1976) could be expected to be proportional to the extent of tissue damage. Maas (1977) produced experimental brain lesion in cats by cold and showed the augmentation of intracellular enzymes in the CSF being proportional to the severity and extent of brain damage. Pasaglu *et al.* (1989) studying LDH, CK-BB and CPK in the cerebrospinal fluid in 20 head injured patients found that all the enzymes correlated with GCS whereas the best correlation was found with CK-BB. However, the data of prognostic value of the changes in CSF enzyme activity are controversial. Florez *et al.* (1975) on 35 patients with head injures, showed the AST activity in the CSF to correlate well with the severity of brain lesion, but they could not find such correlation for the CPK activity. A high prognostic significance of raised AST activity was demonstrated also by Agrawal *et al.* (1989) and Roslõi (1991). They found in BM patients who either expired or recovered with residual complications very high AST values comparing to cases with complete and uneventful recovery. Belsey (1969) reported extensive brain lesions on autopsy in patients with very high CSF AST levels.

Brain-specific CPK isoenzyme (CK-BB) seems to be the best marker for CNS damage that we have. The concentration of CK-BB in CSF has shown to be high in several neurologic diseases and to correlate with the frequency of neurologic sequelae (Belton 1970; Praeter *et al.* 1991; Haldre *et al.* 1991; Talvik 1992). Sööt (1989) found in asphyxiated newborns with hypoxic-ishaemic encephalopathy of III degree significantly higher CK-BB levels than in those who had it of I–II degree. Briem (1982) showed a correlation between high level of CK-BB in the CSF and poor outcome in 5 patients with meningoencephalitis. However, in some previous studies no correlation between concentration of CK-BB in the CSF and prognosis of patients was

found (Katz *et al.* 1970; Florez *et al.* 1975; Maas 1977). Moreover some patients can be clinically in a very serious condition and still have a low activities of the enzymes in the CSF (Pasaglu *et al.* 1989; Bödvarson *et al.* 1990). It was shown, that the concentration of CK-BB raises rapidly within the first hours of the brain lesion and reaches the maximal level to the 3rd day (Maas 1977; Smirnov *et al.* 1989; Bödvarson *et al.* 1990). It must, however, be borne in mind that prognosis is not only determined by the degree, but also by the site of brain damage, while small lesions in the lifethreating areas could be prognostically important (Vaagenes *et al.* 1980).

Because the controversy of data concerning intracellular enzymes in CSF and their prognostic value of patients with ICNS we undertook this study.

2.2. PATIENTS AND METHODS

The patients studied on admission included 16 children with AM and encephalitis, 25 children with BM and 15 patients having no infection of the central nervous system, whom lumbar puncture was performed due to meningeal syndrome. Diagnostic criteria for BM and AM are listed above (pp. 18). Of 16 children with AM two had enteroviral meningitis and seven TBE. In 7 cases the etiology remained unknown. The etiologic structure of BM was as follows: *N. meningitidis* in 14 children, Hib in 4, *S. pneumoniae, E. coli, P. aeruginosa and Klebsiella pneumoniae* each in one patients and in three cases the etiology of BM remained unknown. Fifteen children without ICNS had following diagnoses — six patients had acute respiratory infection, three diarrhoea, two epilepsy; hemolytic-uremic syndrome, polyradiculoneuropathia, malignant brain tumour and drug intoxication were diagnosed each in one patient. The age and sex distribution of patients studied on admission is shown in Table 13.

Table 13

Patients characteristics on admission

Characteristic	AM (n=16)	BM (n=25)	Meningism (n=15)
Age			
0–29 days	0	2	1
1–12 mo	0	15	5
1–5 years	7	7	4
6–15 years	9	1	5
Sex			
male/female	11/5	15/10	7/8
Seizures (n of patients)	1	8	3
Unconsciousness (n of patients)	1	5	2
CSF (range)			
pleocytosis(cells/mm^3)	105 (43–251)	681 (236–1484)	3 (2–6)
protein g/l	0.58 (0.47–1.0)	1.22 (0.67–2.1)	0.5 (0.19–1.0)

Ultrasonography of the brain was carried out using a scanner of 5 and 7.5 MHz with sonolayer "Neuroimager" in 15 infants with an open fontanelle. Enlargement of the side ventricles (ventriculomegaly) was diagnosed on the basis of ventricular size on coronal scans as mild if the highest diameter of lateral ventricle was 7–14 mm, moderate if it was 15–25 mm and severe if > 25 mm. The patients were grouped according to the presence or absence of enlargement of lateral ventricles. There were 7 patients who developed ventriculomegaly after BM and 8 having normal findings.

The outcome of the survivors was assessed by a multidisciplinary team (pediatrician, pediatric neurologist, speech therapist, psychologist) at least 12 months after the acute illness. Children were divided into two groups. The good recovery group (n=32); included 17 children with BM and 15 with AM being normal or having impairment which did not disturb everyday life. The second group consisted of nine children (8 with BM and 1 with AM), four dying during the acute illness and five having severe impairments (hydrocephalus, severe motor disability, deafness, intractable epilepsy). All five children had combined disturbances.

The first CSF was collected on the 1–3rd day of disease and in 15 patients with BM the second sample was taken on the 7–10th day of treatment. The CSF was sampled by lumbar puncture and centrifuged immediately. Samples were frozen to -20^0 C and stored up to three months before analysis. In all cases routine laboratory investigations i.e. CSF protein, sugar, cell count and bacterial cultures were examined.

The immunoenzymatic technique type "*Sandwich*" described by Haldre (1988) was used for the measurement of CK-BB concentration. The activity of CPK, LDH, AST and GGT was measured by photocolorimetric assay using commercial kits (Labsystem FP-900). The normal values of enzymes used have been found from literature and are shown in Table 14.

Statistical analysis. The results are given as median with lower and upper quartiles. Computerised statistical package STATWIEV 512 was used. This included nonparametric Mann-Whitney test for unpaired samples, the Wilcoxon test for paired samples and the Spearman's rank correlation coefficient.

Table 14

Concentartion of CK-BB and activity of CPK, LDH, AST and GGT in the CSF in adults with nonneurological diseases

Enzyme	Activity/concentration	Author
CPK (U/L)	0.4–6.3	Pasaglu *et al.* 1989
AST (U/L)	0–12	Agrawal *et al.* 1989
LDH (U/L)	3–17	Nelson *et al.* 1975
GGT (U/L)	0	Radzavil *et al.* 1986
CK-BB (ng/l)	5.3±1.2	Haldre 1988

2.3. RESULTS

2.3.1. Activity of AST, LDH, CPK and GGT in the CSF on admission and on the 7–10th day of therapy

Table 15 shows the results of CSF enzyme determinations on admission. An increase in all three diagnostic groups was noted. The activity of AST was two fold higher in patients with BM comparing with those without ($p<0.05$), nevertheless it did not exceed the quoted references range. The median value of activity of LDH (33.8 U/l) was highest in those with BM and lowest in patients with meningismus, but statistically significant differences was not found. All patients had raised activity of the GGT in the CSF. A statistically significant increase ($p<0.005$) was noted in patients with BM on admission in comparison those with AM and meningism.

Table 15

Activity of the AST, CPK, LDH, GGT and concentration of CK-BB in the CSF in patients on admission

Enzyme (reference level)	AM (quartile) n=16	BM (quartile) n=25	Meningism (quartile) n=15
CK-BB (ng/l) (5.3±1.2)	37.5 (24.0–43.0)	31.0 (15–59)	39 (34–46)
CPK (U/l) (0.4–6.3)	4.3 (2.0–2.9)	4.2 (2.6–5.5)	3.3 (2.6–5.3)
AST (U/L) (0–12)	4.0 (3.6–7.3)	8.8 (6.1–11.0)*	4.7 (3.5–6.3)
LDH (U/L) (3–17)	28.1 (4.8–52.2)	33.8 (19.7–70.2)	15.4 (7.6–20.6)
GGT (U/L) (0)	1.7 (0.6–4.5)	5.3 (2.1–8.7)**	1.5 (1.0–2.0)

* $p< 0.05$ in comparison with patients without BM
** $p< 0.005$ in comparison with patients without BM

The activity of AST, CPK, LDH, GGT and concentration of CK-BB in the CSF on the 7–10 day of therapy was estimated only in patients with BM. Figure 6 demonstrates that the median activity of AST decreased with the treatment from 8.2 to 5.6 U/l, LDH form 33.8 to 27.3 U/l and GGT from 5.3 to 1.6 U/l, but that of CPK and the concentration of CK-BB remained the same being on the 7–10th day of therapy approximately 6 fold higher than reference value.

AST activity was simultaneously estimated in the CSF and blood serum in 40 patients: no correlation was found between the levels of AST in the CSF and in serum ($r=-0.362$), although significantly higher activity of AST in the CSF (14.1 U/l) as well in the blood serum (23.5 U/l) was found in patients with poor

prognosis in comparison to those with good prognosis 8.4 U/l and 7.3 U/l respectively.

The activity of LDH correlated with the count of PMNL in the CSF on admission (r=0.538), but no correlation was found on the 7–10th day of therapy. There were 3 patients with *E. coli* meningitis having more than 1000 PMNL in the CSF on the 10th day of therapy, but the activity of LDH was 2.5; 4.3 and 91.5 U/l respectively.

2.3.2. Prognostic value of intracellular enzyme determinations in the CSF

The relationship between the enzymatic determinations and the outcome is shown in Table 16.

Table 16

Enzymes data on admission in relation with outcome of ICNS

Outcome (quartile)	CK-BB (ng/l)	CPK (U/l)	AST (U/l)	LDH (U/l)	GGT (U/l)
Dead/severely impaired n=9	9.5 (2–37)	3.8 (2.6–4.5)	12.1* (5.0–17.4)	60.5 (37.1–235.4)*	2.7 (1.8–11.4)
Good recovery n=32	38.0 (30–49)	4.5 (1.7–6.5)	6.7 (4.0–9.0)	27.5 (15.2–46.3)	2.9 (0.9–8.1)

*p< 0.05

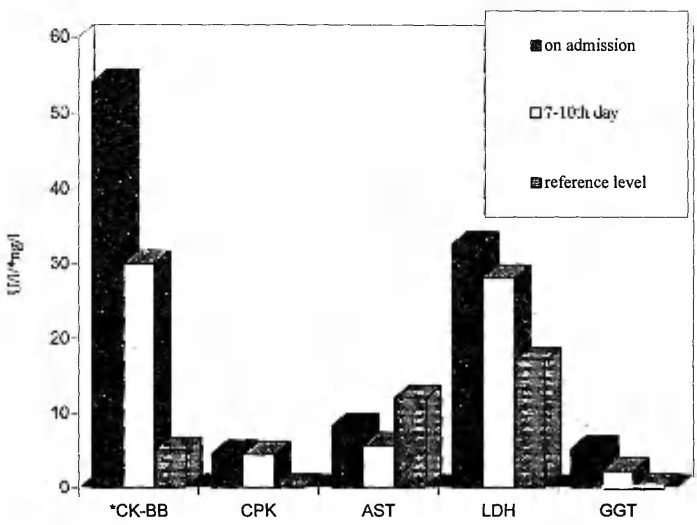


Figure 6. Activity of CPK, AST, LDH and GGT, and concentration of CK-BB in BM patients in CSF on admission and on days 7 to 10 of therapy.

The patients of ICNS who died or recovered with residual impairments had significantly higher median CSF AST and LDH activity ($p<0.05$) as compared to those with good recovery. Although the concentration of CK-BB was higher in patients with good prognosis, the difference was not statistically significant. With the therapy the activity of all intracellular enzymes but CK-BB concentration decreased in both groups. It is interesting to mention that the median concentration of CK-BB decreased in patients with good outcome from 49 ng/l to 31 ng/l and increased from 9.5 ng/l to 37 ng/l in those with poor prognosis, but the difference was not statistically significant.

2.3.3. Activity and concentration of intracellular enzymes and cerebral ultrasound findings

Table 17 shows the results of CSF enzyme determination according to the cerebral ultrasound findings.

Table 17

Enzyme data in relation to cerebral ultrasound findings in patients with BM

Sonographic finding Enzyme activity	CPK (U/L)	AST (U/L)	LDH (U/L)	GGT (U/L)
Ventriculomegaly n=7	4.5 (3.2–7.7)	12.1* (10.5–15.1)	71.1* (69.7–235.4)	2.7 (2.6–7.2)
Normal n=8	3.5 (2.7–5.4)	8.0 (7.4–8.9)	23.4 (18.7–27.5)	2.5 (1.1–5.2)

*$p< 0.05$

The activity of AST and LDH was significantly higher in patients who developed ventriculomegaly in comparison to those having normal findings ($p<0.05$). The highest value of AST and LDH activity 211.3 U/l and 14.1 U/l respectively was seen in patients with ventriculomegaly developing hydrocephalus.

2.4. DISCUSSION

In this study our aim was to estimate the level of some intracellular enzymes in the CSF in different infections of the central nervous system and to establish whether any of the measured enzyme levels would correlate with the CNS dysfunction thus assessing their prognostic value and determing their usefulness in clinical practice. An elevation of AST, LDH and GGT activity in patients with BM on admission, demonstrating neuronal cell injury as well as altered permeability of BBB, has been reported by several authors (Nelson *et al.* 1975; Sirkis

1982; Landaas *et al.* 1985; Radzavil *et al.* 1986; Nand *et al.* 1992). The increased activity of AST and GGT in BM patients was registered in this study also, but no statistically significant increase of median value of LDH activity was seen, although some patients with BM had very high levels.

The data of CSF activity of AST in patients with AM are controversial. We in contrast to Sirkis (1982) and like Roslõi (1991) could not find an elevation of AST in patients with AM in comparison with the control group. However, as Sirkis (1982) and Agrawal *et al.* (1989) we saw a significant increase in AST activity in CSF in patients with BM in comparison with those with AM and meningism and pointed to its prognostic value. Differences in enzyme activities between AM and BM are most probably connected to the different pathomechanisms of those two diseases. By BM the components of bacterial cell walls stimulate the local production of inflammatory cytokines in CSF, leading to inflammation and alterations in the cerebral microvasculature, causing hypoxic-ischaemic damage of brain tissue and cytolysis (Quagiliarello *et al.* 1992). Although the activity of AST in patients with a poor prognosis raises rapidly in the CSF and in blood serum, we like Sirkis (1982) and Radzavil *et al.* (1986) could not find any correlation between serum and the CSF activity of AST ($r=-0.362$). Therefore we can assume that the main sources of AST activity in the CSF is brain tissue, although we can not exclude that in severely ill patient the enzyme can cross to BBB due to raised permeability of it.

The benefit of the measuring of the activity of LDH in differentiation of AM and BM was very poor in our study confirming the work of Landaas *et al.* (1985). This is in contrast to others (Neeches *et al.* 1968; Feldman 1975; Knight 1981) who have claimed significantly higher concentration of LDH in BM. We also found the activity of LDH higher in BM compared to AM and meningismus but the differences has not been statistically significant. The good correlation ($r=0.538$) between CSF PMNL count and the activity of LDH confirms the opinion of several studies that PMNL are the main sources of the LDH activity in the CSF in BM patients (Riekkinen *et al.* 1970; Nelson *et al.* 1975; Roslõi 1991), although the exact origin of the enzymes may be differentiated only by isoenzyme studies. However, the good correlation was found only during the acute period of BM. The low activity of LDH on the 7–10th day of therapy, despite the high amount of PMNL in the CSF also suggests a cerebral origin of LDH in the acute period of brain injury.

The present study like previous ones (Belsey *et al.* 1969; Maas 1977; Agrawal *et al.* 1989; Roslõi *et al.* 1991), establishes a definite relation between CSF AST and LDH activity and the extent of the brain injury. The patients who either died or recovered with residual complications had significantly higher ($p<0.05$) AST and LDH activity than cases with complete recovery. The higher activity of AST and LDH in the CSF ($p<0.05$) was found also in patients who had enlargement of the lateral ventricles during the acute illness, which strongly suggests that one of the reasons of enlargement of lateral ventricles after BM is brain atrophy developing due to necrosis of brain tissue.

Raised activity of CPK in the CSF seems to be a reliable factor characterising a brain damage, because its concentration in the normal CSF is low (Maiuri

et al. 1989; Bach *et al.* 1989; Smirnov *et al.* 1989). However the present study like previous ones (Katz *et al.* 1970; Briem 1982; Smirnov *et al.* 1989) indicates that CSF CPK activity is not reliable in differentiating between bacterial and nonbacterial CNS infections. The three-fold increased activity of CPK shows disturbances of the energy balance in the brain tissue in patients with BM and AM as well as with meningismus. We in contrary to Pasaglu *et al.* (1989) and like Florez *et al.* (1975) could not found any correlation between poor outcome of ICNS and raised CPK activity in the CSF. Moreover the patients who died or were severely impaired had even lower activity of CPK in comparison to those with good recovery, although the difference was nonsignificant.

The high concentration of isoenzyme CK-BB in the CSF seems to be best at predicting bad prognosis in head injured patients in several studies (Belton 1970; Bach *et al.* 1989; Praeter *et al.* 1991; Haldre *et al.* 1991; Talvik 1992). It was a surprise finding that the concentration of CK-BB in those with a bad prognosis was even lower (9.5 ng/l) compared to those with a good outcome (38.0 ng/l). The fact that some patients with bad prognosis did not have an increase of CK-BB concentration in the CSF was also shown in previous studies (Pasaglu *et al.* 1989; Bödvarson *et al.* 1990). The variable increase in CK-BB concentration in different patients is not completely understood. The concentration of CK-BB in the CSF changes rapidly during the first hours of brain injury (Smirnov *et al.* 1989; Bödvarson *et al.* 1990), thus the results depend up on the time of collecting the CSF. In this study the wide time spectrum from 1 to 3 days of illness could account for that. The various regional distribution of CK-BB in the brain has also been reported (Maas 1977; Vaagenes *et al.* 1980), so a small focal lesion in functionally important region of the brain may cause severe impairment with minimal enzyme release. Raised concentration of CK-BB in patient with meningismus was an unpredicted finding and shows that even in those cases the hypoxic-ischaemic damage of the brain and disturbances of the energy metabolism tissue occur. It must, however be born in mind that prognosis is not only determined by the degree, but also by the site of brain damage. A definite prognosis for the individual patients cannot be established on the basis of the enzyme activity of the CSF alone. The prognostic value of CSF enzyme estimations depends on the consistency with which enzymes released into the extracellular fluid and will be transported towards CSF.

In summary: The increased activity/concentration of intracellular enzymes in the CSF caused most probably by cytolysis going on, was found in patients with BM as well as with AM, whereas their levels in cases of BM were higher. The measurement of activity of AST and GGT seems to be the best in differentiation between AM and BM. The origins of enzyme activity could be either CSF PMNL as it was shown for LDH or cells of the brain tissue as for AST, CPK and CK-BB. Our study demonstrated that high activity of AST and LDH in the acute period of illness will correlate with bad prognosis, whereas surprisingly, the prognostic value of increased concentration of CK-BB was very poor. That is why the definite prognosis for individual patient cannot be established on the basis of enzyme activities alone, but depends on several factors.

PART III

FOLLOW-UP AND LONG-TERM OUTCOME OF CHILDREN AFTER BACTERIAL MENINGITIS

3.1. REVIEW OF LITERATURE

It is demonstrated that 11–27% of the survivors of BM had some sequelae at the time of hospital discharge (Grubbauer *et al.* 1982; Giustina *et al.* 1986; Salih *et al.* 1990), but there is a tendency for even major neurological defects to resolve unpredictably with the time. In an large prospective study of BM in children Klein *et al.* (1986) revealed that 32.8% of children had abnormalities detectable on neurologic examination at the time of hospital discharge. Five years after discharge, however, specific deficits were noted in only 11.1%. Table 18 demonstrates the long-term sequelae of BM in children.

Table 18

Long-term sequelae of BM reported in literature

Author Sequelae (%)	Sell (1983)	Lebel *et al.* (1989)	Salih *et al.* (1991)	Odio *et al.* (1991)
Mortality (%)	13	0.5	19	2
Patients with sequelae	50	14.4	27	20.2
Hearing disturbances	10–11	15.9	22	11.9
Seizures	2–8	?	11	4.0
Motor abnormalities	3–7	3.3	7	?
Speech delay	15	?	7	?
Mental retardation	10–11	8.5	?	?
Behaviour problems	9	?	7	?
Mean IQ	86	?	92.3	?
Ataxia	?	3.7	?	2

The most precisely quantified sequela of BM is hearing impairment. In a review of the English language literature Fortnum (1992) calculated the occurrence of it at an average of 9.6% in survivors after BM, whereas deafness was registered in 1–4% of the cases. The prevalence of hearing disturbances in previous studies is demonstrated in Table 19. The hearing disorders are often bilateral and profound (Overkamp *et al.* 1982; Schaad *et al.* 1990) and occur particularly in children who are younger than 3 years during acute illness

(Brookhauser *et al.* 1989). The reasons for hearing impairment during BM are not completely clear. Four pathogenic mechanisms are discussed in literature.

Table 19

Incidence of hearing disturbances after BM in the literature

Author	Years	Age of patients during acute BM	n of patients	Orga–nism	Incidence of SNHI (%)	Incidence of profound SNHI (%)
Jadavij *et al.* (1986)	1979–1983	4day–14y	235	All	12.9	—
			165	Hib	7.3	—
			24	men	—	—
			46	pneum	43.3	—
Dodge (1986)	1973–1977	2mo–14y	185	All	10.3	2.2
			118	Hib	5.9	1.7
			19	men	10.5	—
			29	pneum	31	6.9
			19	other	5.3	0
Salwen *et al.* (1987)	1956–1980	1mo–16y	176	All	11.6	3.9
			137	Hib	9.6	—
			14	men	10	—
			25	pneum	33	—
Lebel *et al.* (1989)	1984–1985	2mo–16y	94	All	9.1	—
			30	Hib	9.5	—
			51	pneum	21.4	—
			15	Other	0	—
Salih *et al.* (1990)	1985–1989	?	181	All	22	11
Odio *et al.* (1991)	1990	6w–13y	115	All	10.6	—

men – *N. meningitidis*, pneum – *S. pneumoniae*

Firstly it is assumed, that the cochlear dysfunction is due to a direct invasion of bacteria into the cochlea, spread of infection along the auditory canal and cochlear aqueduct causing serous or purulent labyrinthitis and replacement of the membranous labyrinth with fibrous tissue and new bone (Klein *et al.* 1986; Harada *et al.* 1988; Kaplan *et al.* 1989; Bhatt *et al.* 1991). *A second* mechanism of dysfunction may be due to a damage of the eight nerve by toxins (Kline *et al.* 1979). *A third* possible mechanism is a vascular occlusion and ischemia in the region of the auditory tract (Jiang *et al.* 1990). *A fourth* mechanism is an eight nerve damage by antibiotics. However, the majority of studies do not support the latter argumentation because in most cases hearing impairment is diagnosed already before the introduction of antibacterial therapy (Friebel *et al.* 1984; Dodge *et al.* 1986).

It has been shown that various microorganisms cause hearing disturbances with different frequencies. In their experiments with mice Kaplan *et al.* (1989) tried to verify that different types of Hib have different capabilities of invasion

into the cochlea but got negative results. In most studies the highest ratio of hearing disorders is documented after pneumococcal meningitis (Dodge *et al.* 1986; Jadavij *et al.* 1986; Salwen *et al.* 1987).

The second most frequent complications of BM are motor abnormalities reported in of 3–7% of survivors (Gary *et al.* 1989; Odio *et al.* 1991). Although motor defects are not uncommon during acute infection marked improvement occurs weeks to months later. Pomeroy *et al.* (1990) had 37% of patients who had acute neurologic deficits at the time of hospital discharge. In more than 60% of these patients the abnormalities resolved within 3 months and there were only 8 patients (4%) with residual hemi-or quadriparesis.

Ataxia as the most common motor defect has been reported as a presenting symptom of BM in the same children in whom hearing impairment was noted to develop at a later stage (Klein *et al.* 1986). Both may be a sign of a dysfunction of the cochlea as well as the labyrinth. Ataxia is mostly a transient disorder. Lebel *et al.* (1989) observed ataxia in 14.4% of BM patients on discharge. After 6 weeks it was seen in 3.3% of the patients and after one year it persisted in only 0.3% of the survivors.

Seizures occurring as a late sequelae of meningitis have been reported in 2–8% (Sell *et al.* 1983; Pomeroy *et al.* 1990; Odio *et al.* 1991). Only Salih (1990) in his study in a developing country (Sudan) registered seizures as late complications more often- in 11% of the survivors. Most of the late seizures occur within first five years after meningitis, but an elevated risk remains for up to 20 years (Annegers *et al.* 1988). The risk of epilepsy has been six fold higher for those having seizures in the acute phase and also for children with persistent neurological deficits at the time of discharge (Annegers *et al.* 1988; Pomeroy *et al.* 1990).

Visual impairment has been found in 2–4% of survivors (Sell 1983; Jadavij *et al.* 1986). Reversible abnormality of vision is due to vasospasm of the arteries while the permanent visual impairment is due to cerebral occipital haemorrhage and atrophy (Kabany *et al.* 1992).

Mental retardation in various degree have been registered relatively frequently following BM. IQ scores of less than 70 has been reported in approximately 10–11% (Sell *et al.* 1983) and in the study of Jiang *et al.* (1990) even in 17% of survivors. In their follow-up study of postmeningitic children in comparison to their siblings Sell *et al.* (1972) showed a mean IQ significantly lower in the index group, 29% of the survivors scored less than 1 SD below their controls. In contrast to these results Lebel *et al.* (1989) reported no differences in the average IQ score between the index group and their siblings in a sibling controlled developmental outcome study.

More subtle findings of attention deficits and behavioural problems have been reported in 7–9% of survivors (Sell *et al.* 1983; Salih *et al.* 1990) and are thought to be more presumptive than documented. The learning problems have been investigated in a study by Feldmann *et al.* (1988). They compared the academic achievement of 23 children 10 to 12 years after the treatment of Hib meningitis to age match sibling controls. Their findings suggest that children who recovered from meningitis can maintain scores and grades comparable to

their siblings. They also concluded, that their academic success involved more school and family support to compensate for the child's IQ deficits.

The frequency of language disorders or delay has been commented on by a number of investigators and varies from 7–23.3% (Lebel *et al.* 1989; Gary *et al.* 1989; Salih *et al.* 1990). The language disorders are most likely to be associated with a hearing loss occurring before the child has learned to speak or with brain damage in the region of the speech centre.

Prospective studies have permitted the assessment of factors that herald a poor prognosis and that may be discernible at or near the time of admission to the hospital. The association between high concentration of pathogenic microorganisms (Feldmann *et al.* 1982) or a high concentration of endotoxine in the CSF (Mertsola *et al.* 1991), the delayed sterilisation of CSF (Lebel *et al.* 1989), low concentration of glucose in the CSF and seizures at the time of admission (Dodge *et al.* 1984; Klein *et al.* 1986; Taylor *et al.* 1990; Letson *et al.* 1992) proved to be the most reliable predictor of permanent sequelae of BM. A significant correlation between hearing loss and neurological sequelae at the time of discharge as well as on follow up examinations after several years has been documented (Jadavij *et al.* 1986; Taylor *et al.* 1990).

The data about the duration of symptoms before therapy and the outcome of BM are controversial in literature. In a review of 22 studies Radetsky (1992) described that in 13 studies (55%) a relation between the outcome of BM and the duration of symptoms before the hospitalisation was found whereas in 9 (41%) there was none. Bhatt *et al.* (1991) demonstrated in an animal model that the incidence and severity of hearing disturbances correlated strongly with the duration of meningitis. A Finnish study showed better outcome of patients whose duration of symptoms before the antibacterial therapy was longer, but it will be always difficult to determine the exact onset of the disease (Kilpi *et al.* 1993).

3.2. PATIENTS AND METHODS

3.2.1. Patients of follow-up examinations

Fifty six children (26 girls and 30 boys) treated at Tartu University Children's Hospital from 1986 to 1990 for BM were followed up during a period of 12 months. They were examined if one months and one year passed from acute illness. Twenty five children (44.6%) had meningococcal meningitis, five (8.9%) pneumococcal meningitis, eight (14.2%) Hib meningitis and in 18 (32.1%) cases the etiology of BM remained unknown. The median age of children during the acute illness was 18 months.

3.2.2. Patients of long-term follow-up examinations

In order to assess the long term outcome of BM we recalled 91 out of 123 children treated for BM except neonatal meningitis at Tartu University Children's Hospital from 1982 to 1990 and still living in this area (Figure 7).

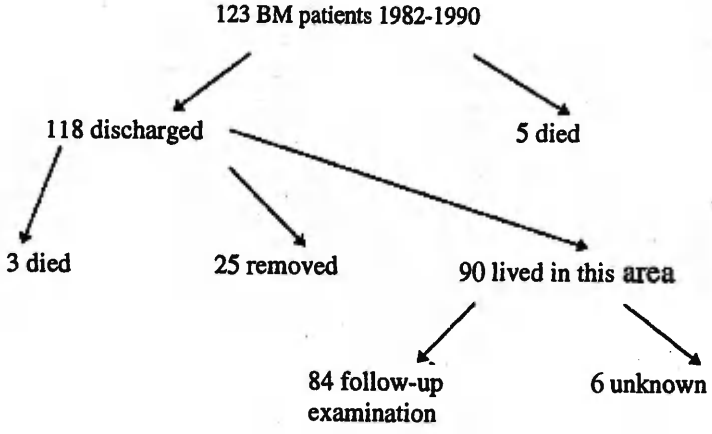


Figure 7. Characteristic of patients treated with BM in 1982–1990.

Recalling criteria were an age of at least 4 years and a lapse of 3 or more years since the onset of BM. 84 (68.2%) children were included in the follow up examination, the median age was 8 years (from 4 to 18 years) and an average of 6 years (from 3 to 9 years) had passed since the acute period. 64 (74.6%) out of 84 were normal, 14 (16.8%) had mild and 7 (8.4%) severe damage at the time of discharge. Forty-two children (50%) had meningococcal, 12 (14.2%) Hib, 7 (8.3%) pneumococcal meningitis and in 23 cases (27.3%) the etiology of BM remained unknown.

3.2.3. Study procedures

The data of acute period of the disease were obtained from hospital records. The children were examined by multidisciplinary team (pediatrician, pediatric neurologist, speech therapist) motor defects, language disorders and hearing disturbances were estimated using special scoring system described below.

Children with *motor defects* were divided into three classes according to functional capability as described by Talvik (1992):
1 – mild changes of muscle tonus and elevated reflexes without functional disturbances, all activities possible without special aids; 2 – function is acquired

trough special aids; 3 – limited voluntary action, enable to walk, to sit without aid, often bedridden.

Speech development was estimated using 7 – graded scoring system according the age as follows:

at the age of 18 months:

0 – no vocalisation; 1 – babbling; 2 – understanding of language; 3 – single words with meaning; 4 – one word utterance; 5 – two word utterance.

at the age of 2 years:

0 – no vocalisation; 1 – babbling; 2 – understanding of language; 3 – single words with meaning; 4 – one word utterance; 5 – two word utterance; 6 – simple sentence.

According to the speech development the children were divided as follows: normal or mild disturbances — 5–6 class; moderate language disorders — 3–4 class; severe language disorders — 0–2 class.

Hearing tests were performed using pure tone audiometry and estimated by ENT specialist with a MA-31 audiometer (DDR), Thresholds were determined at 500, 1000, 2000, 4000 and 8000 Hz. The divisions are based on the hearing level for speech (from 500 to 1000 Hz). The four classes of hearing are defined in terms of hearing levels for speech described by Dodge *et al.* (1984) (Table 20)

Table 20

Hearing classification

Estimated hearing level for speech (dB)	Hearing class	Functional definition
<30	1 – Normal	Hearing that is near or within normal limits
30 – 55	2 – Mild loss	Difficult with conversational speech beyond 6 meter; hearing aid helpful
55–70	3 – Moderate loss	Hearing aids and special training in speech and language essential
>70	4 – Deaf	Deaf: cannot rely on hearing as primary channel of communication

At the time of hospital discharge and during the follow up examination all children were divided into the three groups:

1 — *normal or mild disturbances* — motor disturbances of first classes, one sided hearing disturbances, mild language disorders

2 — *moderate disturbances* — motor disturbances of 2 classes, two sided mild to moderate hearing disturbances, moderate language disorders, seizures controlled by antiepileptic drugs, impairment corrected by rehabilitation

3 — *severe disturbances* — handicapped children who need special aid-multiple disturbances not corrected with the rehabilitation, MA 3–4 classes, deafness, alalia, intractable epilepsy.

Statistical analysis. The chi-square test and Student's t-test were employed to determine whether there were significant differences between variables. The Spermann correlation test was conducted to assess the association of outcomes and acute period variables.

3.3. RESULTS

3.3.1. Follow-up of children after BM

The follow-up data of 56 children after BM if one and twelve months were passed from acute period are shown in Table 21.

Table 21

Sequelae of BM in children at discharge, one and twelve months after the acute illness

sequelae	at the discharge n=56 (%)	after 1 mo n=56 (%)	after 12 mo n=56 (%)
Ataxia	8 (14.3)	5 (8.9)	2 (3.5)
Hydrocephalus	1 (1.7)	1 (1.7)	1 (1.7)
Motor defects	16 (28.5)	12 (21.4)	8 (14.3)
Hearing disturbances	2 (3.5)**	2 (3.5)**	5 (8.9)
Cranial nerve involvement	3 (5.3)	1 (1.7)	—
Seizures	–	1 (1.7)	5 (8.9)
Cognitive disturbances	1 (1.7)	11 (19.6)	3 (5.3)
Speech delay*			20 (35.7)
–moderate			12 (21.4)
–severe			8 (14.3)

* Speech development was examined only in children who at the time of acute illness were younger than 20 months

** No audiometry was performed

Motor abnormalities occurred with the highest frequency at the time of discharge (28.5%) but dropped down to percentages of 21.4% and 14.3% after one and 12 months respectively. The same applies also to their severity — at the time of hospital discharge 11 (19.6%) children had motor defects 2nd degree and 5 (8.9%) of 3rd degree. Hemiparesis was diagnosed in 6 patients, spastic quadriparesis or spastic diplegia both in 5 children. Out of the 5 children with severe motor disturbances during the follow-up period three improved their motor abilities to a 2nd degree motor abnormalities. In two children their degree did not change. After one year motor abnormalities persisted in 3 out of 11 children having moderate disturbances at the time of hospital discharge.

Ataxia was a relatively common symptom on discharge diagnosed in 8 patients (14.3%). The frequency of ataxia decreased during the follow up period, after one months it was found in 5 (8.9%) children and after one year it only persisted in two children whereas the severity of it decreased remarkably.

None of children was discharged with seizures. They occurred mostly from one to six months after acute illness and were seen in 5 (8.9%) children one year after BM.

Clinically reliable hearing disturbances (audiometry was not performed) have been diagnosed in two children at the time of hospital discharge, unilateral in one case and bilateral in another. Ataxia was seen in both during the acute period.

Cognitive disorders have been relatively common one month after discharge and were found in 11 (19.6%) children. The patients were irritable, ill-tempered, had sleeping disturbances. The above mentioned signs persisted after one year only in three patients. Mental retardation was diagnosed in two patients 12 months after the acute period respectively.

Cranial nerve involvement (except 8th nerve) was documented in 3 children (5.3%). One child had facial nerve paresis at the time of discharge, which persisted as a mild paresis after one months and has improved after one year. Two children had sixth nerve paresis at the time of discharge and slight paresis after 12 months.

One year after BM speech delay was rather common finding diagnosed as a mild in 12 children (21.4%) and as a severe in 8 (14.3%) of children.

According to the general condition of children they were divided into 3 groups at every examination (Figure 8). Eight children were disabled at the time of hospital discharge (14.3%) and five of them remained seriously handicapped one year after as well. Figure 8 shows also declining of mild to moderate sequelae during the follow up period. 13 children (23.2%) have had mild to moderate sequelae at the discharge, one year after they persisted only in eight (14.3%). No one of studied the neurologic state did not become worse during the study period, that or improved or remained the same.

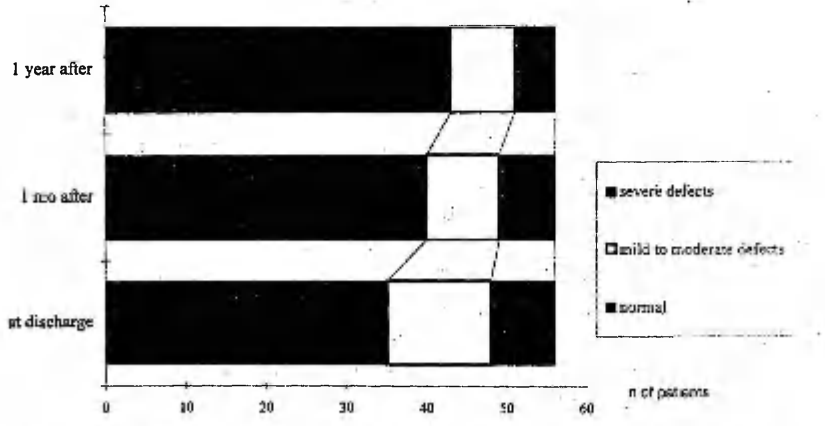


Figure 8. General condition of children at discharge, one months and one year after BM

3.3.2. Long term outcome of children with BM

During the long term follow up examination 68 children (80%) have been normal, 11 (13.3%) had mild to moderate disturbances and 5 (5.9%) children were handicapped. Long term sequelae are outlined in Table 22.

Table 22

Long-term sequelae of BM

Sequelae	number of patients	%
1. Motor disturbances	10	11.9
– mild to moderate	8	9.5
– severe	2	2.3
2. Ataxia	3	3.5
3. Hydrocephalus	2	2.3
4. Seizures	6	7.1
– epilepsy	4	
– febrile seizures	2	4.7
5. Respiratory affects	2	2.3
6. Hearing disturbances	7	2.3
– unilateral	3	8.3
– bilateral	4	3.5
7. Hearing level based on the better ear		4.7
– normal (<30db)	80	
– mild loss (30–50 db)	3	95.2
– moderate loss (50–70db)	—	3.5
– severe loss (>70 db)	1	—
8. Cognitive abnormalities		1.1
– lability	11	
– mental retardation	4	13
9. Speech delay	8	4.7
		9.5

Motor abnormalities were the most common finding at that time, diagnosed in 10 children (11.9%), 8 of them were classified as 1st and 2nd degree. Two patients (2.3%) had severe disturbances 3rd degree (spastic tetraparesis). Ataxia was diagnosed in 3 (3.5%) of the children studied combined with the hearing disturbances in two cases.

Of the 84 children followed-up 6 (7.1%) had seizures (Table 23). Febrile seizures were registered in two cases, starting at the age of 1.5 to 5 years. Nonfebrile seizures were documented in 4 (4.7%) children. The seizures that were clearly focal or had focal onset started from half to seven years after the acute illness. Good control of seizures was achieved in 3 of the 4 patients with monotherapy. Moreover history of affect-seizures was found out in two children. One of them had those already before the BM, but after BM they occurred

more often, in another child affect-seizures were firstly diagnosed 3 months after BM.

Table 23

Characteristics of patients with epilepsy during acute illness and the follow-up study

	Acute period						Follow-up period		
Pat. number	Age on admission (mo)	Sex	n of days before	Organism	Seizures	Unconsciousness	Time to seizures onset (years)	Type of seizures	Neurologic deficit
6.	2	m	3	*N. meningitidis*	+	–	0.5	focal	Tetraparesis III Ataxia HD
26.	37	f	3	*N. meningitidis*	–	–	7	"	Normal
67.	7	m	2	*S. pneumoniae*	+	+	1	"	MR Obesity HD
71.	41	m	1	–	–	–	1	"	Cognitive disorders

MR – mental retardatation; HD – hearing deficit

Seven children (8.3%) had a SNHI at follow-up (Table 24). There was bilateral impairment in 4 (4.7%) and unilateral impairment in 3 children (3.5%). Two out of seven had profound hearing loss — one uni- and another bilateral. Moderate unilateral hearing disturbances were registered in two children and bilateral mild hearing impairment in three patients. According the estimated hearing level for speech based on the better ear the patients with hearing disturbances were divided as follows: three children (3.5%) had mild hearing disturbances and one child was deaf (1.8%) using hearing aid.

Five children out of 15 with sequelae at the follow-up examination had combined disturbances (patient n 6, 7, 15, 67, 68 in Tables 23 and 24). In 3 of the cases it remained doubtful whether BM was the only etiologic factor for the brain damage. Hydrocephalus following congenital toxoplasmosis was diagnosed in patient no 7 before the onset of BM. Mucopolysaccharidosis with motor disturbances was documented in patient n 14. Patient n 60 suffered a traffic accident two years after BM, brain contusion was diagnosed.

Table 24

Characteristics of patients with hearing impairment following BM during acute illness and follow-up period

Acute period						Follow-up period		
Patient number	Age at onset (mo)	Sex	No of days sick before	Organism	Seizures	Duration of fever (days)	Hearing class	Follow-up evaluation
4.	43	f	3	—	—	10	r-4 l-1	Normal
6.	2	m	3	*N. meningitidis*	+	1	r-2 l-2	Spastic tetraparesis III Ataxia EP Hydrocephalus
7.	21	m	2	—	—	9	r-4 l-4	Ataxia
15.	38	f	10	Hib	—	1	r-3 l-1	Normal
42.	6	f	2	Hib	—	8	r-2 l-2	Normal
67.	7	m	2	*S. pneumoniae*	+	5	r-3 l-1	EP Debility
68.	3	m	7	*S. pneumoniae*	+	4	r-3 l-3	Diencephalic obesity MR Hydrocephalus

m – male f – female; l – left r – right
Hearing level classes 1 = <30 db normal; 2 = 30–50 db mild hearing loss;
3 = 50–70 db moderate hearing loss; 4 = >70 db deaf

3.3.3. Prognostic value of clinical symptoms and syndromes

Table 25 demonstrates prognostic value of different clinical syndromes and symptoms.

There was a significant correlation between duration of illness before admission and development of hearing disturbances and motor defects ($p<0.05$). No other differences between hearing disturbances, EP and motor abnormalities and the occurrence of unconsciousness, duration of illness, CSF findings on admission, etiologic structure of BM and therapy used was statistically significant.

All but one child of those developing hearing disturbances were discharged with neurological sequelae — five had severe and one had mild impairments. A highly significant correlation between the severe neurologic deficits at the time of hospital discharge and hearing impairment at the follow up was found ($p=0.0001$).

All but one of those with MA had been discharged with sequelae — three had mild and six severe disturbances. The correlation between sequelae at the

discharge and MA in long term follow up was highly statistically significant ($p<0.0001$). Two out of four children with sequelae on discharge developed EP, but a statistically significant correlation did not exist ($p=0.532$).

Table 25

Characteristics of the acute phase of BM in a sample of children who had hearing disturbances, EP and motor defects after 5 years

Characteristics Number of patients	Normal n=68	Hearing defects n=7	EP n=4	Motor defects n=10
1. Age on admission				
up to 1 year	31	4	2	5
up to 3 years	53	6	2	9
2. Course of illness				
days before admission	2.6	4.1*	2.2	3.7*
unconsciousness	7	2	1	2
seizures	13	3	2	4
temperature on admission	38.5	38.4	38.3	37.8
3. Laboratory findings				
CSF WBC (per mm^3)	8254	3618	1587	8533
CSF protein(mg/dl)	1902	2112	1480	1947
CSF glucose(mg/dl)	2.08	1.7	2.6	2.2
4. Treatment				
penicillin	51	4	4	7
ampicillin	24	5	2	5
gentamycin	9	1	1	0
chloramphenicol	20	1	1	3
dexamethasone	21	2	2	5
duration of AB therapy	13.0	18.5	15.2	17.1
5. Organism				
N. meningitidis	37	1	2	2
S. pneumoniae	5	2	1	2
H. influenzae	7	2	–	3
unknown	19	2	1	3

* $p<0.05$

A high correlation between motor abnormalities and hearing disturbances was seen during the follow-up period. So five out of seven children with hearing defects had also motor abnormalities and five out of ten with the motor abnormalities had also hearing impairment ($p<0.0001$).

EP in combination with hearing disturbances was seen in two children and with motor abnormalities in two, but the correlation was weak ($p=0.176$ and $p=0.119$ respectively).

3.4. DISCUSSION

Sell (1983) reported on extremely poor long term prognosis of BM — 50% of survivors had some sequelae at long term follow ups. Our study, however, in accordance with other recently published investigations (Jadavij et *al. 1986*; Lebel *et al.* 1989; Gary *et al.* 1989) indicates that the long term prognosis may not be as gloomy as initially thought — 80% of the children were normal, 13.1% had moderate disturbances and only 5.9% were handicapped 5 years after BM in this study.

The frequency of hearing disturbances found by us in 8.3% of children was rather similar to that calculated by Fortnum (1992) in the review of the English language literature. As suggested in previous studies (Dodge *et al.* 1984; Salwen *et al* .1987) the hearing impairment mostly was mild to moderate in our study, not disturbing an independent life and only one (1.1%) deaf child using hearing aid was found. Due to the fact that no but one audiometric examinations were performed in the acute period of the diseases we were not able to determine the time of occurrence of hearing impairment. However, the early onset of it is shown in most studies. So Vienny *et al.* (1984) even found hearing disturbances in 31.4% of their patients during the first 48 hours of hospitalisation, with therapy the hearing disturbances improved. Persistence of symptoms were observed in 5.4% of the patients on discharge and no new cases were diagnosed during the follow-up-period. While the development of hearing defects after acute BM is excluded in most studies (Lütschg 1992), we have to stress that the examination of the auditory system should be performed at the time of hospital discharge to find out children with hearing disturbances in order to start early rehabilitation if needed and to prognosticate children at risk for permanent impairment.

The predominant opinion is that cochlear dysfunction is the most likely pathogenic factor of hearing defects (Klein *et al.* 1986; Kaplan *et al.* 1989; Harada *et al.* 1988; Bhatt *et al.* 1991). Our study as the study of Dodge *et al.* (1984) revealed a significant correlation between hearing and motor defects during the follow-up examination as well as between later hearing disturbances and severe neurologic deficits on discharge ($p<0.05$) and we cannot agree with Feigin *et al.* (1992) that hearing disorders are not associated with brain damage. Therefore we assume that hearing disturbances do not arise due to purulent labyrintitis alone, but are also caused by extensive brain damage due to vasculitis and ischemia in the region of the auditory tract as demonstrated by Jiang *et al.* (1990). In this study like in most others (Dodge *et al.* 1984; Jadavij *et al.* 1986; Salwen *et al.* 1987) the highest ratio of hearing impairment was registered among those with *S. pneumoniae* meningitis (2 out of 7), but most probably due to low number of cases in each group no statistically significant association between various microorganisms and hearing disturbances was found.

No statistically significant association between different antibacterial drugs and the development of hearing disturbances was found in our study. There is one study showing the highest frequency of hearing loss in those treated with

ampicillin in comparison to those with chloramphenicol (Gamstrop *et al.* 1974). Recently most studies demonstrated an early occurrence of hearing defects, even before antibiotics have been introduced and no association between different antibiotics and hearing loss was registered (Friebel *et al.* 1984; Dodge *et al.* 1986; Salwen *et al.* 1987).

The overall prevalence of nonfebrile seizures that required medication for years (4.7%) was remarkably higher among postmeningitic children than in Estonian children's population — 1:1000 (Sander *et al.* 1991) and was similar to the data of the meta-analysis made by Baraff *et al.* (1993) — 4.2%. Like Annegers *et al.* (1988) we found that mostly seizures occurred within a few years after the infection, the relative risk was highest during the first five years. Despite the fact that half of those having late seizures and only 18.3% of those without had also seizures in the acute period we did not find any statistically significant correlation between late and acute seizures as did Annegers *et al.* (1988) and Pomeroy *et al.* (1990). Neither did we find a correlation between other abnormalities and epilepsy like Pomeroy *et al.* (1990), although from six patients with combined disturbances two also had seizures.

Long term motor abnormalities such as hemiparesis, diplegia or quadriparesis and ataxia have been diagnosed more often (11.9% and 3.5% respectively) in this study than in others (Sell 1983; Odio *et al.* 1991; Kabany *et al.* 1992). However, they have been partially of a mild degree and in 3 cases of 10 other factors than infection for brain damage (traffic accident, congenital disease) are hard to exclude. Our data support the results of the above mentioned studies that motor abnormalities, detected soon after the acute illness, do not always persist (Pomeroy *et al.* 1990). If 28.5% of survivors had some motor defects at time of hospital discharge, after one months these persisted in 21.4% and one year later in only 14.3% of the children followed. The decrease of severity of motor defects with time was even more prominent. While motor abnormalities of third degree were seen in 8.9% of patients immediately after the acute period, they persisted in only 2.3% of cases 5 years later. Ataxia, occurring concomitantly with hearing disturbances most probably as a result of labyrinthitis, was another motor defect having a tendency to resolve with time (Kabany *et al.* 1992; Feigin *et al.* 1992). In a study by Lebel *et al.* (1989) ataxia was registered in 14.4% at the time of hospital discharge, but one year afterwards it only persisted in 0.6% of the survivors. Our data with the frequency of ataxia of 14.3% at the time of hospital discharge and 3.5% a year later do not show such a dramatic decrease in incidence, nevertheless we support the opinion that the severity has a tendency to decrease with time. There is no common explanation why motor defects occur and then resolve in patients with BM. Recovery after insults to the developing nervous system is frequently ascribed to its "plasticity", but this explanation is far from satisfying (Pomeroy *et al.* 1990).

Prospective assessment of speech development in young children following meningitis has rarely been reported. We like others found language disorders in almost 10% of postmeningitic children (Lebel *et al.* 1989; Gary *et al.* 1989; Salih *et al.* 1990). The speech delay in previous studies was mostly connected

with the hearing disturbances. The results of this study did not reveal any correlation between hearing impairment and language disorders in children after nonneonatal meningitis. Therefore we as Letson *et al.* (1993) assume that not only the hearing function but also degree of brain damage is important in development of speech delay after BM.

Several studies tried to find prognostically significant symptoms during the acute period in order to predict a poor outcome. The youngest age on admission, the highest frequency of seizures and unconsciousness were documented in this study in those having poor outcome in comparison to those with a good outcome, but none of those differences was statistically significant.

The data about the duration of symptoms before the therapy and outcome of BM are controversial in literature. The delay of hospital admission was the single characteristic of BM, which correlated with the development of motor defects and hearing disturbances ($p<0.05$). However, Kilpi *et al.* (1992) in a study which consisted of 286 children with BM showed better outcome of those patients whose duration of symptoms before the antibacterial therapy was longer. It is possible that especially meningococcal meningitis is sometimes rapidly progressive and patients die within first hours of illness. However, we as Radetsky (1992) believe that the prompt diagnosis and therapy of BM remains a clinical challenge, for no physician would knowingly delay the appropriate therapy.

Like Jadavij *et al.* (1986) and Taylor *et al.* (1990) found a significant correlation between hearing disturbances and neurological sequelae at the time of hospital discharge as well as during the follow-up examination this study showed also a strong correlation between different sequelae but epilepsy during the long term follow-up and severe neurologic deficits on discharge ($p<0.0001$). In general it shows that the greater the extent of damage the child has suffered, the poorer the long term prognosis. From practical and economical point of view this indicates which children need a careful follow-up after BM.

In summary: Our study showed that after BM only 5.9% of survivors are handicapped. The most common long-term sequelae of BM are hearing disturbances, motor defects and late seizures. The prognosis of patients can be determined already at the time of hospital discharge, while mild to moderate disturbances have tendency to resolve whereas severe defects are permanent. So we recommend to follow up only children with severe neurological deficit at the time of hospital discharge.

PART IV

SHORT COURSE OF ANTIBACTERIAL THERAPY FOR BACTERIAL MENINGITIS IN CHILDREN

4.1. REVIEW OF LITERATURE

The variation in length of the therapy of BM in English language literature was recently reviewed by Radetsky (1990). There is general consent that MM needs shorter therapy, even to an one-dose therapy, than Hib and pneumococcal meningitis, which have to be treated for longer periods. Still reports from some countries suggest that shorter treatment periods, especially in MM are sufficient and safe in uncomplicated cases (Helwig 1992). In a comparative trial Lin *et al.* (1985) confirmed that there is no significant difference in outcome, lenght of fever, complications, or sequelae whether the children with BM are treated with ceftriaxone for seven or ten days. A Finnish multicenter study which included 220 BM patients and was performed by Peltola et al. (1989) concluded that a 7-day course of ampicillin, cefotaxime, or ceftriaxone is sufficient in Hib, MM and pneumococcal meningitis in children. The prospective Swiss multicenter study randomly assigned 119 children with BM to either short course (four, six, seven days) or full course (eight, 12, 14 days) ceftriaxone therapy depending on whether they had contracted MM, Hib or *S. pneumoniae* meningitis. The results of this study suggest that short course treatment of acute BM in children is as efficacious as full course therapy (Martin *et al.* 1990). A retrospective study which originated from Italy described 122 children with BM (*N. meningitidis* — 47.5%, Hib — 20.5%; *S. pneumoniae* — 15.6%; others — 4.1%) and showed that 90% of patients were cured with ceftriaxone monotherapy for from three to six days (Pecco *et al.* 1991).

The late sequelae of acute BM in children who were treated with ampicillin and chloramphenicol for seven days have been investigated for a minimum of one year following their illness by Jadavij *et al.* (1986). The frequency of observed sequelae (20%) among these patients was similar to that previously reported in children treated for ten to 14 days. Our previous study (unpublished data) showed that 79% of patients with MM and 71% of those with pneumococcal meningitis are in good general condition by day 5 of antibacterial therapy. They are afebrile, the meningeal symptoms are gone, and they have almost normal findings of CSF examination. A shorter course of antibacterial therapy will result in fewer days of hospitalization, lower costs and lesser frequency of complications caused by antibiotics.

4.2. PATIENTS AND METHODS

Throughout October 1990 and June 1994 all children between one month and 15 years of age admitted to Tartu University Children's Hospital with microbiologically confirmed BM were enrolled in this study.

Table 26

Clinical and laboratory characteristics of the patients on admission

Characteristic	Study group n = 36	Control group n = 49	p =
Age (mo)	39.2±7.8	24.6±4.6	0.076
(range)	(8–135)	(1–156)	
Sex			
male	21	30	0.63
female	15	19	
History:			
No given antibiotic therapy before (%)	7 (19.4)	13 (26.5)	0.47
Duration of antibacterial therapy before (days)	0.8±1.9	0.5±0.5	0.22
Duration of symptoms (days)	3.6±0.6	2.9±0.26	0.23
No (%) with features on admission:			
Temperature > 38.5^0	25	37	0.47
Seizures	7 (20)	13 (26)	0.68
Unconsciousness	3 (8)	4 (8)	0.76
Shock	4 (11)	7 (14)	0.67
No(%) infected with:			
N. meningitidis	23 (67)	33 (67)	0.56
H. influenzae type b	7 (20)	10 (20)	
Spneumoniae	5 (14)	6 (12)	
Br.catharralis	1 (3)	—	
Laboratory findings:			
CSF WBC 10^{-6}/l	5591	7958	0.50
(range)	(612–8540)	(1135–9236)	
CSF protein g/l	1077	1780	0.19
(range)	(588–955)	(624–3077)	
CSF glucose mmol/l	2.4	2.1	0.31
(range)	(1.8–2.9)	(0.7–3.0)	
ESR mm/h	36 (22–58)	40 (29–52)	0.25
Total WBC	18.8 (13.4–24.0)	16.4 (11.6–20.1)	0.1

During this period 42 patients with BM met the inclusion criteria. A historical comparison-group consisting of 49 patients with a diagnosis of microbiologically confirmed BM treated at our hospital in 1983–1989 was used. After initial investigation, the patients were examined at least once a day throughout the hospital stay. In addition, several tests of CSF, blood and urine were done. There were no significant differences between the groups in patient characteristics, clinical and laboratory features (Table 26). Therapeutic regimes

for antibacterial therapy used in study and comparison group are shown in Table 27. The antimicrobials in study group were given for 5 days.

Table 27

Duration and choice of antibacterial therapy in children with BM

		Study group (n = 26)		Comparison group (n = 49)				
		Initial therapy		Initial therapy		Corrected therapy		
Etiology	Anti-biotic	n of patient	duration (days)	n of patient	dura-tion (days)	second course used	n of patient	duration (days)
N. menin-gitidis	Pen.	18	5.0	21	9.1	4	—	—
	Amp.	—	—	5	6.4	4	—	—
	Pen.+Chl.	—	—	6	10.2	2	3	9
	Ceph.	—	—	1	9	1	8	7.8
S. pneumo-niae	Pen.	2	5.0	3	9.3	—	—	—
	Amp.	—	—	1	7	—	—	—
	Pen.+Chl.	—	—	2	10.5	2	1	6
	Ceph.	—	—	—	—	—	1	5
H. influen-zae	Pen.	6	5.0	5	8	4	—	—
	Amp.	—	—	4	6.7	4	—	—
	Pen.+Chl.	—	—	—	—	—	4	11.7
	Ceph.	—	—	1	7	—	4	10.8

Pen – Penicillin G; Amp. – Ampicillin; Chl. – Chloramphenicol; Ceph. – Cephotaxime
Antibiotics were administered intravenously as follows: Penicillini 300 mg/kg/die:6; Ampicillini 200 mg/kg/die:6; Chloramphenicoli 100 mg/kg/die:4; Cephotaxime 150 mg/kg/die:3

A second lumbar puncture was done on day 5 of AB therapy. The criteria for the termination of the AB therapy in the study group were as follows: (1) meningeal symptoms mild or absent, (2) body temperature less than 38^0C, (3) sterile CSF, (4) CSF WBC count < 100 mm^3, CSF protein < 1500 g/l, CSF glucose/blood glucose ratio > 0.6.

The children were followed by a multidisciplinary team (pediatrician, pediatric neurologist, speech therapist and audiologists). The follow-up time was at least 6 mo. Follow-up of children was performed according to the criteriae described in part III (pp. 50–52).

Statistical analysis. Values are expressed as means ± 1SD. Differences between the groups in the frequencies of various findings were tested with either the chi-square or t-test.

4.3. RESULTS

Antibacterial therapy was completed as indicated in protocol (for 5 days) in 36 cases out of 42. The treatment was extended to last longer than 5 days in six cases (Table 28). The reasons for extension of antibacterial therapy were particulary either fever (>38.5^{0}C) or persistent CSF leucocytosis (> 100 WBC/ml) on day 5. One patient (n 80) had MM which complicated with bilateral coxitis and the another (n 77) was in poor condition on day 5.

Tabel 28

Cases of extended antibacterial therapy

Sheduled antibiotic and patient no	Age (mo)	Etiology	Duration of therapy (days)	Reason for extension/ changes in therapy
Penicillin				
22	2	*N. meningitidis*	12	Persisting CSF leucocytosis/ Cefotaxime
80	36	*N. meningitidis*	14	Fever, bilateral coxitis/ Cefotaxime
84*	8	Hib	8	Persisting CSF leucocytosis/ Ampicillin
90	11	*N. meningitidis*	11	Fever/ Cefotaxime
Ampicillin				
2	8	Hib	11	Fever/ Chloramphenicol
Cefotaxime				
44	77	*S. pneumoniae*	7	Poor condition, VI nerve paresis/ —

* patients was initially treated with Penicillin

Table 29

Clinical and laboratory findings at the time of termination of antibacterial therapy

	Study group n = 36	Control group n = 49
Clinical feature:		
To 37–38^0	5	11
No of seizures	—	3
Negative meningeal syndrome	33	45
Laboratory findings:		
CSF WBC 10^{-6}/l	45 (4–89)	59 (2–102)
CSF protein g/l	758 (305–1388)	1047
CSF glucose mmol/l	2.4 (2.1–2.8)	2.6 (2.2–3.6)
ESR mm/h	34 (18–46)	42
Total WBC 10^{-6}/l	11.4	12.1

At the time of termination of antibacterial therapy clinical feature and laboratory findings of patients in study and comparison group have been similar and are shown in Table 29. The negative meningeal syndrome has been registered more than 90% of patients, six children in study group still had fever from 37 to 38^0 C.

The duration of antibacterial therapy as well as the duration of hospitalisation and the number of hospital-acquired respiratory infections were significantly lower in the study group ($p<0.005$) (Table 30).

Table 30

Hospital course of patients studied

Variable (range)	Study group n = 36	Control group n = 49
Duration of antibacterial therapy (days)	5.0	13 (7–43) *
Duration of hospitalisation	10.2 (7–18)	22.5 (9–116) *
Number of nosocomial infections	—	8 *
Completely recovered (n)	30	36
Mild disturbances (n)	4	8
Severe disturbances (n)	2	5
Died	—	1

* $p < 0.005$

The mean hospital stay with the short-course antibacterial therapy was 10.2 days in contrast to 22.5 days for conventional therapy. No one from the study group received any hospital-acquired respiratory infections whereas there were eight cases among those hospitalised longer. The outcome of children at the time of hospital discharge was almost the same in both groups: 81% of the children in the study group and 75% in the comparison group recovered completely. There were no relapses in either group. On the examination at discharge abnormalities were still present in seven children in the study group and 14 in the control group. They included six cases of ataxia in the study and three in the comparison group, three cases of other motor defects in the study and eight cases in the control group. Three control and one study group children were discharged using anticonvulsive drugs. At the time of hospital discharge one child was deaf after pneumococcal meningitis, the another had bilateral mild hearing disturbances and third child an unilateral severe hearing impairment in the study group. The frequency of hearing defects in comparison group is not clear while audiometric investigation has not been as a routine in our hospital at that time.

There were 34 children examined in the study and 47 in the control group at least 6 mo after hospital discharge (Tabel 31).

79 % of children in comparison and 88% in the study group were normally healthy during the follow-up examination. Four of the children who had received five days of antibacterial therapy had sequelae: two had ataxia one of them in combination with one-sided moderate hearing impairment, one child had learning problems and one was deaf using hearing aid.

Table 31

Outcome of BM patients during the follow-up examination

	Study group n=34	Control group n=49
Normal	30	37
Mild to moderate disturbances	3	8
Severely impaired	1	3
Motor abnormalities	2	7
Hearing impairment	2	3
Late seizures	—	5
Irritability	1	?

4.4. DISCUSSION

Our preliminary results showed that the short term as well as long term outcome in children treated for five days for BM was similar to that when treated longer. However, the children treated for five days had a significantly shorter duration of hospitalisation ($p<0.005$) and no cases of hospital-acquired respiratory infection were registered. There were no relapses in either group, which is not surprising because the bacteria, especially in MM, are usually eliminated from the CSF within 24 to 48 hours of initiating parenteral antibacterial therapy (Peltola *et al.* 1989).

The limitation of this study was that it was not a prospective double-blind study and a historical comparison group was used as a control. The recently decreasing number of BM cases in Europe and in North America due to the introduction of vaccination against Hib and nonepidemic period of meningococcal infection (Peltola *et al.* 1992; Kostjukova *et al.* 1992; Adams *et al.* 1993) makes it difficult to organise any trial with a sufficient number of patients. This would require, e.g., approximately 1,400 patients to be randomly assigned to two treatment groups and to be followed for 5 years in order to detect a 50% increase in sequelae with an 80% of certainty (Helwig 1992).

We would also like to stress that six out of 42 children (14%) who met the inclusion criteriae did not complete the study according to the protocol. The reasons for that were mainly fever or persisting CSF pleocytosis. However, it is also shown that children who have received apparently adequate treatment (10 to 14 days) can show persistent increases in the CSF WBC which was not connected with the sequelae (Connolly 1981). In a series of cases of pediatric BM which analysed repeat CSF total WBC counts after completion of a course of adequate AB therapy, 62% with Hib and 22% with *S. pneumoniae* meningitis still manifested of persistent CSF pleocytosis (Chartrand *et al.* 1976). The persistence of fever on day 5 in three patients out of 42 is not suprising while according to the data of La Via *et al.* (1992) by the day 5 of the AB therapy 20 to 25% of BM patients still have a fever. Although neither persistent pleocytosis

nor fever are indications for following AB therapy it is not possible to complete AB therapy without special investigations to rule out CNS complications.

In this study penicillin was used for the therapy of *N. meningitidis* and *S. pneumoniae* while resistant meningococci and pneumococci are still uncommon in Estonia. Resistant isolates of *S. pneumoniae* are now being recognised in 10% of cases in Estonia (Mikelsaar, personal communications) and it is likely that it will be an important factor influencing the selection of antibiotics in the future. Tuncer *et al.* (1988) in a randomised study compared the effectiveness of a four-day therapy with ceftriaxone and penicillin in 44 children with meningococcal infection and did not find any differences between the two drugs in the outcome in noncomplicated cases.

A shorter courses of antibacterial therapy (4–5 days) than recommended in the textbooks (McGee *et al.* 1990; Feigin *et al.* 1992), have been reported to be highly effective in some previous studies in uncomplicated cases of meningococcal meningitis (Viladrich *et al.* 1986; Tuncer *et al.* 1988; Pecco *et al.* 1991). Martin *et al.* (1990) used ceftriaxone monotherapy for 4 days in patients with MM, for 6 days in cases of Hib meningitis and for 7 days in pneumococcal meningitis and showed that these regimes were as effective as longer periods of therapy. Although a 5-day therapy in our study was effective also in Hib and pneumococcal meningitis, it has to be said that in 7 out of 12 children antibiotics had been administered before hospital admission and we agree that Hib and *S. pneumoniae* meningitis may require longer treatment. (Viladrich *et al.* 1986; Peltola *et al.* 1989; Helwig 1992).

The longer treatment is needed in cases of complicated course of BM. The child with bilateral coxitis had fever on day 5 and was treated longer. The longer treatment periods may also be needed for children who have moderate or severe hearing impairment on day 5, while penetration of AB into labyrinth is even worse than it is into CSF (Harrison 1993).

In summary: We found short and long-term outcome of bacteriologically confirmed BM being similar in children treated with antibiotics for five days or significantly longer. However, the childern with short course therapy were hospitalised shorter and had no hospital aquired respiratory infections. Thus, we suggest five days of antibacterial therapy for children with uncomplicated meningococcal meningitis, however, we feel the second lumbar tap is necessary.

GENERAL DISCUSSION

In this study our aim was to answer several questions on which most pediatricians are interested in. They were as follows:
1. How common are the infections of the central nervous system in Estonia and which are the predominant etiological agents?
2. Is there any additional possibility except common tests to distinguish between bacterial and aseptic meningitis?
3. Would it be possible to prognosticate the outcome already on admission?
4. How long should be a child with BM treated with the antibiotics?
5. Do we need to follow up all children after BM or only some and if we do, which of them should be followed up?

Our retrospective epidemiological study based on annual reports of the hospitals where children with ICNS were treated during the study period (from 1980 to 1989) revealed an incidence rate of ICNS 66.2/100 000 children which was very similar to that reported from Spain (Roca *et al.* 1992). We found it interesting that the incidence rates (29.8 and 25.8/100 000 children respectively) as well as the epidemic course of AM and BM were rather similar. We found the etiological pattern of BM completely different from that in Nordic countries, USA and Australia where the leading cause of community acquired meningitis in children is *H. influenzae* (Wenger *et al.* 1990; Peltola *et al.* 1990; Hanna *et al.* 1991). Our data with the predominance of *N. meningitidis* are very similar to studies performed in the former Soviet Union (Djomina *et al.* 1985; Cibiras et al. 1986; Kostjukova et al. 1992). Due to the fact that in more than half of the cases the etiology of BM remained unknown, we can speculate, that under diagnosing of Hib meningitis was going on. With the improvment of facilities of bacteriological laboratories and introducing new methods the number of unidentified cases decreased, but meningococci were still most frequently found. So we believe that *N. meningitidis* is still predominant agent in the etiology of BM in children but like Iljina *et al.* (1990) we also saw that the importance of Hib raised to the end of the studied period.

Unfortunately the etiology of AM remained unknown in more than 90% of cases, whereas with good laboratory facilities it could be proved in more than 3/4 of cases (Tardieu *et al.* 1986; Koskiniemi *et al.* 1989). The main reason for high number of unidentified cases seems to be that AM as a mild disease was mostly treated at district hospitals with the poor diagnostics facilities and low interest of practising doctors for AM etiology. We feel that the doctors interest will increase if rapid methods will become available.

Like other studies (Nicolosi *et al.* 1986; Etter *et al.* 1991) we showed the relatively good outcome of AM, whereas the prognosis of BM even at the end of the study period when most of children were referred to Tartu University Children's Hospital was serious. The mortality rate of BM was 13.0% and disability rate 8.9%. The worst outcome with the disability and mortality of 53.8% and 45.8% respectively was noted like by others after neonatal meningitis (Bell

et al. 1989; Zaki *et al.*1990). The reasons of extremely bad outcome of neonatal meningitis are not clear thus far. We only can speculate that it is connected with the immature immune system, but also usually with late diagnosis while there are no characteristic symptoms for meningitis in that age (Schaad *et al.* 1992). We also saw that during the study period the number of neonatal meningitis cases increased and it could be connected to the opening of NICU, concentrating patients there and spreading of nosocomial infection. Therefore we agree with Schaad *et al.* (1992) that the most important factor in preventing poor outcome will be profylaxis of neonatal infection.

Despite the fact that from 22 studies only 13 showed that prognosis of BM patients depends on the time of onset of antibacterial therapy (Radetsky 1992) our study demonstrated that duration of illness before hospitalisation was the single clinical characteristic being prognostically important. However, in some cases it will be extremely difficult to distinguish between BM and AM using common tests of CSF (Rodewald *et al.* 1991). Our work based on the different pathogenesis of BM and AM, measured the activity/concentration of some intracellular enzymes (AST, GGT, LDH, CPK and CK-BB) to differentiate between BM and AM and tried to found out their prognostic value. We like Sirkis (1982); Agrawal *et al.* (1989) and Nand et al. (1992) found that patients with BM had significantly higher activity of AST and GGT than those with AM and meningism, however the activity of AST didn't increase the reference levels. We also showed as Agrawal *et al.* (1989) and Roslõi *et al.* (1991) the prognostic value of raised AST activity. Due to the fact that we could not find any correlation between the activity of AST in CSF and blood serum we suggest that local releasing of AST is going on and its raised activity most probably shows the cytolysis of the brain tissue. The benefit of measuring LHD activity in differentiation of AM and BM was also very poor in this study (Landaas *et al.* 1985), but a good correlation between bad prognosis and high LDH activity on admission was found. It was a surprise that the benefit of measuring of CK-BB was poor, while the CK-BB seems to be one of the best markers in the estimation of brain damage that we have (Belton *et al.* 1970; Sööt *et al.* 1989; Praeter *et al.* 1991). In contrast to Haldre *et al.* (1991) and Talvik (1992) who found good prognostic value of CK-BB in the CSF in patients with head injury and hypoxic-ischaemic brain damage respectively, we found even lower concentration of CK-BB in the CSF in children who either died or recovered with permanent sequelae on admission. The same was also shown by Briem (1982) in patients with meningoencephalitis and we speculate that the prognosis of BM patients depends not only on the extent of brain injury but also on the site of damage. The ground of pathologic process is diffuse vasculitis of the brain (Quagiliarello *et al.* 1992), but some areas are more affected than others. It was demonstrated by Delanghe *et al.* (1990) that the distribution of CK-BB in the brain is different, the highest concentrations were found in cortex and capsula interna, while only limited amounts were measured in pons, cerebellum and medulla oblongata. So we suggest that the importance of estimation of intracellular enzymes in differential diagnosis of meningitis

can not be overestimated, nevertheless they can give us some additional information in understanding the pathogenesis of BM and AM.

The data of the duration of antibacterial therapy vary largely in the literature and there are few controlled clinical trials thus far. According to the fact that the CSF is sterile in meningococcal meningitis mostly after 24 hours of antibacterial therapy and by Hib and pneumococcal meningitis after 72 hours we decided to use five-day therapy (Peltola *et al.* 1989; Lebel *et al.* 1989). From 42 patients who met the inclusion criteria 36 completed the study according to the study protocol. Main reasons for extended therapy were either prolonged fever, persistent pleocytosis or complicated course of meningitis. Although neither the persistent pleocytosis nor fever are indications for continuing AB therapy (Chartrand *et al.* 1976; La Via *et al.* 1992) it is not possible to complete the AB therapy without special investigations. There was no differences in outcome at the time of hospital discharge and one year after acute illness between children treated for five days and longer. However, the patients who got the five-day therapy were hospitalised for significantly shorter periods and had no hospital acquired respiratory infections. The disadvantage of this study is that it was not a randomised study and historical comparison group was used as a control. It would be not possible to set up a randomised, double-blind study in any country while this would require e.g., approximately 1,400 patients to be followed for 5 years in order to detect a 50% increase in a sequelae with an 80% of certainty (Helwig 1992). Therefore the experience of several small studies could be valuable in elaborating the general rules. Our data showed that five-days of AB therapy would be sufficient for noncomplicated meningococcal meningitis, but due to the small number of patients we cannot recommend it for patients with pneumococcal and Hib meningitis. However, we still believe that in patients treated for five days the second lumbar tap is necessary.

The fact that no antibacterial therapy is needed after fifth day does not mean the child's complete recovery. We like Klein *et al.* (1986) and Lebel *et al.* (1989) showed that at the time of hospital discharge 28.5% of patients had changes of muscle tones and 14.3% had ataxia. Both defects were reversible and during the long term follow-up they persisted in only 11.9% and 3.5% of children respectively and were in most cases of mild degree. Our enzyme studies showed also that at the end of antibacterial therapy the activity of CPK and the concentration of CK-BB was still over the reference value which most probably speaks of cytolysis going on. There are no studies published thus far concerning the treatment of BM meningitis if the CSF is sterile and we doubt wheather any medicine will be needed at all. Nevertheless, for patients with permanent defects (hearing disturbances and severe motor abnormalities) rehabilitation had to be started as early as possible. Our study found a highly significant correlation between severe neurological defects at the time of hospital discharge and motor abnormalities and hearing disturbances during the long term follow-up investigation, so we concluded that following up was needed only for those children. We like Annegers *at al.* (1988) demonstrated that the BM patients have a higher risk later epilepsy. Nevertheless, it was not

possible to prognosticate the development of late seizures, while there was no difference neither in clinical symptoms nor in laboratory tests during the acute illness and at the time of hospital discharge.

As in most studies (Baraff *et al.* 1993) the most common sequelae after BM were hearing disturbances, found in 8.3% of children during the long-term follow-up investigations. Although we didn't find any differences between language disorders and hearing defects however, we as Brookhauser *et al.* (1989) believe that hearing disorders should be diagnosed immediately after the acute illness and early rehabilitation should be started. The fact that in two children ataxia was combined with the hearing disturbances supports the opinion of Harada *et al.* (1988); Kaplan *et al.* (1989) and Bhatt *et al.* (1992) that they are results of labyrinthitis. However, the significant correlation between hearing disturbances and motor defects supports the data of Jiang *et al.* (1990) that ischaemia in the area of auditory tract may be also important for the development of hearing disturbances.

In conclusion this study of more than ten years demonstrated that although the annual number of patients with ICNS in South-Estonia is not high permanent sequelae and deaths still occur. Therefore patients with BM, complicated forms of AM and encephalitis should be concentrated to the hospitals with better laboratory facilities, possibilities for sophisticated methods of intensive care and with the doctors experienced in the care of such patients.

CONCLUSIONS

1. Our data revealed a constant incidence rate of infections of the central nervous system of 66.2/ 100 000 children in the 1980s in South-Estonia, which includes 25.8 for bacterial meningitis, 29.8 for aseptic meningitis, 7.6 for tick-borne encephalitis and 3.0/100 000 children for encephalitis caused by other viruses.

2. Bacterial meningitis in contrast to the aseptic meningitis was predominantly a disease of the early childhood — 84.3% of the patients with bacterial meningitis were younger than five years whereas among aseptic meningitis and encephalitis patients more than 80% were over 5 years.

3. *Neisseria meningitis* which caused 34.9% of bacterial meningitis cases during the study period was the leading micro-organism among the etiologic factors. The importance of *Haemophilus influenzae* in the etiology of bacterial meningitis increased from 0.9% at the beginning of the 1980s to 8.9% at the end of it.

4. A significant rise in AST and GGT activities in CSF was found in patients with bacterial meningitis during the first days of illness. The significantly in-

creased activities of AST and LDH could be an indicator of the extent of brain damage and therefore prognostically important.

5. For children with non complicated cases of meningococcal meningitis a five-day antibacterial therapy will be adequate, but due to a small number of patients we can not recommend it for Hib and pneumococcal meningitis.

6. Motor abnormalities, hearing impairment, late seizures and cognitive disorders have been the most common long-term sequelae of bacterial meningitis found out in 20% of children.

7. Motor defects detected soon after acute illness in 27.3% of patients had tendency to resolve with the time and were seen during the long term follow-up examination in only 13.1% of children.

7. There was a significant correlation between different sequelae (but for epilepsy) during the long term follow-up and severe neurologic defects at the time of hospital discharge. It means that only children with severe neurological deficits are at a higher risk for permanent neurological sequelae and hearing disturbances. Those showing no or only mild disturbances have an excellent chance of escaping serious sequelae except epilepsy.

8. The mortality rate of ICNS was 5.4% and 4.1% of the survivors were discharged with sequelae. The vast majority of those who died or developed disabilities were children after bacterial meningitis. The mortality rate of bacterial meningitis was 13% and the disability rate 10.3%. With the concentration of patients to the Tartu University Children's Hospital, the mortality as well as the disability rates decreased dramatically during these 10 years, which shows that the concentration of patients to the tertiary care hospitals is necessary.

REFERENCES

Abrikossova NYu, Kostjukova NN [Epidemiology of neonatal meningitis.] Zh Microbiol Epidemiol Inf 1991; (2): 41–42 (Russ).

Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, Wenger JD Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. JAMA 1993; 269: 221–226.

Agrawal M, Bhandari NR. CSF glutamic oxalacetic transaminase levels in CNS infections. Indian Pediatr 1989; 26: 1245–1248.

Annegers JF, Hauser WA, Beghi E, Nicolosi A, Kurland T The risk of unprovoked seizures after encephalitis and meningitis. Neurology 1988; 38: 1407–1410.

Apak S, Kuremal N, Ozmen M Neurologische Dauerschäden bei bakterieller Neugeboren meningitis. Kinderarzt 1983; 10: 1234–1236.

Awapara M, Bhandari NR CSF glutamic oxalacetic transaminase levels in CNS infections. Indian Pediatrics 1989; 26: 1245–1248.

Bach F, Bach FW, Pedersen AG, Larsen PM, Dombernowsky P. Creatine kinase BB in the cerebrospinal fluid as a marker of CNS metastases and leptomeningealcarcinomatosis in patients with breast cancer. Eur J Cancer Clin Oncol 1989; 25: 1703–1709.

Baraff LJ, Lee SI, Schriger DL Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993; 12: 389–394.

Beaty HN, Oppenheimer S. Cerebrospinal fluid lactic dehydrogenase and its isoenzymes in infections of the central nervous system. N Engl J Med 1968; 279: 1197–1202.

Beghi E, Nicolosi A; Kurland LT; Mulder DW; Hauser WA; Shuster L Encephalitis and aseptic meningitis, Olmsted County, Minnesota, 1950–1981; I Epidemiology. Ann Neurol. 1984; 16: 283–294.

Bell AH, Brow D, Halliday HL, McLure G, McReid M Meningitis in the newborn — a 14 year review. Arch Dis Child 1989; 64: 873–874.

Belsey MA CSF GOT in acute bacterial meningitis. Am J Dis Child 1969; 117: 288–292.

Belton NR Creatine phosphokinase (CPK), blood and CSF levels in newborn infants and children. Arch Dis Child 1970; 45: 600.

Bennhagen R, Svenningsen NW, Bekassy AN Changing pattern of neonatal meningitis in Sweden: a comparative study 1976 vs 1983. Scand J Infect Dis 1987;19:587–593.

Bhatt S, Halpin C, Hsu W, Thediger BA, Levine RA, Tuomanen E, Nadol JB Hearing loss and pneumococcal meningitis: an animal model. Laryngoscope 1991; 101: 1285–1292.

Botsvadze ES, Brteschvadze TT [Clinical characteristics and management of pneumococcal meningitis.] Pediatria 1983; (1): 59–60 (Russ).

Boyde TR Serum levels of mitochondrial aspartate aminotransferase in myocardial infarction and muscular dystrophy. Enzymol Biol Clin 1968; 9: 385.

Briem H Cerebrospinal fluid in patients with meningitis and encephalitis. Academic dissertation, Stockholm 1982.
Brookhauser PE, Auslander MC Aided auditory thresholds in children with postmeningitic deafness. Laryngoscope 1989; 99: 800–808.
Bryan JP, Silva HR, Tavares A, Rocha H, Scheld WM Etiology and mortality of bacterial meningitis in Northeastern Brazil. Rev Inf Dis 1990; 12: 708–715.
Bödvarson A, Franzson L, Briem H Creatine kinase isoenzyme BB in the cerebrospinal fluid of patients with acute neurological diseases. J Internal Medicine 1990; 227: 5–9.
Carter PE, Parclay SM, Galloway WH, Cole GF Changes in bacterial meningitis. Arch Dis Child 1990; 65: 495–498.
Chartrand SA, Cho CT Persistent pleocytosis in bacterial meningitis. J Pediatrics 1976; 88: 424–426.
Chatterley S, Sun T, Lien Y Diagnostic value of lactate dehydrogenase isoenzymes in cerebrospinal fluid. J Clinical Laboratory Analyses 1991; 5: 168–174.
Cho HW, Prilipko L, Meltzer HY *et al* Isoenzymes of creatine phosphokinase in white blood cells. Experientia 1977; 33: 166–167.
Cibiras PP, Broslavski EI, Kelminskene SA [Etiology of bacterial meningitis in Lithuania.] Abstracts of the meeting Meningococcal infection and bacterial meningitis. Arhangelsk 1986: 45–47. (Russ)
Cizman M, Mozetic M, Radescek–Rakar R, Pleterski–Rigler D, Susec–Mitchieli M Aseptic meningitis after vaccination against measles and mumps. Ped Infect Dis J 1989; 8: 302–308.
David DHO, Hirsch MS Acute viral encephalitis. Med Clin North America 1985; 69: 415–429.
Delanghe JR, Winter HAD, Buyzere LD, Camaert JJ, Martens FE, Praeter ML Mass concentration measurments of creatine kinase BB isoenzyme as an index brain tissue damage. Clin Chimica Acta 1990; 193: 125–136.
Devjatkina NP, Djomina AA, Piluschkov AV [Epidemiology of meningococcal infection in USSR.] Zh Microbiol Epidemiol Immonobiol 1989; (12): 36–40.(Russ).
Djomina AA, Iljina TA [Etiology of the bacterial meningitis today.] Zh Microbiol Epidemiol Immunobiol 1985; (3): 3–6. (Russ)
Djomina AA, Pokrovski VI, Iljina TV, Larina LI, Devjatkina NP, Markova AI [Etiology of the bacterial meningitis.] Zh Micrrobiol Epidemiol Immunobiol 1984; (12): 32–36.(Russ).
Dodge PR Sequelae of bacterial meningitis. Pediatr Infect Dis J 1986; 5: 618–620.
Dodge PR, Davis H, Feigin RD Prospective evaluation of hearing impairment as a sequelae of acute bacterial meningitis. N Engl J Med 1984; 311: 869–874.
Etter CG; Wedgwood J; Schaad UB. Aseptische Meningitiden in Pädiatrie. Schweiz Med Wochenschrift 1991; 121: 1120–1126.
Feigin RD Bacterial meningitis beyond the neonatal period. in *R.D.Feigin and J.D.Cherry (eds.)*: Textbook of Pediatric Infectious Diseases. ed by 3rd ed. Saunders-Company 1992: 401–428.

Feigin RD, McCracken GH Jr, Klein JO Diagnosis and management of meningitis. Pediatr Infect Dis J 1992; 11: 785–814.
Feldman HM, Michaels RH Academic achievement in children ten to 12 years after *Haemophilus influenzae* meningitis. Pediatrics 1988; 81: 339–344.
Feldman WE Cerebrospinal fluid lactic acid dehydrogenase activity. Am J Dis Child 1975; 129: 77–80.
Feldmann WE, Ginsburg CM, McCracken GH, Allen D, Ahmann P, Graham J, Graham L Relation of concentrations of *Haemophilus influenzae* type b in cerebrospinal fluid to late sequelae of patients with meningitis. J Pediatrics 1982; 100: 209–212.
Florez G, Cabeza A, Gonzales JM, Garcia J, Ucar S Serum and cerebrospinal fluid enzymatic modifications in head injury. Fifth European Congress of Neurological Surgery. Oxford, 1975, Abstract 92.
Fortnum HM Hearing impairment after bacterial meningitis: a review. Arch Dis Child 1992; 67: 1128–1133.
Francis BM, Gilbert GL Survey of neonatal meningitis in Australia: 1987–1989. Med J Austr 1992; 156: 240–243.
Friebel D, Henker J, Fritsche F Hörstörungen bei Kindern mit Meningitis purulenta durch Ampicillin. Kinderärzl. Praxis 1984; 10: 465–469.
Fröber R, Müller G Epidemiologische und katamnestische Untersuchungen bei Meningitis purulenta im Kindesalter. Kinderärzl Praxis 1977; (5): 203–211.
Fuijnaga T, Motegi Y, Tamura H, Kuroume T A prefecture-wide survey of mumps meningitis associated with measles, mumps and rubella vaccine. Pediatr Infect Dis J. 1991; 10: 204–209.
Gamstrop I, Klockhoff I Bilateral, severe, sensoneural hearing loss after *Haemophilus influenzae* meningitis in childhood. Neuropediatrics 1974; 5: 121–124.
Gary N, Powers N, Todd JK Clinical identification and comparative prognosis of high-risk patients with *Haemophilus influenzae* meningitis. Am J Dis Child 1989; 143: 307–311.
Gilbert GL, Dickson KE, Waters MY, Kennet ML, Land SA, Sneddor M Outbreak of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. Ped Infect Dis J 1988; 7: 484–488.
Giustina D, Forese S, Pace P 20 anni (1960–1980) di meningite bacterica nell infanzia. Ped Med Chir 1985; 7: 195–202. (Italian)
Go KG, Patberg WR, Teelken AW, Gazendam J The Starling hypothesis of capillary fluid exchange in relation to brain edema. In Workshop on dynamic aspects of brain edema. Edited by H.M.Pappius. Spinger Verlag: New York, 1976.
Goetz O, Peller P Epidemiologie und Klinik der Meningokokken Infektion. Münch Med Wochenschrift 1980; (41): 1411–1412.
Grubbauer HM Risikofaktoren bei eitrigen Meningitides im Kindesalter. Klin Pädiatrie 1982; 194: 11–13.
Haldre S, Kaasik A-E, Piirsoo A [Brain-specific isoenzyme of creatine phosphokinase in the cerebrospinal fluid: its concentration and prognostic value in

patients with ischaemic damage of the brain]. Zh Nevrol Psikhiatr 1991; 91(7): 60–63 (Russ.)
Haldre SJ [Cerebral creatine kinase isoenzyme in the cerebrospinal fluid:importance of its measuring for prognosis of the disease outcome in cerebral ischemic disorders.] Academic dissertation. Tartu; 1988 (Russ).
Halsensten A, Pedersen SHJ, Haneberg B, Bjorvath B, Solberg CO Case fatality of meningococcal disease in Western Norway. Scand J Infect Dis 1987; 19: 35–42.
Hanna JN, Wold BE Bacterial meningitis in children under five years of age in Western Australia. Med J Australia 1991; 155: 160–164.
Harada T, Semba T, Suzuki M, Kikuchi S, Murofushi T Audiological characteristics of hearing loss following meningitis. Acta Otolarygol (Stockh.) 1988; 456: 61–67 (Suppl.).
Harrison CJ Rational selection of antimicrobials for pediatric upper respiratory infections. Pediatr Infect Dis J 1993; 12: S29–S36.
Havens PL, Garland JS, Brook MM, Troschinski J Trends mortality in children hospitalized with meningococcal infection 1957–1987. Ped Infect Dis J 1989; 8: 8–11.
Hayden GF, Preblod SR, Orenstein WA, et al. Current status of mumps and mumps vaccine in the United States. Pediatrics 1978; 62: 965–969.
Helin I, Widell A, Borulf S, Walder M, Ulmsten U Outbreak of coxsackievirus A-14 meningitis among newborns in maternity hospital ward Acta Paediatr Scand 1987; 76: 234–238.
Helwig H Duration of treatment of bacterial meningitis. in Bacterial meningitis ed by H.Schönefeld and H.Helwig. Antibiot Chemother 1992; 45: 153–160.
Hensel M, Gutjahr W, Kamin W, Schmitt HJ Meningitis bei 154 Kindern einer Kinderklinik in Deutschland: klinische und epidemiologische Aspekte. Klinische Pädiatrie 1992; 204: 163–170.
Iljina TV [Changing pattern of the etiology of bacterial meningitis during 10 years.] Abstracts of the conference "Meningococcal infection and bacterial meningitis" Novosibirsk 1990: 26–28 (Russ).
Jadavij T, Biggan WD, Gold R Sequelae of acute bacterial meningitis in children treated for seven days. Pediatrics 1986; 78: 21–25.
Jiang ZD, Liu XY, Wu YY, Zheng MS, Liu HC Long term impaiments of brain and auditory functions of children recovered from purulent meningitis. Dev Med Child Neurology 1990; 32: 473–480.
Kabany A, Jadavji T Sequelae of acute bacterial meningitis in children. in Bacterial meningitis. Edited by Schönefeld H. and Helwig H. Antibiot Chemother Basel, Karger. 1992; 45: 209–217.
Kaplan SL, Hawkins EP, Kline MW, Patrick GS, Mason EO Invasion of the inner ear by *Haemophilus influenzae* type b in experimental meningitis. J Infect Dis 1989; 159: 923–930.
Katz RM, Liebmann W Creatine phosphokinase activity in central nervous system disorders and infections. Am J Dis Child 1970; 120: 543–546.

Kilpi T, Anttila M, Kallio MJT, Peltola H Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. Pediatr Infect Dis J 1993; 12: 184–188.
Kirilenko VA, Martsinkovski LT, Sikov VP, Orihitsch LG [Morbidity and outcome of meningococcal infection.] Abstracts of the conference "Meningococcal infection and bacterial meningitis" Novosibirsk 1990: 47 (Russ).
Klatte–Meyer A, Primavesi CA, Schmiegel S, Farady AA, Mielens C Ergebnisse virologischen Untersuchungen bei 620 Kindern mit abakteriller Meningitis in 15 Jahren (1971–1985). Mschr Kinderheilkunde 1987; 135: 135–137.
Klein NJ, Feigin RD, McCracken GH Report of task force on diagnosis and management of meningitis. Pediatrics 1986; 78: 959–982.
Klein NJ, Heyderman RS, Levin M. Antibiotic choices for meningitis beyond the neonatal period. Arch Dis Child 1992; 67: 157–161.
Knight JA Early (chemical) diagnosis of bacterial meningitis – cerebrospinal fluid glucose, lactate and lactate dehydrogenase compared. Clin Chem 1981; 27: 1431–1434.
Koskiniemi M-L Malignancy markers in the cerebrospinal fluid. Eur J Pediatr 1988; 148: 3–8.
Koskiniemi M-L, Donner M, Pettay O Clinical appearance and outcome in mumps encephalitis in children. Acta Pediatr Scand 1983; 72: 603–609.
Koskiniemi M-L, Vaheri A Effect of measles, mumps, rubella vaccination on pattern of encephalitis in children. Lancet 1989; ii: 31–34.
Kostjukova NN, Korzhueva NA, Derkach SA, Bagirova LSh Merzenyuk ZA, Gulman LA, Volkova MO [Etiological structure of acute bacterial meningitis in different regions] Zh Mikrobiol Epidemiol Immunobiol 1992; (7–8); 14–17 (Russ)
Kühn E, Pfeifer G Keimspektrum der eitrigen Meningitis unter besonderer Errücksichtung des Patientengutes. Anäst Intesivther Notfallmed. 1987; 23: 39–44.
Kutsar K [Acute enteroviral neuroinfections and distribution of enteroviruses in Estionia] Academic Dissertation. Tallinn 1971 (Russ)
Kutsar K, Kuslap T, Jõgi A, Vall S Aseptilise meningiidi puhang Pärnus 1967 aastal. Nõukogude Eesti Tervishid 1968; (5): 326–328.
La Via WV, Marks MI Prolonged and secondary fevers in childhood bacterial meningitis. in Bacterial meningitis. Edited by Schönefeld H. and Helwig H. Antibiot Chemotherapy Basel, Karger 1992; 45: 201–208.
Lampl Y, Paniri Y, Eschel Y, Savora–Pinhas I LDH isoenzymes in cerebrospinal fluid in various brain tumors. J Neurol Neurosurg Psychatry 1990; 53: 697–699.
Landaas S, Lippe B Chemical analyses for early differential diagnosis between bacterial and viral meningitis. Scan J Clin Lab Invest 1985; 45: 525–529.
Laxer RM, Marks MJ Pneumococcal meningitis in children. Am J Dis Child 1977; 131: 850–853.

Lebel MH, McCracken GH Jr Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989; 83: 161–167.
Lennon D, Voss L, Sinclair J, Heffernan H An outbreak of meningococcal disease in Auckland, New Zealand. Ped Infect Dis J 1989; 8: 11–15.
Letson GW, Gellin BG, Bulkow LR, Parks DJ, Ward JI Severity and frequency of sequelae of bacterial meningitis in Alaska native infants. Correlation with a scoring system for severity of sequelae. Am J Dis Child 1992; 146: 560–566.
Lietz R, Handrick W, Rieske K Herpes simplex-virus Encephalitis im Kindesalter. Kinderärzl Praxis 1986; (5): 243–248.
Lin TY, Chrane DF, Nelson JD, McCracken GH Jr Seven days of ceftriaxone therapy is as effective as ten days treatment for bacterial meningitis. J Am Med Assoc 1985; 253: 3559–3563.
Lindquist L, Linne T, Hansson L-O, Kalin M, Axelson G Value of cerebrospinal fluid analysis in differential diagnosis of meningitis: a study in 710 patients with suspected central nervous system infection. Eur J Microbiol Infect Dis 1988; 7: 374–380.
Lütschg J Hearing disorders in meningitis. in Bacterial meningitis. Edited by Schönefeld H. and Helwig H. Antibiot Chemother Basel, Karger. 1992; 45: 218–225.
Maiuri F, Benvenuti D, Carrier P, Orefice G, Carbone M, Caradente M Serum and cerebrospinal fluid enzymes in subarachnoid hemorrhage. Neurological Research 1989; 11: 6–8.
Martin E, Hohl P, Guggi T, Kayser FH, Fernex M and members of the Swiss Multicenter meningitis study group: Short course, single daily dose ceftriaxone monotherapy for acute bacterial meningitis in children. 1. Clinical results. Infection 1990; 18: 70–77.
McCracken HM Jr. Current management of bacterial meningitis in infants and children. Pediatr Infect Dis J 1992; 11: 169–174.
McDonald JD, Moore DL, Quennec P Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. Ped Infect Dis J 1989; 8: 751–755.
McGee ZA, Baringer JR Acute meningitis. in *G.L.Mandell, R.G.Douglas, J.E.Bennett (eds)* : Principles and Praxis of infectious diseases. ed by 3rd ed. Churchill Livingstone 1990: 741–754.
Meade RH Bacterial meningitis in the neonatal infant. Med Clin North Am 1985; 69: 257–267.
Mertsola J, Kennedy WA, Waagner D, Saez–Llorens X, Olsen K, Hansen EJ, McCracken GH Jr Endotoxin concentration in cerebrospinal fluid correlate with clinical severity and neurologic outcome of *Haemophilus influenzae* type b meningitis. Am J Dis Child 1991; 145: 1099–1103.
Michaels RH, Ali O A decline in *Heamophilus influenzae* type b meningitis. J Pediatr 1993; 122: 407–409.

Maas AIR Cerebrospinal fluid enzymes in acute brain injury.1. Dynamics of changes in CSF enzyme activity after acute experimental brain injury. J Neurol Neurosurg Psychiatry 1977; 40: 655–665.
Maas AIR Cerebrospinal fluid enzymes in acute brain injury.2. Relation of CSF enzyme activity to extent of brain injury. J Neurol Neurosurg Psychiatry 1977; 40: 666–674.
Nand N, Sharma M, Saini DS, Khosla SN Gamma glutamyl transpeptidase in meningitis. J Assoc Physicians India.1992;40: 167–169.
Neeches W, Platt M Cerebrospinal fluid LDH in 287 children including 53 cases of meningitis at bacterial and nonbacterial etiology. Pediatrics 1968; 41: 1097–1100.
Nelson PV, Carey WF, Pollard AC Diagnostic significance and sources of lactate dehydrogenase and its isoenzymes in cerebrospinal fluid of children with variety of neurological disorders. J Clin Pathology1975; 28: 828–833.
Nesheim SR, Dean N Systemic *Haemophilus influenzae* disease in children. Clin Pediatrics 1986; 25: 605–609.
Nicolosi A, Hauser WA, Beghi E, Kurland LT Epidemiology of central nervous system infections in Olmsted County, Minnesota, 1950–1981. J Infect Dis 1986; 154: 399–408.
Odio CM, Faingezieht I, Paris M, Nassar M, Baltodano A, Rogers J, Saez–Llorens X, Olsen KD, McCracken GH Jr The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med. 1991; 324: 1524–1531.
Overkamp H, Berg M, Bumm P, Harns D Hörstörungen nach Meningitis purulenta. Klin Pädiatrie 1982; 194: 31–34.
Pasaglu A, Pasaglu H Enzymatic changes in the cerebrospinal fluid as indices of pathological change. Acta Neurochir (Wien) 1989; 97: 71–76.
Pecco P, Pavesio D, Peisino MG [Rational bases of current etiopathogenetic therapy of bacterial meningitis. Rewiev of the literature and personal experience in 122 pediatric cases.] Minerva Pediatr 1991; 43: 753–775. (Italian)
Peltola H, Anttila M, Renkonen O-V Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Lancet 1989; i: 1281–1287.
Peltola H, Kilpi T, Anttila M Rapid disappearance of *Haemophilus influenzae type B* meningitis after routine childhood immunisation with conjugate vaccines. Lancet 1992; 340: 592–594.
Peltola H, Rod TO, Jonsdottir K, Böttiger M, Cooldige JAS Life-threating *Haemophilus influenzae* infections in Scandinavia: a five-country analysis of the incidence and the main clinical and bacteriologic characteristics. Rev Infect Dis 1990; 12: 708–715.
Pfeiffer FE, Homburger HA, Yanagihara T Creatine kinase **BB** isoenzyme in CSF in neurologic diseases. Arch Neurol 1983; 40: 169–172.
Pokrovskaja NYa, Petrunin YuP [Bacterial meningitis due to *Haemophilus influenzae* in childhood.] Pediatria 1983; (7): 33–34. (Russ)

Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990; 323: 1651–1657.
Popovitsch PI, Lubarova LG [Isoenzymes of lactic dehydrogenase in the blood serum and cerebrospinal fluid in patients with bacterial and viral meningitis.] Abstracts of the meeting "Meningococcal infection and bacterial meningitis" Arhangelsk 1986: 203–205 (Russ)
Pototski A Puukentsefaliit Eestis. Nõukogude Eesti Tervishoid 1988; (2): 100–103.
Praeter CD, Vanhaesebrouck P, Govaert P, Delanghe J, Leroy J Creatine kinase isoenzyme BB concentrations in the cerebrospinal fluid of newborns: relationship to short term outcome. Pediatrics 1991; 88: 1204–1210.
Quagiliarello V, Scheld WM Bacterial meningitis: Pathogenesis, pathophysiology, and progress. N Engl J Med 1992; 327: 864–872.
Radetsky M Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of delay in diagnosis. Pediatr Infect Dis J 1992; 11: 694–698.
Radetsky M Duration of treatment in bacterial meningitis: a historical inquiry. Pediatr Infect Dis J 1990; 9: 2–9.
Radzavil GG, Roslõi IM, Abdalla ShA, Segedi SA [Enzymatic changes in the cerebrospinal fluid and brain injury in complicated forms of meningococcal infection.] Abstracts of the meeting "Meningococcal infection and purulent meningitis" Arhangelsk 1986: 1985–1989 (Russ.) .
Rantakallio P, Leskinenen M, von Wendt L Incidence and prognosis of central nervous system infections in a birth cohort of 12000 children. Scand J Infect Dis 1986; 18: 287–294.
Rantala H, Uhari M Occurrence of childhood encephalitis: a population based study. Pediatr Infect Dis J 1989; 8: 426–430.
Ratzan KR Viral meningitis. Med Clin North Am 1985; 69: 399–413.
Raudam E [Acute viral neuroinfections in Estonia] Academic Dissertation. Tartu 1967 (Russ.).
Raudam E, Tamm O, Vassiljeva K Puukentsefaliidi levik Eesti NSV-s. NET 1972; (5): 393–398.
Riekkinen PJ, Rinne UK Enzymes of human cerebrospinal fluid in normal conditions and neurological disorders. Turku, 1970.
Rieske K, Spencker FB, Handrick W Infektion durch *Haemophilus influenzae*. Pädiatrie und Grenzgebiete 1985; (4): 289–293.
Roca J, Campos J, Monso G, Trujillo G, Riverola A, Suris JC, Garcia–Tornel S, Barnadas M [Meningitis in pediatrics. Clinical and epidemiological study of 173 cases]. Enferm Infecc Microbiol Clin 1992; 10: 79–88 (Spanish).
Rodewald LE, Woodin KA, Szilagy PG, Arvan DA, Raubertas RF, Powell KR Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. J Pediatrics 1991; 119: 363–369.
Rorabaugh ML, Berlin LE, Heldrich F, Roberts K, Rosenberg LA, Doran T, Modlin JF Aseptic meningitis in infants younger than 2 years of age: acute illness and neurologic complications. Pediatrics 1993; 92: 206–211.

Rosenthal J, Dagan R, Press J, Sofer S Differences in the epidemiology of childhood community acquired bacterial meningitis between two ethnic populations cohabiting in one geographic area. Pediatr Infect Dis J 1988; 7: 630–633.

Roslõi IM [Biochemical changes in the blood serum and cerebrospinal fluid in patients with severe pneumococcal infection.] Sov Medicina 1991; (4): 74–76 (Russ)

Roslõi IM [Biochemical changes in the cerebrospinal fluid and blood sera in patients with meningococcal infection and bacterial meningitis.] Academic dissertation. Moscow 1991 (Russ).

Roslõi IM [Enzymatic changes in the cerebrospinal fluid in patients with pneumococcal and meningococcal meningitis.] Zh Nevrol Psikhiatr 1991; 91: 50–54. (Russ.)

Salih MAM, Hag AIE, Ahmed HS, Bushara IY, Yasin I, Omer MIA, Hofvander Y, Olcen P. Endemic bacterial meningitis in Sudanese children. Etiology, clinical findings, treatment and short-term outcome. Ann Trop Paediatr 1991; 11: 243–248.

Salih MAM, Khaleefa OH, Bushara M, Taha ZB, Musa ZA, Kamil I, Hofvander Y, Olcen P Long term sequelae of childhood acute bacterial meningitis in a developing country: a study from the Sudan. Scand J Infect Dis 1991; 324: 1525–1531.

Salwen KM, Vikerfors T, Olcen P Increased incidence of childhood bacterial meningitis: a 25-year study in a defined population in Sweden. Scand J Infect Dis 1987; 19: 1–11.

Samsõgina GA, Dias KE, Tserskaja RS, Dorbiva OS [Clinical characteristics and etiology of neonatal meningitis.] Abstractsof the meeting "Meningococcal infection nad bacterial meningitis". Arhangelsk, 1986: 152–154 (Russ)

Sander V, Talvik T Motor and mental disability in children with epilepsy. Abstracts of the second International Conference of Baltic Child Neurology Association. Riga 1993: 54

Schattuck KE, Chonmaitree T The changing spectrum of neonatal meningitis over a fifteen – year period. Clin Pediatr (Phila) 1992; 31: 130–136.

Scheibe J, Schulz KR Diagnostische Aspekte bei der Meningitis und Enzephalitis. Das Deutsche Gesundheitswesen 1983; 43: 1687–1691.

Schaad UB Etiology and management of neonatal bacterial meningitis. in Bacterial meningitis. Edited by Schönefeld H. and Helwig H. Antibiot Chemother Basel, Karger 1992; 45: 192–200

Schaad UB, Suter S, Gianella–Borradori A, Pfenninger J, Auckenthaler R, Bernath O, Cheseaux JJ, Wedgwood J A comparison of cephtriaxone for treatment of bacterial meningitis in children. N Engl J Med 1990; 322: 141–147.

Sell SHW Long-term sequelae of bacterial meningitis in children. Pediatr Infect Dis J 1983; 2: 90–93.

Sell SHW, Webb WW, Pate JE Psychological sequelae to bacterial meningitis. Two controlled studies. Pediatrics 1972; 49: 212–217.

Sirkis SI [Enzymes levels in the cerebrospinal fluid and blood sera in patients with meningitis and their importance in differential diagnosis.] Zh Nevropatol Psikhiatr 1982; 82: 193–197 (Russ).
Smirnov VV, Skoriakov VI, Popov AS, Shestakova TI, Khotko LP [Creatine phosphokinase in the cerebrospinal fluid of patients with acute meningitis.] Vrach Delo 1989; Jul.(7): 112–113 (Russ) .
Sugiora A, Yamada A Aseptic meningitis on a complication of mumps vaccination. Pediatr Infect Dis J 1991; 10: 209–213.
Sööt A [Clinical, biochemical and computed tomographical investigation of the central nervous system in premature babies.] Academic Dissrtation. Tartu, 1989 (Russ).
Talvik T Hypoxic-ischemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Academic dissertation. Tartu 1992: 37–45.
Tammpere AJ, Talvik TA, Kaasik A-E [Changes in biochemical parameters of cerebrospinal fluid and blood in newborns with spastic conditions.] Pediatria 1987: 81–84 (Russ).
Tardieu M, Dussiax E, Lebon P, Landrieu P Etude prospective de 59 meningites virales de L'enfant. Arch Fr Pediatr 1986; 43: 9–14.
Taylor HG, Mills EL, Ciampi A, Berger RD, Watters GV, Gold R, McDonald N, Michaels RH The sequelae of *Haemophilus influenzae* meningitis in scool-age children. N Engl J Med 1990; 323: 1657–1663.
Thompson APJ, Hart CA, Sills JA Meningococcal disease in Liverpool children 1977–1987: mode of presentation. Ped Rev Commun 1990; 5: 109–116.
Thompson RJ, Graham JG, McQeen INF et al. Radioimmunoassay of brain types creatine kinase-BB isoenzymes in human tissues and in serum of patients with neurological disorders. Neurol Sci 1980; 47: 241–251.
Thompson RJ, Kynoch PAM, Sarjant J Immunohistochemical localisation of creatine kinase-BB isoenzyme to astrocytes in human brain. Brain Res 1980; 201: 423–426.
Tikhomirov E Meningococcal meningitis: global situation and control measures. Wld Health Statist Quart. 1987; 40: 98–109.
Trollfors B *Haemophilus influenzae* meningitis in Sweden. Arch Dis Child 1987; 62: 1220–1223.
Tulmin E Mädaste meningiitide etioloogiast ja ravist. Nõukogude Eesti Tervishoid 1961; (5): 13–15.
Tuncer AM, Gür I, Ertem U, Ece A, Türkmen S, Deniz B, Gurman I, Tuncer S Once-daily ceftriaxone for meningococcemia and meningococcal meningitis. Pediatr Infect Dis J 1988; 7 ; 711–713.
Valmari P, Kataja M, Peltola H Invasive *Haemophilus influenzae* and meningococcal infection in Finland. Scand J Infect Dis 1987; 19: 19–27.
Vassilenko VA, Pototski AA, Tsernosova MG [Tick-borne encephalitis in Estonia.] Zh Microbiol Epidemiol Immunobiol 1990; (9): 43–47. (Russ).
Vienny H, Despland PA, Lütschg J Early diagnosis and evolution of deafness in childhood bacterial meningitis: a study using brainstem auditory evoked potentials. Pediatrics 1984; 73: 579–586.

Viladrich PF, Pallares R, Ariza J, Rufi G, Gudiol F Four days of penicillin therapy for meningococcal meningitis. Arch Intern Med 1986; 146: 2380–2382.
Voss L, Lennon D, Sinclair J The clinical features of pediatric meningococcal disease in Auckland 1985–1987. N Zealand Med J 1989; 102: 243–245.
Vaagenes P, Kjehus J, Torvik A The relationship between cerebrospinal fluid creatine kinase and morphologic changes in the brain after transient cardiac arrest. Circulation 1980; 61: 1194–1199.
Wagner N, Staab D, Rohskamp R Zerebrale Komplikationen bei Varicellen: Fallbericht und Übersicht. Klin Pädiatrie 1987; (5): 312–324.
Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV and the Bacterial Meningitis Study group. Bacterial meningitis in the United States, 1986: Report of a multistate surveillance study. J Infect Dis 1990; 162: 1316–1323.
Wiedemann G, Böttcher R, Lindenau B, Menzel K Die Bestimmung der Kreatinkinase – Isoenzym – Unterheiten CK-MB und CK-BB. Zeitschrift Med Lab Diagnostik 1989; 30: 104–107.
Wildin S, Chonmaitru F The importance of the virology laboratory in the diagnosis and management of viral meningitis. Am J Dis Child 1987; 141: 454–457.
Wood M, Anderson M Neurological infections. WB Saunders Company. London, Philadelphia, Toronto, Sidney, Tokyo 1988.
Worley G, Lipman B, Gewolb IH, Green JA, Schmechel DE, Roe CR, Gross SJ Creatine kinase brain isoenzyme: relationship of cerebrospinal fluid concentration to the neurologic condition of newborns and cellular localization in the human brain. Pediatrics 1985; 76: 15–21.
Yamashita K, Miyamura K, Yamadera S, Kato N, **Akatsuka M, Inouye S, Yamazaki S.** Enteroviral aseptic meningitis in Japan, 1981–1991. A report of the National Epidemiological Surveillance of infectious agents in Japan. Jpn J Med Sci Biol. 1992; 45: 151–161.
Zaki M, Daoud AS, Saleh AlQ, Abd Alrasool MM Bacterial meningitis in the newborn: a Kuwait experience. J Tropical Pediatr 1990; 36: 63–65.
Zakim D Evaluation of hepatic function. Biochemical tests for liver disease. in Hepatology: a textbook of liver disease. ed by D.Zakim et T.D.Boyer Philadelphia, London, Toronto 1982: 598–612.

KESKNÄRVISÜSTEEMI PÕLETIKULISED HAIGUSED LASTEL. (KLIINILIS-EPIDEMIOLOOGILINE ISELOOMUSTUS JA KAUGTULEMUSED)

Kokkuvõte

Kesknärvisüsteemi põletikulised haigused (meningiidid ja entsefaliidid) kuuluvad oma tõsise lõppe tõttu raskeimate nakkushaiguste hulka lapseeas. Uute antimikroobsete ravimite kasutuselevõtu ja intensiivravi arenguga on bakteriaalse meningiidi suremus tänapäeval arenenud maades langenud 3–7%-ni, kuid 17–26%-l paranenutest esinevad haiguse põdemise järgselt jääk-nähud, nagu kuulmishäired, epilepsia ja psühhomotoorse arengu peetus (Salwen ja k.a. 1987; Valmari ja k.a. 1987; Carter ja k.a. 1987). Viimastel aastatel on paljudes arenenud maades haigestumus bakteriaalsesse meningiiti märgatavalt langenud, mida peamiselt seostatakse Hib infektsiooni vastase vaktsineerimisega (Peltola et al. 1992). Eestis on mädaste meningiitide etioloogiat ja ravi aastatel 1921–1958 kirjeldanud E.Tulmin (1961). Enim on uuritud aseptilise meningiidi ja puukentsefaliidi epidemioloogiat (Raudam, 1967; Kutsar, 1971; Raudam ja k.a. 1972; Vassilenko ja k.a. 1990), kuid andmeid selle kohta missugune on kesknärvisüsteemi põletikuliste haiguste esinemisagedus, etioloogiline struktuur ja prognoos lastel Eestis tänapäeval publitseeritud ei ole.

Meningiidi prognoos sõltub peamiselt õigeaegsest diagnoosist ja adekvaatsest ravist. Sageli osutuvad igapäevases diagnostikas kasutuselolevad rutiinmeetodid (leukotsüütide arvu, suhkru ja valgu kontsentratsiooni määramine seljaajuvedelikus) väheinformatiivseks eriti just prognoosi hindamise seisukohalt (Lindquist ja k.a. 1988). Eelnevad uurimused on näidanud, et aju haiguste korral, millega kaasneb hüpoksia ja nekroos, tõuseb intratsellulaarsete fermentide kontsentratsioon seljaajuvedelikus (Riekkinen ja k.a. 1970; Maas, 1977; Nelson ja k.a. 1975; Landaas ja k.a. 1985; Talvik, 1992). Andmed nende kasutamisest kesknärvisüsteemi põletike diagnostikas ja haigete prognoosi hindamisel on kirjanduses vasturääkivad. Samuti puudub kirjanduses ühene vastus küsimusele, kui kaua ravida bakteriaalset meningiiti. Enamuse käsiraamatute (Feigin ja k.a. 1992; McCracken ja k.a. 1992) soovitus antibakteriaalse ravi kestuse kohta — 7 päeva meningokokilise, 10 päeva hemofiiluse ja 14 päeva pneumokokilise meningiidi korral — ei põhine mitte kontrollitud kliinilistel uuringutel, vaid lihtsalt arvamustel (Radetsky, 1992). Ometi on mõned autorid näidanud, et lühemad antibakteriaalse ravi kuurid on sama efektiivsed, eriti menigokokilise meningiidi korral, võimaldades haigete ravi muuta tunduvalt odavamaks (Lin ja k.a. 1985; Tuncer ja k.a. 1988; Pecco ja k.a. 1991).

Antud töö *eesmärgiks* oli:

— analüüsida retrospektiivselt kesknärvisüsteemi põletike epidemioloogiat Lõuna Eesti lastel aastatel 1980–1989;

— määrata mõnede intratsellulaarsete fermentide (AST, LDH, GGT, CPK, CK-BB) aktiivsust/ kontsentratsiooni seljaajuvedelikus ning hinnata nende prognostilist tähtsust;

— uurida bakteriaalse meningiidi lühi- ja pikaaegset prognoosi ning teha kindlaks ägeda perioodi sümptoomid, mis omavad prognostilist tähtsust;

— hinnata 5-päevase antibakteriaalse ravi efektiivsust bakteriaalse meningiidi ravis lastel;

Aastatel 1980–1989 registreeriti Lõuna Eestis kesknärvisüsteemi põletikke 573 lapsel, nendest 223 olid bakteriaalsed ja 350 aseptilised meningiidid ja entsefaliidid. Seega haigestumus bakteriaalsesse meningiiti oli 25,8/100 000 lapse kohta. Aseptilise meningiidi ja puukentsefaliidi sagedus oli vastavalt 29,8 ja 7,6/100 000 lapse kohta. Neonataalne meningiit esines sagedusega 0,42/1000 elusalt sündinu kohta. Nii bakteriaalne kui ka aseptiline meningiit esinesid ühtlase sagedusega kogu Lõuna Eestis, kuid puukentsefaliiti täheldati vaid Peipsi järve ümbritsevates piirkondades s.t. Tartu linnas ja maakonnas ning Jõgeva maakonnas. Valdav osa bakteriaalse meningiidi juhte (84,3%) diagnoositi alla 5 aasta vanustel lastel, seevastu aseptilisse meningiiti ja puukentsefaliiti haigestusid peamiselt koolilapsed, kes moodustasid vastavalt 80,2% ja 95,4% haigetest. Mädase meningiidi juhud esinesid aastaringselt ühtlase sagedusega, kuid aseptilise meningiidi ja puukentsefaliidi sagedus tõusis oluliselt suve- ja sügiskuudel s.t. ajal, mil ühelt poolt on puugid aktiivsed ja teisalt esineb enteroviiruslike nakkuste kõrgperiood. Bakteriaalse meningiidi etioloogilises struktuuris, sarnaselt andmetele endisest Nõukogude Liidust, prevaleerus *Neisseria meningitidis* 34,9%-ga, *Steptococcus pneumoniae* ja *Haemophilus influenzae* esinesid vastavalt 4,4% ja 4,0% haigetest, kuid 1980ndate aastate lõpuks täheldati Hib osatähtsuse tõusu meningiiditekitajate hulgas. Neonataalse meningiidi tekitajatena olid valdavaks Gram-negatiivsed tinglikult patogeensed mikroobid, milledest *E. coli* esines kõige sagedamini. Kahjuks jäi aseptilise meningiidi etioloogia 95,4% juhtudest ebaselgaks.

Kesknärvisüsteemi põletike letaalsus uurimiperioodi vältel oli 5,4% ning 4,1% põdenutest jäid invaliidiks, halvim oli sealjuures bakteriaalse meningiidi prognoos — letaalsus 9% ja invaliidsus 7,1%. Tõsiseks probleemiks oli neonataalne meningiit oma kõrge letaalsuse ja invaliidsuse tõttu vastavalt 45,8% ja 53,8%. Bakteriaalse meningiidi kaugprognoosi hinnati vähemalt 3 aasta möödudes 84 bakteriaalset meningiiti põdenud lapsel. 80% uuritutest olid täiesti terved, 13,3% esinesid kerged kõrvalekalded normist ning 6,6% olid invaliidid. Sagedaseimateks jääknähtudeks olid motoorika häired ning kuulmislangus esinedes vastavalt 11,9% ja 8,3%-l lastest, epilepsiat ja vaimse arengu mahajäämust diagnoositi 4,7% uuritutest. Antud uurimus leidis statistiliselt tõenäose seose väljakirjutamisel esinevate neuroloogiliste komplikatsioonide ja hilisemate jääknähtude (välja arvatud epilepsia) vahel ($p<0,005$). Seega on haigete prognoosi võimalik määrata juba väljakirjutamisel ning edasist jälgimist bakte-

riaalse meningiidi järgselt vajavad vaid neuroloogilise sümptomatoloogia (ataksia, lihastoonuse muutused) või kuulmishäiretega lapsed.

Intratsellulaarsete fermentide (LDH, AST, GGT, CPK ja CK-BB) aktiivsust/konsentratsiooni määrati seljaajuvedelikus 25 bakteriaalse, 16 aseptilise meningiidiga haigel ning 15 meningismiga lapsel. Bakteriaalse meningiidi korral oli haiguse alguses AST ja GGT aktiivsus liikvoris olulist kõrgem võrreldes aseptilise meningiidi ja meningismiga ($p<0,05$). Kõikide intratsellulaarsete fermentide aktiivsus seljaajuvedelikus langes ravi käigus. Huvitav on märkida, et CK-BB isoensüümi kontsentratsioon liikvoris oli haiguse alguses tõusnud nii bakteriaalse kui ka aseptilise meningiidi aga ka meningismi haigetel. Prognostilist tähtsust omas AST ja LDH aktiivsuse tõus haiguse alul, olles tunduvalt kõrgem neil, kes surid või invaliidistusid ($p<0,05$). Samas esinesid antud uurimuses halva prognoosiga haiged, kelle seljaajuvedeliku intratsellulaarsete fermentide aktiivsus oli madal. See näitab, et ensüümuuringute tähtsust liikvoris ei tohi üle hinnata, kuna haigete prognoos ei sõltu ainult protsessi ulatusest, vaid ka asukohast ja nimelt ka minimaalne elutähtsate piirkondade kahjustus võib olla prognostiliselt väga tõsine.

Antud uurimus näitas, et 5-päevane antibakteriaalne ravi 23-l meningokokilise, 7-l hemofiilus ja 5-l pneumokokilise meningiidi haigel lapsel oli sama efektiivne kui pikem ravi, kusjuures hospitaliseerimise aeg oli tunduvalt lühem 5-päevase ravi korral ($p<0,005$).

Kokkuvõtteks võib öelda, et kesknärvisüsteemi põletikud ei ole küll sagedased haigused, kuid nende lõpe on endiselt tõsine. Prognostiliselt osutuvad ebasoodsaks nii intratsellulaarsete fermentide (AST, LDH) kõrge aktiivsus seljaajuvedelikus haiguse alul kui ka väljendunud neuroloogilise sümptomatoloogia esinemine haiglast väljakirjutamisel. Mittekomplitseeritud meningokokilise meningiidi raviks lastel on 5-päevase antibakteriaalse ravi küllaldane, kuid haigete väikese arvu tõttu antud uuringus me ei saa seda soovitada pneumokokilise ja hemofiilus meningiidi haigetele.

ACKNOWLEDGEMENTS

This work was carried out at the Department of Pediatrics, Tartu University Children's Hospital and at the All Union Institute of Epidemiology during the years 1989–1994.

I wish to express my sincere gratitude to:

My supervisor, Professor Tiina Talvik, who introduced me to pediatric neurology and clinical research. She inspired me to undertake this work with her wide knowledge of pediatric neurology. I am especially indebted to her skilful review of the manuscript and the suggestion to improve it.

An essential part of this study has been performed under the supervision of Professor Anna Djomina in Moscow. She introduced me into the field of the epidemiology of infections in the central nervous system. Her advice and positive criticism have been invaluable for the completion of the first part of this work.

Dr. Endla Kööbi, who encouraged me to do this study and supported me throughout the years.

Dr. Margit Närska for her stimulating support in patients care and collaboration during the follow-up study.

My co-workers from the departments of infection diseases, neonatology and intensive care: Aime Pütsepp, Aasa Gontmacher, Siiri Torm, Eda Tamm, Marja-Liis Mägi, Anne Ormisson, Lea Maipuu, Viktor Rüütel, Ever Kütt, Ilmar Kutman and Tuuli Kokk for their friendly support and help in collecting specimens from the patients.

Dr. Milvi Topmann and Mare Kiisk, for kindly sharing their knowledge and putting laboratory resources at our disposal during the enzymes studies.

Dr. Sulev Haldre, for his valuable help in creatine-kinase studies.

My colleagues pediatricians from the district hospitals of South-Estonia: Aasa Põder, Aime Olesk, Mare Udras, Kai Tamm and Mare Parik for their help in collecting epidemiological data

Dr. Toomas Siirde, for sharing his knowledge and performing audiometric investigations.

Mrs. Tiiu Soopõld, speech therapist, for her skilful help in studying the speech development.

Dr. Kaljo Mitt, chief of the hospital, for his friendly support throughout the study.

Professor Marika Mikelsaar, head of the Institute of Microbiology, for kindly sharing her knowledge in microbiology, for critical reading of the manuscript as well as giving warm support.

All the patients and also their parents, for their kind co-operation during the follow-up study.

My friend Jutta Köhler and Mrs. Terje Keldoja and Mrs. Kersti Unt for revising most of my English.

Mrs. Liina Mai Tooding for her support and advice in the statistics.

Mr. Argo Kõvamees, gratefully acknowledged for his support. It came when it was most needed.

All my friends and co-workers at Tartu University Children's Hospital for their fruitful and everlasting struggle to treat infectious diseases in children.

Finally, I am greatly indebted to my aunt, Katrin and Lauri for creating a positive atmosphere to live in, which considerably stimulated my work.

PUBLICATIONS

I

Eesti Arst 1993; 6: 408–413

Eesti Arst, 1993, 6, 408-413

UDK 616.981.232-036.2(474.2)«1980/1991»

Mädase meningiidi epidemioloogia Lõuna-Eesti lastel aastail 1980...1991

Irja Lutsar • Tartu
Aasa Põder • Valga
Aime Olesk • Jõgeva
Mare Udras • Võru
Kai Tamm • Põlva

mädane meningiit, vastsündinu meningiit, esinemissagedus, meningokokkinfektsioon, letaalsus, invaliidsus

Vaatamata meditsiini arengule ja järjest uute mikroobidevastaste ravimite kasutuselevõtule, on mädane meningiit jäänud tõsiseks lapseea probleemiks. Ka viimastel aastatel on letaalsus bakteriaalse meningiidi tagajärjel püsinud 1,8...12% piires (4, 5, 17, 18). Eestis on mädase meningiidi epidemioloogiat veel vähe uuritud, viimased kirjanduse andmed pärinevad 1961. aastast (22). Ametlikule registreerimisele on siiani kuulunud vaid meningokokkmeningiidi juhud.

Käesoleva töö eesmärk oli uurida lapseea mädase meningiidi epidemioloogiat, etioloogilist struktuuri, haigusest põhjustatud letaalsust ning invaliidsusjuhte Lõuna-Eestis aastail 1980...1991.

Uurimismaterjal ja -metoodika. Uurimine korraldati Lõuna-Eestis (Tartu linn, Tartu, Jõgeva, Põlva, Valga ja Võru maakond), kus keskmine elanike arv sel ajal oli 400 000, neist lapsi 86 000. Linna- ja maaelanike suhe oli 1:1. Uuriti haiguslugusid, lahanguprotokolle ning haiglate ja osakondade aastaaruandeid ajavahemikust 1980...1991. Uurimisrühma kuulusid 0...14 aasta vanused mädast meningiiti põdenud, keda oli ravitud Lõuna-Eesti maakondade keskhaiglates, Tartu Kliinilises Haiglas, Tartu Linna Nakkushaiglas või Tartu Lastekliinikus ja kes elasid nimetatud piirkonnas. Mädase meningiidi diagnostiliseks kriteeriumiks oli kas mikroobi leidmine seljaajuvedelikus või liikvori pleotsütoos üle 100 raku milliliitris.

Haigusluguside ja lahanguprotokolle analüüsiti retrospektiivselt järgmiste tunnuste alusel: lapse vanus, sugu, elukoht, haigestumise aeg, haiguse tekitaja, haiguse kestus ja lõpe. Eraldi analüüsiti mädase meningiidi esinemissagedust, etioloogilisi faktoreid ja lõpet aastail 1980...1986 ja 1987...1991. Demograafilised andmed on saadud Eesti Tervishoiuministeeriumi statistikakogumikest (1980...1991).

Uurimistulemused ja arutelu. Ajavahemikul 1980...1991 diagnoositi mädast meningiiti 250 Lõuna-Eesti lapsel. Nendest 29 olid 0...29 päeva vanused ja 221 last 30 päeva kuni 15 aasta vanused

Tabel. Mädase meningiidi etioloogiline struktuur eri vanuses lastel aastail 1980...1991

Tekitaja	Vanus											
	0...29 päeva	(%)	0...11 kuud	(%)	0...4 aastat	(%)	5...9 aastat	(%)	10...14 aastat	(%)	Kokku	(%)
Neisseria meningitidis	2	(6,8)	39	(30,0)	74	(35,0)	8	(33,3)	6	(50,0)	88	(35,2)
Streptococcus pneumoniae	1	(3,4)	8	(6,2)	10	(4,7)	1	(4,1)	—		11	(4,4)
Haemophilus-influenzae B	—		7	(5,4)	9	(4,2)	2	(8,3)	—		11	(4,4)
Tinglikult patogeenne mikrofloora	14	(48,2)	17	(13,2)	17	(8,0)	—		—		17	(6,8)
Muud	1	(3,4)	3	(2,3)	3	(1,4)	—		—		3	(1,2)
Tundmata	11	(37,9)	62	(48,4)	101	(47,8)	13	(54,1)	6	(50,0)	120	(48,0)
Kokku (%)	29	(11,6)	136	(51,2)	214	(85,6)	24	(9,6)	12	(4,8)	250	(100)

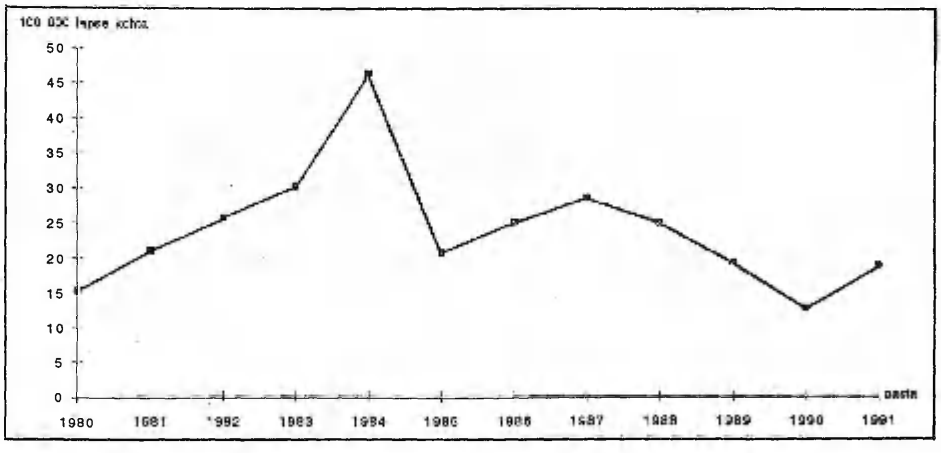
(*excl.*). Haigestumus moodustas 23,5 100 000 lapse kohta, kõikudes 12,7-st 1990. aastal 46,5-ni 1984. aastal (vt. joonis 1). Haigestumus oli kõige suurem Põlva ja Viljandi maakonnas ning kõige väiksem Tartu linnas, vastavalt 41,1, 37,0 ja 20,3 juhtu 100 000 lapse kohta. Poiss- ja tütarlaste suhe oli 1,7:1 ning maa- ja linnalaste suhe 1,3:1.

Meningiidi esinemissagedus vastsündinute hulgas oli 0,41 juhtu 1000 elusalt sündinu kohta, kõige väiksem oli see 1980. ja 1985. aastal, mil ei diagnoositud ühtegi haigusjuhtu, ja kõige suurem 1986. aastal, mil diagnoositi 1,16 juhtu 1000 kohta. 29 vastsündinust haigestus kuue esimese elupäeva jooksul 15 (50%) ilmse intrauteriinse või intranataalse infektsiooni tõttu. 3 last haigestus esimese elukuu jooksul kodus ning 12 last (40%) nakatus intensiivraviosakonnas või vastsündinute osakonnas. Nende puhul on ilmselt tegemist haiglasisese nakkusega.

Enamik mädase meningiidi juhte (85,6%) esines alla viieaastastel lastel, kusjuures 51,2% haigetest olid esimese eluaasta lapsed. Vanemas eas esines vaid üksikuid haigusjuhte (vt. tabel). Peamine mädase meningiidi tekitaja oli *Neisseria meningitidis*, mis põhjustas 1/3 haigusjuhtudest kõigis vanuserühmades, välja arvatud vastsündinuiga. *Streptococcus pneumoniae* ja *Haemophilus influenzae* B esinesid võrdse sagedusega, põhjustades 4,4% mädastest meningiitidest. Suur oli tundmatu tekitajaga haigusjuhtude arv (48%), eriti esimese viie uurimisaasta jooksul (vt. joonis 2). Uurimise lõpp-perioodil (ajavahemikul 1987...1991) paranesid bakterioloogilise diagnoosimise võimalused tunduvalt ning vaid 1/4-l juhtudest jäi mädase meningiidi tekitaja avastamata. Võrreldes bakteriaalse meningiidi tekitajaid 1980-ndate aastate algul ja lõpul, selgub, et mõlemal perioodil oli peamiseks haigusetekitajaks *Neisseria meningitidis*, põhjustades vastavalt 22,9% ja 51,3% haigusjuhtudest.

Haemophilus influenzae osatähtsus bakteriaalse meningiidi etioloogias suurenes 1,4%-lt uurimise algperioodil 16,8%-le selle lõpul.

Mädase meningiidi etioloogia vastsündinueas lastel oli erinev. Uuritud ajavahemikul oli 48,2%-l juhtudest haiguse tekitajaks tinglikult patogeenne floora: *E. coli* 8 juhul, *Staphylococcus aureus* 2 juhul, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Streptococcus* B ja *Citrobacter freundii* igaüks ühel juhul. Klassikalisi meningiidi tekitajaid — *Neisseria meningitidis*, *Haemophi-*



Joonis 1. Bakteriaalse meningiidi esinemissagedus Lõuna-Eesti lastel aastail 1980...1991.

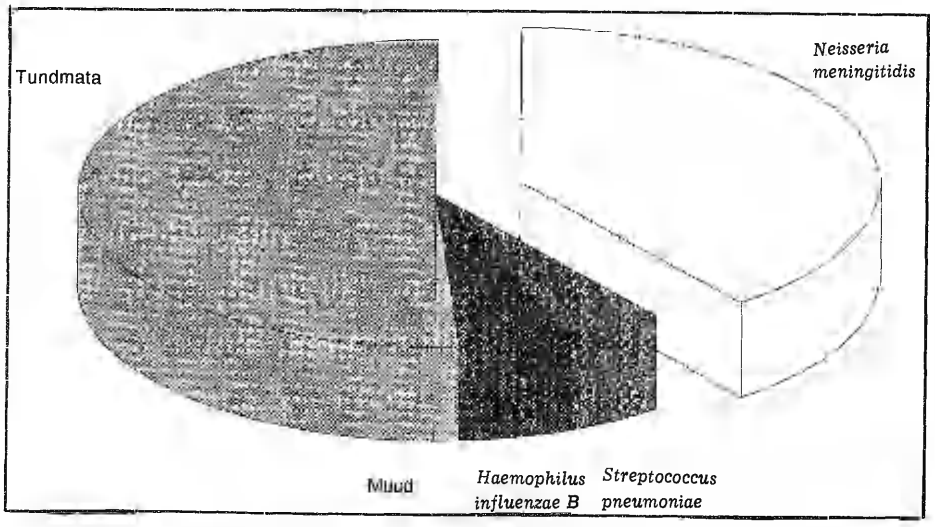
lus influenzae B ja *Streptococcus pneumoniae* — esines kolmel juhul (vt. joonis 3).

Ajavahemikul 1980...1991 suri mädase meningiidi tagajärjel 30 last (letaalsus 12%), neist 11 vastsündinut. Seega oli letaalsus bakteriaalse meningiidi tagajärjel vastsündinuperioodil 37,9% ja alates teisest elukuust 8,5%. Suurimat letaalsust täheldati tinglikult patogeense mikrofloora põhjustatud meningiidi tagajärjel (41,1%), järgnesid pneumokokkmeningiit (18,1%), tundmatu etioloogiaga (10,0%) ja *Haemophilus influenzae* B meningiit (9,0%). Väikseim oli letaalsus meningokokkmeningiidi korral (6,8%).

Raskeid neurootilisi jääknähte esines 21 lapsel, s.o. 9,1%-l ellujäänuist, nendest 8 olid vastsündinud (27,5%) ja 13 (6,4%) üle ühe kuu vanused lapsed. Sagedamini oli invaliidsuse põhjuseks progresseeruv hüdrotsefaalia, mis tekkis 9 lapsel; kahel lapsel täheldati kliiniliselt olulist kuulmise nõrgenemist, kolmel lapsel arenes epilepsia ning 7 lapsel hemi- või tetraparees koos tunduva psühhomotoorse arengu mahajäämusega. 2/3-l lastest oli mitu sündroomi üheaegselt.

Uurimise algperioodi (1980...1986) andmeid lõpp-perioodi (1987...1991) andmetega võrreldes täheldasime üle ühe kuu vanuste laste puhul nii letaalsuse langust kui ka invaliidsusjuhtude vähenemist vastavalt 11,8%-lt 2,6%-le ja 7,6%-lt 2,6%-le. Samal ajal jäid neonataalse meningiidi ravi tulemused kogu uurimise ajaks muutumatuks.

Arutelu. Mädase meningiidi haigestumus Lõuna-Eestis 1980-ndail aastail — 23,5 juhtu 100 000 lapse kohta — oli üsna sarnane haigestumusega kapitalistlikes riikides, näiteks Šotimaal 17,8 (4) ja Rootsis 22,4 juhtu 100 000 lapse kohta (18). Madala sotsiaal-majandusliku tasemega elanike hulgas on täheldatud tunduvalt suuremat haigestumust. Nii oli haigestumus Ameerika indiaanlaste hulgas ja Aafrikas vastavalt 180 ja 517 juhtu 100 000 elaniku kohta (20, 23). Nüüdisajal on paljudes riikides alustatud vaktsineerimist *Haemophilus influenzae B* vastu. Seoses sellega on näiteks Soomes bakteriaalse meningiidi haigestumus oluliselt vähenenud, sest meningiiditekitajate hulgas on seal esikohal *Haemophilus influenzae B* (15). Arenenud riikides on mädane meningiit põhiliselt alla viieaastaste laste haigus, kes moodustavad kuni 72% haigetest (9, 15, 16). Ka meie uurimuse



Joonis 2. Mädase meningiidi etioloogiline struktuur Lõuna-Eesti lastel aastail 1980...1991.

andmed kinnitavad alla viieaastaste laste suurt osatähtsust haigestunute hulgas (84,4%).

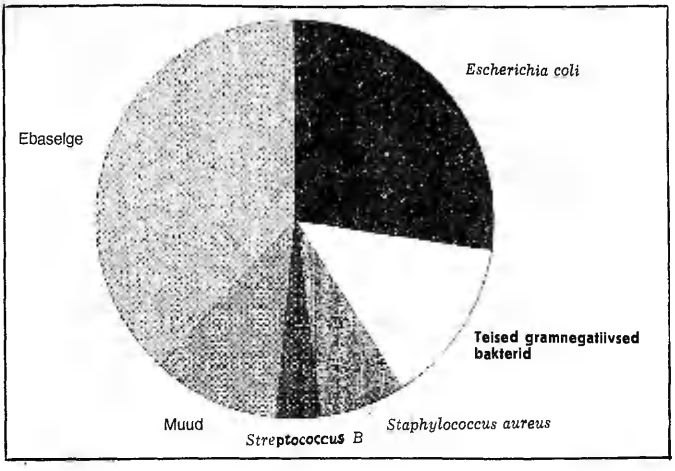
Bakteriaalse meningiidi etioloogiline struktuur on paikkonniti erinev. Nii on 1960-ndatest aastatest alates täheldatud Ameerikas ja 1970-ndatest aastatest ka Euroopa riikides *Haemophilus influenzae B* osatähtsuse suurenemist meningiiditekitajate hulgas. Võrrelnud mädase meningiidi tekitajaid Šotimaal kahel perioodil, aastail 1947...1961 ja 1971...1986, leidsid P. E. Carter ja kaasautorid (4), et kui esimesel perioodil *Haemophilus influenzae* B põhjustas vaid 9,1%, siis teisel perioodil juba 36,8% kõigist lapseea bakteriaalsetest meningiitidest. Eriti suur oli selle tekitaja tähtsus alla viie aasta vanuste laste puhul, põhjustades kuni 70% kõikidest haigusjuhtudest (10).

Meie käsutuses olnud venekeelses kirjanduses bakteriaalse meningiidi etioloogia kohta endises Nõukogude Liidus oli kõigi uurimuste järgi peamiseks meningiidi tekitajaks meningokokk, esinedes 72,6...83,2%-l haigetest (5, 11, 21), kuid samal ajal oli seal täheldatud ka *Haemophilus influenzae* B osatähtsuse suurenemist (6). *Neisseria meningitidis*'e prevaleerimise põhjuseks on N. Kostjukova ja kaasautorite (14) arvates meningokokkinfektsiooni epideemia, mis NSV Liidus kestis aastail 1967...1984. Taolist epideemiat ei ole kirjeldatud mitte kõigis maailma riikides. Seega on mädase meningiidi etioloogiline struktuur Lõuna-Eestis *Neisseria meningitidis*'e ülekaaluga üsna sarnane struktuuriga endises NSV Liidus, erineb aga Lääne-Euroopa ja Ameerika andmetest (4, 11, 18).

Suur oli meie uurimuse põhjal tundmatu haigusetekitajaga juhtude arv, eriti uurimise algperioodil. Võib tekkida arvamus, et ka *Haemophilus influenzae B* põhjustatud meningiit võis olla nende hulgas. Kuigi bakterioloogiline diagnoosimine II uurimisperioodil paranes, jäi mädase meningiidi etioloogiline struktuur oluliselt muutumatuks. *Neisseria meningitidis* jäi ikkagi mädase meningiidi valdavaks tekitajaks Lõuna-Eestis.

Võrreldes letaalsust mädase meningiidi tagajärjel Eestis aastail 1940...1950, kui see E. Tulmini (22) andmeil oli 32,9%, ilmneb tunduv langus viimase 30 aasta jooksul. Letaalsus 12% on küll võrreldav G. C. Yosti ja kaasautorite (23) andmetega (12%), kes uurisid bakteriaalse meningiidi epidemioloogiat Ameerika indiaanlaste hulgas, jääb aga tunduvalt kõrgemaks letaalsusest Šotimaal (1,2%) ja Rootsis (3,4%) (4, 18).

Bakteriaalse meningiidi korral ei ole probleemiks mitte ainult letaalsus, vaid ka haiguse tagajärjel tekkiv invaliidsus. Raskeid neuroloogilisi jääknähte esines meie andmeil 9,1%-l paranenuist, mis on lähedane kirjanduse andmetele — 5,4...11,9% (2, 3, 4, 7, 17, 18). Sagedamateks mädase meningiidi hilistüsistusteks



Joonis 3. Vastsündinu meningiidi etioloogia aastail 1980...1991.

on ajuvatsakeste laienemine ja kuulmise nõrgenemine (7, 8, 12). Hüdrotsefaaliat diagnoositi 4%-l ellujäänuist. See on lähedane D. Giustina ja kaasautorite (7) andmetele, kes leidsid hüdrotsefaaliat 4,7%-l paranenuist. Enamik autoreid on kuulmise nõrgenemist leidnud 2,7...9%-l bakteriaalset meningiiti põdenud lastest (8, 10, 18, 19, 28), kuid meie andmeil esines seda ainult 0,9%-l paranenuist. Kuulmise nõrgenemine on põhjustatud kas mikroobi otsesest kahjustavast toimest (tekib mädane labürintiit) või aju isheemiast (2). Antibiootikumide osa kuulmiskahjustuse kujunemisel meningiidi korral eitatakse, sest enamikul haigetel on seda esinenud juba hospitaliseerimise ajal (12, 18). Üks kuulmishäirete vähesuse põhjusi võis olla see, et audiomeetrilisi uuringuid ei tehtud meil süstemaatiliselt. Seetõttu registreeriti ainult lapsed, kellel oli kuulmise nõrgenemine kliiniliselt väljendunud. Varajaseks kuulmiskahjustuse avastamiseks tuleks audiomeetrilisi uuringuid teha kõigil bakteriaalset meningiiti põdenuil juba siis, kui nad haiglast välja kirjutatakse.

Letaalsuse ja invaliidsusjuhtude tunduv vähenemine üle ühe kuu vanuste laste hulgas oli uuringuperioodil ilmselt tingitud nii diagnoosimis- kui ka intensiivravivõimaluste paranemisest 1980-ndatel aastatel. Muret tekitav oma halva prognoosi tõttu on neonataalne meningiit. Vastsündinu meningiit Lõuna-Eestis sagedusega 0,41 juhtu 1000 elusalt sündinu kohta sarnaneb kirjanduses avaldatuga: 0,37...0,67 juhtu 1000 kohta (2, 3, 19). Neonataalse meningiidi tekitajana on paljudes maailma riikides ja ka meie andmeil ülekaalus *E. coli* K1 (1, 2, 13). Alates 1960-ndate aastate algusest on vastsündinu meningiidi tekitajate hulgas täheldatud B-grupi streptokoki osatähtsuse tunduvat suurenemist. Ebaselgeks jääb, miks nimetatud mikroobi esines meie andmeil ainult ühel juhul. Letaalsus oli kõrge neonataalse meningiidi tagajärjel (37,9%), seda on täheldanud ka teised autorid. Nii oli S. Apaki ja kaasautorite (1) andmeil letaalsus Saksa DV-s 45,3% ja A. H. Belli ja kaasautorite (2) andmeil Inglismaal 49%. Erinevalt teistest leidis R. Bennhagen kaasautoritega (3) vastsündinute meningiidi letaalsuseks Rootsis vaid 3,5%, kuid see uurimus hõlmas ainult ühte aastat (1983) ning valdavaks tekitajaks ei olnud mitte gramnegatiivne tinglikult patogeenne mikrofloora, vaid B-grupi streptokokk. Vastsündinu meningiidi ravi äärmisest komplitseeritusest räägib fakt, et vaatamata intensiivravi võimaluste paranemisele ei ole uurimisperioodil täheldatud ei letaalsuse langust ega invaliidsusjuhtude vähenemist. Probleemiks jääb küllaltki suur nosokomiaalinfektsiooni osatähtsus, meie andmeil pooled vastsündinuist haigestusid ravil olles. Kirjanduses on avaldatud arvamust, et neonataalse meningiidi prognoosi parandamiseks tuleks rohkem tähelepanu pöörata profülaktikale, s.t. vältida haiglasisest nakkust ja otsida immunoprofülaktika rakendamise võimalusi (13, 19).

Järeldused.

1. Sarnaselt endise NSV Liiduga ja erinevalt Euroopa ja Ameerika riikidest oli aastail 1980...1991 Lõuna-Eestis valdavaks bakteriaalse meningiidi tekitajaks lastel meningokokk, kusjuures 1980-ndate aastate lõpust täheldati *Haemophilus influenzae* B osatähtsuse suurenemist.

2. Paremaks ülevaate saamiseks ja võimalikuks immunoprofülaktikaks oleks ametlikult vaja registreerida kõik mädase meningiidi juhud.

3. Ehkki 1940...1950 aastate andmetega võrreldes on mädase meningiidi prognoos tunduvalt paranenud, jäävad letaalsus ja invaliidsus Eestis suhteliselt kõrgeks, mistõttu mädast meningiiti põdevaid lapsi peaks ravitama haiglas, kus on nüüdisaegsed diagnoosimis- ja intensiivravivõimalused.

4. Endiselt jääb probleemiks neonataalne meningiit oma halva prognoosi tõttu. Et ravi on äärmiselt komplitseeritud, tuleks rohkem tähelepanu pöörata neonataalse infektsiooni profülaktikale.

KIRJANDUS: 1. *Apak, S., Ozmen, M.* Kinderarzt, 1983, 10, 1234—1236. — 2. *Bell, A. H., Brow, H. L. Hallyday, H. L. a.o.* Arch. Dis. Childhood, 1989, 64, 873-874. — 3. *Bennhagen, R. Svenningsen, N. W., Bekassy, A. N.* Scand. J. Inf. Dis. 1987, 19, 587-593. — 4. *Carter, P. E., Barclay, S. M., Galloway, W. H.*

Arch. Dis. Childhood, 1990, 40, 89-109. — 5. *Djomina, A., Iljina, T.* ŽMEI, 1982, 3, 3-6. — 6. *Djomina, A., Pokrovski, V., Iljina, T. i dr.* ŽMEI, 1984, 12, 32-36. — 7. *Giustina, D., Forese, S., Pace, P.* Ped. Med. Chir., 1985, 7, 195-214. — 8. *Grubbauer, H. M.* Klin. Pädiatr., 1982, 194, 11-13. — 9. *Halstensen, A., Pedersen, S.H.J., Haneberg, B. a.o.* Scand. J. Infect. Dis., 1987, 19, 35-42. — 10. *Hanna, J. N,. Wild, B. E.* Med. J. Australia, 1991, 155, 160-164. — 11. *Iljina, T.* V sb.: Tezisõ dokladov: meningokokkovaja infektsija i gnoinõe meningitõ, 1990, 26-28. — 12. *Jiang, Z. D., Liu, X. Y., Wu, Y. Y. a.o.* Dev. Med. Child Neurol., 1990, 32, 473-480. — 13. *Meade, R. H.* Med. Clin. North. Am., 1985, 69, 257-267. — 14. *Kostjukova, N.* V sb.: Ostrõe meningitõ. M., 1982, 5-9. — 15. *Peltola, H., Käythy, H., Virtanen, M. a.o.* New Engl. J. Med., 1984, 310, 1566-1569. — 16. *Rieske, K., Spencker, F. B., Handrik, W.* Pädiatr. Granzgeb., 1985, 4, 289-293. — 17. *Rosenthal, J., Dagan, R., Press, J. a.o.* Pediatr. Infect. Dis. J. 1988, 7, 630-633. — 18. *Salwen, K. M., Vikerfors, T., Olcen, P.* Scand. J. Infect. Dis. 1987, 19, 1-11. — 19. *Zaki, M., Daoud, A. S., Saleh, Q. a.o.* J. Tropical Pediatr., 1990, 36, 63-65. — 20. *Tikhomirov, E.* World Health Stat. Rep., 1987, 40, 90-109. — 21. *Tšibiras, P., Broslavskii, J., Kelminskene, C.* V sb.: Tezisõ dokladov: meningokokkovaja infektsija i gnoinõe bakterialnõje meningitõ. Arhangelsk, 1986, 45-47. — 22. *Tulmin, E.* Nõukogude Eesti Tervishoid, 1961, 5, 13-15. — 23. *Yost, G. C., Kaplan, A. M., Busatmante, R. a.o.* Am. J. Dis. Child., 1986, 140, 943-946.

Summary

Epidemiology of bacterial meningitis in children in South-Estonia in 1980—1991. Epidemiology of bacterial meningitis (BM) in children in South-Estonia was investigated. In the period 1980—1991 250 children (29 newborns and 221 children over two months) with BM were identified. The average incidence rate of BM was 23.5 per 100,000 children. Neisseria meningitidis caused 35.2% of the BM in older children, Haemophilus influenzae B and Streptococcus pneumonia 4.4% both, other microorganisms 1.2% and in 48.8% of BM the etiology was unknown. The incidence rate of neonatal meningitis was 0.41 per 1000 births. E. coli was the most common bacteria isolated in 30% of the cases of neonatal meningitis. Among those over two months there were 19 meningitis associated deaths (case fatality rate 8.5%) and 13 (6.4%) those who survived developed disability. The mortality and the disability rate in newborns was higher-11 newborns died (case fatality rate 37.9%) and 8 (27.5) developed disability. The overall mortality rate fell dramatically from 11.8% at the beginning of study to 2.6% in the end of it among older children, but showed no changes in newborns. The same applies to the disability rate, decreasing from 7.6% to 2.6% and remaining the same respectively.

Tartu Lastekliinik

Eesti Arst, 1993, 6, 413—420

UDK 616.931-084-06(474.2)

Difteeria Eestis

Ants Jõgiste Toomas Trei • Tallinn

difteeria, immunoprofülaktika, epidemioloogiline järelevalve

Käesoleva töö eesmärk oli anda epidemioloogiline käsitlus difteeria kohta Eestis. Selle ajendiks oli vajadus analüüsida kujunenud olukorda seoses haigestumise taastumisega põhjendamaks profülaktikameetmeid.

Uurimismaterjal ja -metoodika. Epideemiaprotsessi tundmaõppimiseks on analüüsitud statistikaandmeid. Uurimismaterjal XVIII...XIX sajandi ja käesoleva sajandi kahekümnendate-kolmekümnendate aastate kohta on trükis avaldatud (1, 7, 8). Andmestik 1945. aasta ja järgmiste aastate kohta asub Riigi Tervisekaitsekeskuse arhiivis ja on avaldatud ositi.

Haigestumise iseloomustamiseks on kasutatud tavanäitajaid: haigestumus 100 000 inimese kohta, tsüklilisus, sesoonsus, geograafiline levik, haigete vanus. Süvakäsitluse huvides on lisatud andmeid immuunsustausta ja tekitaja ringluse kohta. Et nakkushaiguste epidemioloogilistes käsitlustes keskendub tähelepanu eelkõige epideemiaprotsessi mõjutamise võimalustele, siis on ka käesolevas töös vaadeldud haigestumusnäitajaid seoses aja jooksul täiustunud profülaktikavõimalustega.

Uurimistulemused ja arutelu.

Difteeria XVIII...XIX sajandil. Statistikaandmeid haigestumuse kohta sellest ajast ei ole, kuid epidemioloogilist olukorda on võimalik põhijoontes hinnata meetrikaraamatuisse talletatud surmapõhjuste kaudu (8). Nendel andmetel ei olnud difteeria osatähtsus surma põhjusena suur (0,3...0,4%). Enam ohvreid nõudsid rõuged, tüüfus, düsenteeria ja siberi katk.

Epideemiaprotsessi intensiivsus muutus perioodiliselt. Haigestumise tsüklilised tõusud kordusid nähtavasti 8...9 aasta järel. Sesoonne tõus vältas augustist jaanuarini maksimumiga novembris. Neil kuudel esines 60% aastas registreeritud

II

Acta Padiatr 1994; 83: 1146–1150

Acta Pædiatr 83: 1146–50. 1994

Enzymatic changes in the cerebrospinal fluid in patients with infections of the central nervous system

I Lutsar[1], S Haldre[2], M Topman[3] and T Talvik[4]

Departments of Pediatric Infectious Diseases[1], Pediatrics[4], Biochemical Laboratory[3], Tartu University Children's Hospital and Institute of General and Molecular Pathology[2], University of Tartu, Estonia

Lutsar I, Haldre S, Topman M, Talvik T. Enzymatic changes in the cerebrospinal fluid in patients with infections of the central nervous system. Acta Pædiatr 1994;83:1146–50. Stockholm. ISSN 0803–5253

Enzymatic determinations in cerebrospinal fluid (CSF) of aspartate aminotransferase (AST), lactic dehydrogenase (LDH), gammaglutamyl transpeptidase (GGT), creatine phosphokinase (CPK) and creatine kinase BB (CK-BB) were performed in 16 patients with aseptic meningitis (AM), in 25 children with bacterial meningitis (BM) and in 15 patients with meningism. The activity of AST and GGT was significantly higher in patients with BM on admission compared with those with AM and meningism ($p < 0.05$ and $p < 0.005$, respectively) and decreased with therapy. The highest concentration of AST and LDH appeared in patients with poor outcome as well as in those with ventriculomegaly on neurosonography ($p < 0.05$). The concentration of CK-BB increased in all patient groups on admission and remained higher on termination of therapy. The present study confirms the high activity of AST and GGT in BM patients in the CSF whereas the increased activity of AST and LDH reflects the extent of brain injury. Nevertheless, the prognosis for individual patients cannot be established on the basis of enzyme activity alone, but depends on several factors. □ *Aseptic meningitis, aspartate aminotransferase, bacterial meningitis, cerebrospinal fluid, creatine kinase, gamma-glutamyl transpeptidase, lactic dehydrogenase*

I Lutsar, Department of Pediatric Infectious Diseases, University Children's Hospital, Lunini 6, EE2400 Tartu, Estonia

Disturbances of the enzymatic system are caused by several pathologic processes. Estimations of serum aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT) and creatine kinase (CPK) are widely employed as valuable diagnostic aids in diseases involving necrosis or damage to tissues characteristically rich in these enzymes. The activities of these enzymes have been measured in the cerebrospinal fluid (CSF) of patients with a variety of neurological disorders (1–6). The results obtained, however, were controversial.

The purpose of the present study was to measure the activity of AST, LDH, GGT, CPK and the concentration of its brain type isoenzyme, CK-BB, in the CSF in patients with bacterial and aseptic meningitis and encephalitis, as well as in patients with meningism, to establish if any of these enzymes correlates with brain damage of different etiology and to assess their usefulness in clinical investigations and prognosis.

Patients and methods

The patients studied included 16 children with aseptic meningitis (AM), 25 children with bacterial meningitis (BM) and 15 patients with no infection of the central nervous system (ICNS) in whom lumbar puncture was performed due to meningism. BM was diagnosed if at least one of the following criteria was fulfilled: (1) bacterial grown from CSF, (2) bacterial grown from blood with more than 10 white blood cells (WBC) per mm^3 CSF, (3) sterile CSF, but more than 200×10^6 polymorphonuclear leukocytes (PMNL) per mm^3. The etiologic structure of BM was as follows: *Neisseria meningitidis* in 14 children, *Haemophilus influenzae* B in 4, *Streptococcus pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* in 1 patient each and in 3 cases the etiology of BM remained unknown.

AM was considered if no bacterial infection (as defined above) was found or suspected for patients with clinical signs of meningitis and more than 10 WBC per mm^3 CSF. Of 16 children with AM, 2 had enteroviral meningitis and 7 tick-borne encephalitis, and in 7 cases the etiology was unknown.

Fifteen children with no ICNS had the following diagnoses: 6 patients had acute respiratory infection, 3 diarrhea, 2 epilepsy; hemolytic–uremic syndrome, polyradiculoneuropathy, malignant brain tumor and drug intoxication were diagnosed in 1 patient each. Patient characteristics on admission are shown in Table 1.

The first CSF sample collected on admission was, in most cases, on the first to third day of the disease. In 15 patients with BM, the second sample was collected on

Table 1. Patient characteristics on admission.

Characteristic	AM ($n = 16$)	BM ($n = 25$)	Meningism ($n = 15$)
Age			
0–29 days	0	2	1
1–12 months	0	15	5
1–5 years	7	7	4
6–15 years	9	1	5
Sex			
Male/Female	11/5	15/10	7/8
Seizures (n)	1	8	3
Unconsciousness (n)	1	5	2
CSF			
Pleccytosis (WBC/mm^3)	105(43–251)	681(236–1484)	3(2–6)
Protein (g/l)	0.58(0.47–1.0)	1.22(0.67–2.1)	0.5(0.19–1.0)

days 7–10 of treatment. The CSF was sampled by lumbar puncture and centrifuged immediately. Samples were frozen to −20 °C and stored for up to three months before analysis. In all cases, routine laboratory investigations, i.e. CSF protein, sugar, cell count and bacterial cultures, were examined. The activity of CPK, LDH, AST and GGT was measured by photocolorimetric assay using commercial kits (Labsystem FP-900). The method of enzyme-linked immunosorbent assay used for measurement of CK-BB concentration was an original one, described by Haldre (6). The mean concentration of CK-BB in the control group, including 30 adults with no neurological disorders from whom CSF was taken during spinal anesthesia, was 5.3 ± 1.2 ng/l.

The outcome of the survivors was assessed by a multidisciplinary team (pediatrician, pediatric neurologist, speech therapist, psychologist) at least 12 months after the acute illness. Children were divided into two groups. The good recovery group ($n = 32$) included normal children and those with impairment which did not disturb everyday life. The second group consisted of 9 children; 4 died during the acute illness and 5 had severe impairments (hydrocephalus, severe motor disability, deafness, intractable epilepsy). All 5 children had combined disturbances.

Table 2. Activity of AST, CKP, LDH, GGT and CK-BB in CSF in patients on admission.

Enzyme (quartiles)	AM ($n = 16$)	BM ($n = 25$)	Meningism ($n = 15$)
CK-BB (ng/l)	37.5 (24.0–43.0)	31.0 (15.0–59.0)	39.0 (34.0–46.0)
CPK (U/l)	4.3 (2.0–9.0)	4.2 (2.6–5.5)	3.3 (2.6–5.3)
AST (U/l)	4.0 (3.6–7.3)	8.8* (6.1–11.0)	4.7 (3.5–6.3)
LDH (U/l)	28.1 (4.8–52.2)	33.8 (19.7–70.2)	15.4 (7.6–20.6)
GGT (U/l)	1.67 (0.6–4.45)	5.3** (2.1–8.7)	1.5 (1.0–2.0)

*$p < 0.05$, **$p < 0.005$.

Statistical analysis

The results are given as median with upper and lower quartiles. A computerized statistical package, Statview, was used. This included the non-parametric Mann–Whitney test for unpaired samples, the Wilcoxon test for paired samples and Spearman's rank correlation coefficient.

Results

Table 2 shows the results of CSF enzyme determinations on admission. An increase in CK-BB concentration in

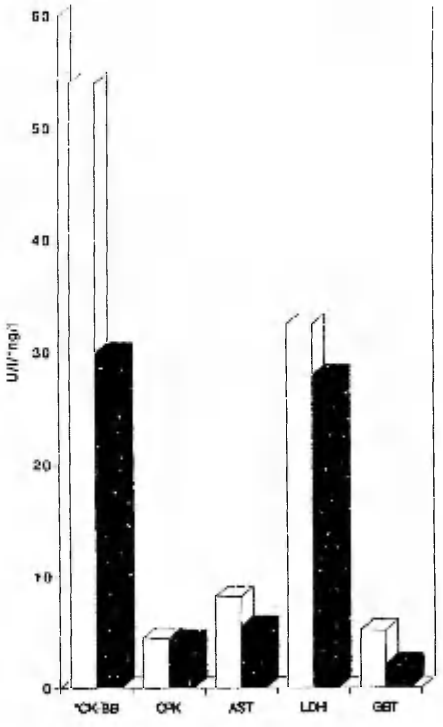


Fig. 1. Activity of CPK, AST, LDH and GGT, and concentration of CK-BB in CSF on admission and on days 7–10 of therapy. The activities of CPK, AST, LDH and GGT are expressed in U/l, and CK-BB concentration in ng/l (□ on admission, ■ 7–10th day).

Table 3. Enzyme data on admission in relation to outcome of infections of the central nervous system.

Outcome (quartiles)	CK-BB (ng/l)	CPK (U/l)	AST (U/l)	LDH (U/l)	GGT (U/l)
Dead/severely impaired ($n = 9$)	9.5 (2–37)	3.8 (2.6–4.5)	12.1* (5.0–17.4)	60.5* (37.1–235.4)	2.7 (1.8–11.4)
Good recovery ($n = 32$)	38.0 (30–49)	4.5 (1.7–6.5)	6.7 (4.0–9.0)	27.5 (15.2–46.3)	2.9 (0.9–8.1)

*$p < 0.05$.

all three diagnostic groups was noted. The activity of AST was two-fold higher in patients with BM compared with those without ($p < 0.05$). The median value of the activity of LDH (33.8 U/l) was highest in those with BM and lowest in patients with meningism, but statistically significant differences were not found. A significant increase in the activity of GGT ($p < 0.005$) was noted in patients with BM on admission compared with those with AM or meningism.

The activity of intracellular enzymes after 7–10 days of treatment was measured in only 15 patients with BM. Figure 1 shows that the concentration of CK-BB and activity of AST, LDH and GGT decreased with treatment, but that of CPK remained the same. AST activity was estimated simultaneously in CSF and serum in 40 patients (25 with BM and 15 with AM): no correlation was found between the levels of AST in CSF and serum ($r = -0.362$). The activity of LDH correlated with the count of PMNL in CSF on admission ($r = 0.538$), but no correlation was found on days 7–10 of therapy ($r = -0.224$). There were 3 patients with *E. coli* meningitis with more than 1000 PMNL in CSF on day 10 of therapy, but the activity of LDH was 2.5, 4.3 and 91.5 U/l, respectively.

As shown in Table 3, patients with ICNS who died or recovered with residual impairments had significantly higher median CSF AST and LDH activities ($p < 0.05$) compared with those with good recovery. Although the concentration of CK-BB was higher in patients with a good prognosis, this difference was not statistically significant.

Table 4 shows that the CSF activity of AST and LDH was significantly higher in patients who developed ventriculomegaly in comparison with those with normal findings ($p < 0.05$). The highest value of AST and LDH activity was seen in 4 patients who developed hydrocephalus.

Discussion

In this study, our aim was to estimate the level of some intracellular enzymes in different ICNS and to establish if any of the measured enzyme levels correlated with central nervous system dysfunction, thus assessing their prognostic value and determining their usefulness in clinical practice. An increase in AST, LDH and GGT activities in patients with BM on admission, demonstrating neuronal cell injury as well as altered permeability of the blood–CSF barrier, has been reported by several authors (1–5). The increased median value of activity and also the appropriate displacement of quartile intervals of AST and GGT in BM patients in comparison with AM and meningism were seen in this study also. In contrast with others (7–9) who have claimed significantly higher concentrations of LDH in BM, the benefit of measuring the activity of LDH, similar to Landaas & Lippe (3), was very poor in our study. Although we found that the activity of LDH was higher in BM compared with AM and meningism, this difference was not statistically significant.

Possible sources of increased enzyme activity in ICNS could be either blood serum or brain tissue. The activity of AST in patients with a poor prognosis was increased in blood serum also, nevertheless we, similar to other authors (2, 4), could not find any correlation between serum and CSF activity of AST ($r = -0.362$). We can assume that the main source of AST activity in

Table 4. Enzyme data in relation to cerebral ultrasound findings in patients with BM.

Neurosonographic finding (quartiles)	CPK (U/l)	AST (U/l)	LDH (U/l)	GGT (U/l)
Ventriculomegaly ($n = 7$)	4.5 (3.2–7.7)	12.1* (10.5–15.1)	71.1* (69.7–235.4)	2.7 (2.6–7.2)
Normal ($n = 8$)	3.5 (2.7–5.4)	8.0 (7.4–8.9)	23.4 (18.7–27.5)	2.5 (1.1–5.2)

*$p < 0.05$.

the CSF is brain tissue, although we cannot exclude the possibility that in severely ill patients, the enzyme can cross through the CSF–blood barrier due to increased permeability. The good correlation ($r = 0.538$) between CSF PMNL count and the activity of LDH confirms the opinion of several studies that PMNL are the main source of LDH activity in the CSF in BM patients (1, 10, 11), although the exact origin of the enzymes may be differentiated only by isoenzyme studies. However, a good correlation was found only during the acute period of BM. The low activity of LDH on days 7–10 of therapy, despite the high amount of PMNL in the CSF, also suggests a cerebral origin of LDH in the acute period of brain injury.

This study, similar to previous ones (11–15), established a definite correlation between raised AST and LDH activities in acute illness and poor prognosis ($p < 0.05$), which most probably is associated with the extent of brain damage. Not only was an increased level of the median value of enzyme activity seen but also a shift of quartile intervals. Augmentation of intracellular enzymes in the CSF being proportional to the severity and extent of brain damage was clearly shown by Maas (16), who produced experimental brain lesions in cats with extremely low temperatures.

Significantly higher activities of AST and LDH in CSF ($p < 0.05$) were found also in patients with enlargement of the lateral ventricles during acute illness. Simultaneous findings of ventriculomegaly on ultrasonography and raised activities of LDH and AST in CSF, strongly suggest that one of the reasons for enlargement of the lateral ventricles after BM is brain atrophy developing after necrosis of brain tissue.

The present study, as well as previous ones (17–19), indicated that CSF CPK activity was not reliable in differentiating between bacterial and non-bacterial CNS infections.

High concentrations of the brain-specific isoenzyme, CK-BB, in CSF seemed to be the best predictor of poor prognosis in patients with head injury in several studies (6, 20–23), while its concentration in other organs than brain was very low (24–27). It was a surprise to find that the concentration of CK-BB in those with a poor prognosis was even lower (9.5 ng/l) compared with those with a good outcome (38.0 ng/l). The fact that some patients with a poor prognosis did not have increased CK-BB concentrations in the CSF was also shown in previous studies (28, 29). The variable increase in CK-BB concentration in different patients is not completely understood. It might be related to the various regional distributions of CK-BB in the brain. This enzyme is localized on astrocytes (30) as well as on neurons (31). The highest tissue CK-BB content was found in the brain cortex and capsula interna, while only small amounts were measured in the pons, cerebellum and medulla oblongata (32). Therefore, a small focal lesion in a functionally important region of the brain may cause severe impairment with minimal enzyme release (15, 33). On the other hand, the concentration of CK-BB in the CSF changes rapidly during the first hours of brain injury (19, 29), thus the results depend on the time of collection of CSF. In this study, the time spectrum from one to three days of illness could account for this. Raised concentration of CK-BB in patients with meningism was an unpredicted finding and shows that even in those patients, hypoxic–ischemic damage of brain tissue can occur.

In conclusion, a significant increase in AST and GGT activities in CSF was found in patients with bacterial meningitis during the first days of brain injury. The remarkably increased activity of AST and LDH in the acute phase of the brain injury may be an indicator of the extent of brain damage and therefore prognostically important. A definite prognosis for an individual patient cannot be established on the basis of enzyme activities alone, but depends on several factors.

Acknowledgements.—The authors would like to express a deep gratitude to Dr Timothy Chambers and Mr Scott M Diel for revising the text and Mrs Liina-Mai Tooding for consultations during statistical analysis.

References

1. Nelson PV, Carey WF, Pollard AC. Diagnostic significance and sources of lactate dehydrogenase and its isoenzymes in cerebrospinal fluid of children with variety of neurological disorders. J Clin Pathol 1975;28:828–33
2. Sirkis SI. Enzymes levels in the cerebrospinal fluid and blood sera in patients with meningitis and their importance in differential diagnosis. Zh Nevropatol Psikhiatr 1982;82:193–7 (in Russian)
3. Landaas S, Lippe B. Chemical analyses for early differential diagnosis between bacterial and viral meningitis. Scan J Clin Lab Invest 1985;45:525–9
4. Radzavil GG, Roslõi IM, Abdalla SHA, Segedi SA. Enzymatic changes in the cerebrospinal fluid and brain injury in complicated forms of meningococcal infection. Meningokokkovaja infektsia i gnoinye meningity. Arhangelsk 1986:1985–9 (in Russian)
5. Nand N, Sharma M, Saini DS, Khosla SN. Gamma glutamyl transpeptidase in meningitis. J Assoc Physicians India 1992; 40:167–9
6. Haldre SJ. Cerebral Creatine Kinase Isoenzyme in the Cerebrospinal Fluid: Importance of its Measuring for Prognosis of the Disease Outcome in Cerebral Ischemic Disorders. Academic dissertation. Tartu, 1988 (in Russian)
7. Neeches W, Platt M. Cerebrospinal fluid LDH in 287 children including 53 cases of meningitis of bacterial and nonbacterial etiology. Pediatrics 1968;41:1097–1100
8. Feldman WE. Cerebrospinal fluid lactic acid dehydrogenase activity. Am J Dis Child 1975;129:77–80
9. Knight JA. Early (chemical) diagnosis of bacterial meningitis—cerebrospinal fluid glucose, lactate and lactate dehydrogenase compared. Clin Chem 1981;27:1431–4
10. Riekkinen PJ, Rinne UK. Enzymes of human cerebrospinal fluid in normal conditions and neurological disorders. Turku 1970
11. Roslõi IM. Biochemical Changes in the Cerebrospinal Fluid and Blood Sera in Patients with Meningococcal Infection and Bacterial Meningitis. Academic dissertation. Moscow, 1991 (in Russian)
12. Agrawai M, Bhandari NR. CSF glutamic oxalacetic transaminase levels in CNS infectious. Indian Pediatr 1989;26:1245–1248
13. Belsey MA. CSF GOT in acute bacterial meningitis. Am J Dis Child 1969;117:288–92
14. Florez G, Cabeza A, Gonzales JM, Garcia J, Ucar S. Serum and

cerebrospinal fluid enzymatic modifications in head injury. Fifth European Congress of Neurological Surgery, Oxford, 1975, abstract 92
15. Maas AIR. Cerebrospinal fluid enzymes in acute brain injury. 2. Relation of CSF enzyme activity to extent of brain injury. J Neurol Neurosurg Psychiatry 1977;40:666–74
16. Maas AIR. Cerebrospinal fluid enzymes in acute brain injury. 1. Dynamics of changes in CSF enzyme activity after acute experimental brain injury. J Neurol Neurosurg Psychiatry 1977;40:655–65
17. Katz RM, Liebmann W. Creatine phosphokinase activity in central nervous system disorders and infections. Am J Dis Child 1970;120:543–6
18. Briem H. Cerebrospinal fluid in patients with meningitis and encephalitis. Academic dissertation. Stockholm, 1982.
19. Smirnov VV, Skoriakov VI, Popov AS, Shestakova TI, Khotko LP. Creatine phosphokinase in the cerebrospinal fluid of patients with acute meningitis. Vrach Delo 1989;7:112–13 (in Russian)
20. Talvik T. Hypoxic–ischemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Academic dissertation. Tartu, 1992;37–45
21. Belton NR. Creatine phosphokinase (CPK), blood and CSF levels in newborn infants and children. Arch Dis Child 1970;45:606
22. Bach F, Bach FW, Pedersen AG, Larsen PM, Dombernowsky P. Creatine kinase BB in the cerebrospinal fluid as a marker of CNS metastases and leptomeningealcarcinomatosis in patients with breast cancer. Eur J Cancer Clin Oncol 1989;25:1703–9
23. Praeter CD, Vanhaesebrouck P, Govaert P, Delanghe J, Leroy J. Creatine kinase isoenzyme BB concentrations in the cerebrospinal fluid of newborns: relationship to short term outcome. Pediatrics 1991;88:1204–10
24. Jockers-Wretou E, Pfleiderer G. Quantitation of creatine kinase isoenzymes in human tissues and sera by an immunologic method. Clin Chem Acta 1975;58:223–32
25. Bell RD, Rosebberg RN, Ting R, et al. Creatine kinase BB isoenzyme levels by radioimmunoassay in patients with neurological diseases. Ann Neurol 1978;3:52–8
26. Chandler WL, Clayson J, Longstreth WT, Fine JR, Fine J. Creatine kinase isoenzymes in human cerebrospinal fluid and brain. Clin Chem 1984;30:1804–6
27. Alatyrtsev VV, Iakunin IUA, Burkova AS, Podkopaev VN, Afonina LG. Creatine kinase BB and lactate in the cerebrospinal fluid of neonates and infants with perinatal injuries of the CNS. Pediatriia 1989;6:33–7 (in Russian)
28. Pasaglu A, Pasaglu H. Enzymatic changes in the cerebrospinal fluid as indices of pathological change. Acta Neurochir (Wien) 1989;97:71–6
29. Bödvarson A, Franzson L, Briem H. Creatine kinase isoenzyme BB in the cerebrospinal fluid of patients with acute neurological diseases. J Intern Med 1990;227:5–9
30. Thompson RJ, Kynoch PAM, Sarjant J. Immunohistochemical localisation of creatine kinase-BB isoenzyme to astrocytes in human brain. Brain Res 1980;201:423–6
31. Worley G, Lipman B, Gewolb IH, Green JA, Schmechel DE, Roe CR, Gross SJ. Creatine kinase brain isoenzyme: relationship of cerebrospinal fluid concentration to the neurologic condition of newborns and cellular localization in the human brain. Pediatrics 1985;76:15–21
32. Delanghe JR, Winter HAD, Buyzere LD, Camaert JJ, Martens FE, Praeter ML. Mass concentration measurements of creatine kinase BB isoenzyme as an index brain tissue damage. Clin Chim Acta 1990;193:125–36
33. Vaagenes P, Kjehus J, Torvik A. The relationship between cerebrospinal fluid creatine kinase and morphologic changes in the brain after transient cardiac arrest. Circulation 1980;61:1194–9

Received Oct. 22, 1993. Accepted May 11, 1994

III

Infection 1995; 23: 113–118

I. Lutsar, A. Gontmacher, M. Närska, V. Rüütel, M. Topman, P. Ilves, T. Siirde, A. Beilmann

Five Days of Antibacterial Therapy for Bacterial Meningitis in Children?

Summary: We evaluated the effectiveness of 5-day antibacterial therapy for bacterial meningitis in children. The study group included 26 children from 2 months to 15 years of age, admitted with microbiologically confirmed bacterial meningitis in 1990–1993 and treated for 5 days. A historical comparison group of 49 patients treated for 8 to 15 days was used. Penicillin monotherapy (300 mg/kg body weight) was used for meningococcal and pneumococcal meningitis and ampicillin (300 mg/kg body weight) for *Haemophilus influenzae b* meningitis. On day 5 of therapy the activity of aspartate aminotransferase (AST), lactic dehydrogenase (LDH), creatine phosphokinase (CPK) and gamma-glutamyl-transpeptidase (γGT) in the CSF was determined by photocolorimetric assay and the concentration of creatine kinase BB (CK-BB) by ELISA. IL-6 was analysed using EIA technique and a cerebral ultrasound was performed at the time of the termination of the antibacterial therapy. The mean follow-up time was 1.3 years for children in the study group and 3.2 in the control group. The time of hospitalisation was shorter in children treated for 5 days ($p<0.005$). Complete clinical recovery was 81% in the study group and 66% in the comparison group at the time of the termination of antibacterial therapy. No relapses occurred. The activity of AST, CPK, LDH, and γGT in the CSF had returned to normal by the 5th day of therapy, but almost a 7-fold higher concentration of CK-BB was registered. The concentration of IL-6 in the CSF decreased with the therapy from 1,800 pg/ml to 685 pg/ml but still remained high. Long term follow-up did not differ between the two groups. We conclude that 5 days of antibacterial therapy is adequate for the treatment of meningococcal meningitis in children.

Introduction

A treatment period of 7 days for meningococcal, 10 days for *Haemophilus influenzae b*, and 14 days for pneumococcal meningitis are the recommendations in most manuals and standard publications [1–5] but they are not based on controlled clinical trials. Reports from some countries suggest that shorter treatment periods, especially in meningococcal meningitis, are sufficient and safe in uncomplicated cases [6–8]. Our previous study showed that 79% of patients with meningococcal and 71% of those with pneumococcal meningitis are in good general condition by day 5 of antibacterial therapy. They are afebrile, the meningeal symptoms are gone, and they have almost normal findings on cerebrospinal fluid (CSF) examination. A shorter course of antibacterial therapy will result in fewer days of hospitalisation and lower costs. Nevertheless, the question still arises whether the child has completely recovered after a 5-day course of antibacterial therapy. An elevation of activity of intracellular enzymes, demonstrating neuronal cell injury and altered permeability of the blood-CSF barrier [9–11], high levels of interleukin-6 (IL-6), playing a central role in host defence mechanisms [12,13] and a changing neurosonography pattern [14,15] have been demonstrated in bacterial meningitis patients during the first days of illness.

The aims of the present study were: 1) to determine whether the incidence of early complications and long term sequelae of bacterial meningitis in children treated for 5 days with intravenous antibiotics was similar to that seen in children treated longer; and 2) to characterise the situation of the brain tissue on days 5–6 by estimating some intracellular enzymes and cytokines in the CSF as well as by neurosonography.

Patients and Methods

Between October 1990 and April 1993 all children between 1 month and 15 years of age consecutively admitted to Tartu University Children's Hospital with microbiologically confirmed bacterial meningitis were enrolled in this study. During this period 28 patients with bacterial meningitis met the inclusion criteria. Two children were excluded from the study: one with meningococcal meningitis due to penicillin resistance of *Neisseria meningitidis* group B; the other with meningitis caused by *H. influenzae b* had high fever on day 6 and was treated for 10 days. A historical comparison-group consisting of 49 patients with a diagnosis of microbiologically confirmed bacterial meningitis treated at our hospital in 1983–1989 was used. There were no significant differences between the groups in patient characteristics, clinical and laboratory features (Table 1). Therapeutic regimens

Received: 16 August 1994/Revision accepted: 12 December 1994

I. Lutsar, M. D., *A. Gontmacher*, M. D., *M. Närska*, M. D., *V. Rüütel*, M. D., *M. Topman*, M. D., *P. Ilves*, M. D., *T. Siirde*, M. D., *A. Beilmann*, M. D., Tartu University Children's Hospital, Lunini 6, EE-2400 Tartu, Estonia.

Table 1: Clinical and laboratory characteristics of the study groups on admission.

Characteristic	Study group n = 26	Control group n = 49	p
Age (months) (range)	39.2 ± 7.8 (8–135)	24.6 ± 4.6 (1–156)	0.076
Sex:			
Male	14	30	0.63
Female	12	19	
History:			
No. given previous antibiotic therapy (%)	5 (22.3)	13 (26.5)	0.47
Duration of previous antibacterial therapy (days)	0.8 ± 1.9	0.5 ± 0.5	0.22
Duration of symptoms (days)	3.6 ± 0.6	2.9 ± 0.26	0.23
No. (%) with features on admission:			
Temperature > 38.5°C	18	37	0.47
Seizures	6 (22)	13 (26)	0.68
Unconsciousness	3 (11)	4 (8)	0.76
Shock	3 (11)	7 (14)	0.67
No. (%) infected with:			
Neisseria meningitidis	18 (69)	33 (67)	0.56
Haemophilus influenzae b	6 (23)	10 (20)	
Streptococcus pneumoniae	2 (7)	6 (12)	
Laboratory characteristics:			
CSF WBC (10^{-6}/l) (range)	5,591 (612–8540)	7,958 (1,135–9236)	0.50
CSF protein (g/l) (range)	1077 (588–955)	1,780 (624–3,077)	0.19
CSF glucose (mmol/l) (range)	2.4 (1.8–2.9)	2.1 (0.7–3.0)	0.31
ESR (mm/h)	36 (22–58)	40 (29–52)	0.25
Total WBC	18.8 (13.4–24.0)	16.4 (11.6–20.1)	0.19
Serum sodium (mmol/l)	137.1	135.7	0.49
Platelet count (range)	206.3 (171–262)	198.8 (151–227)	0.93

for antibacterial therapy used in the study and the comparison group are shown in Table 2.

Criteria for the termination of the antibacterial therapy in the study group were as follows: 1. meningeal symptoms mild or absent, 2. body temperature less than 38°C, 3. CSF WBC count < 100/mm^3, CSF protein < 1,500 g/l, CSF glucose/blood glucose ratio > 0.6. On admission to the hospital cultures and routine examinations of blood and CSF were done. A second lumbar puncture was performed on day 5 of antibacterial therapy. Samples of the CSF were centrifuged and stored at -20°C for up to 6 months until they were assayed. CSF samples from day 5 were examined: 1. The activity of aspartate aminotransferase (AST), lactic dehydrogenase (LDH), creatine phosphokinase (CPK) and gamma-glutamyl-transpeptidase (γGT) in the CSF were determined by photocolorimetric assay in the biochemical laboratory of Tartu University Children's Hospital in 25 patients. 2. The CSF concentration of CK-BB was estimated by ELISA in the laboratory of the Institute of General and Molecular Pathology of Tartu University. 3. IL-6 was analysed in 15 patients in the study group by enzyme immunoassay in the bacteriological laboratory of Danderyd Hospital (Stockholm). 4. Ultrasonography of the brain was carried out using a scanner of 5 and 7.5 MHz with sonolayer "Neuroimager" in 21 infants with an open fontanelle. Enlargement of the side ventricles was diagnosed on the basis of ventricular size on coronal scans as mild if the highest diameter of lateral ventricle was 7–14 mm, moderate if it was 15–25 mm and severe if > 25 mm. 5. Electroencephalograms (EEG) were obtained by a Medicor electroencephalograph (EEG-80, "Medicor", Hungary) and a 21-lead montage, recorded during wakefulness for 30 min in 29 patients (14 children in the study and 15 in the control group). The EEGs were classified according to the presence or absence of dysrhythmia, generalised delta waves, generalised suppression, epileptiform discharges, focal findings (focal suppression, focal delta waves, background asymmetry).

The children were followed by a multidisciplinary team (paediatrician, paediatric neurologist, speech therapist and audiologists). The follow-up time was at least 1 year. At their discharge from the hospital and during the follow-up examinations, all children were divided into three groups: 1. normal or mild disturbances: mild changes in the muscle tone or elevated reflexes without functional disturbances, one-sided hearing disturbances, mild speech disorders; 2. moderate disturbances: motor function corrected by rehabilitation, two-sided mild to moderate hearing disturbances, moderate language disorders, late seizures controlled by antiepileptic drugs; 3. severe disability: handicapped children needing special aid; limited voluntary action, inability to walk, not corrected by rehabilitation, deafness, alalia, late seizures not controlled with antiepileptics.

Statistical analysis: Values are expressed as means ± 1 SD. Differences between the groups in the frequencies of various findings were tested with either the chi-square or t-test.

Results

At the time of termination of antibacterial therapy, clinical features and laboratory findings of patients in the study and comparison groups were similar and are detailed in Table 3.

The duration of antibacterial therapy as well as the duration of hospitalisation and the number of hospital-acquired respiratory infections were significantly lower in the study group ($p < 0.005$) (Table 4). The mean hospital stay with the short-course antibacterial therapy was 10.2 days in contrast to 22.5 days for conventional therapy. None of the study group contracted hospital-acquired respiratory infections, whereas there were eight such cases among those hospitalised longer. The outcome of children at the time of hospital discharge was almost the same in both groups: 81% of the children in the study group and 75% in

Table 2: Duration and choice of antibacterial therapy in children with bacterial meningitis.

	Study group n = 26			Comparison group n = 49				
	Initial therapy			Initial therapy		Second course used	Corrected therapy	
Etiology	Antibiotic*	No. of patients	Duration (days)	No. of patients	Duration (days)	No. of patients	No. of patients	Duration (days)
Neisseria meningitidis	Pen.	18	5.0	21	9.1	4	–	–
	Amp.	–	–	5	6.4	4	–	–
	Pen.+Chl.	–	–	6	10.2	2	3	9
	Cef.	–	–	1	9	1	8	7.8
Streptococcus pneumoniae	Pen.	2	5.0	3	9.3	–	–	–
	Amp.	–	–	1	7	–	–	–
	Pen.+Chl.	–	–	2	10.5	2	1	6
	Cef.	–	–	–	–	–	1	5
Haemophilus influenzae b	Pen.	–	–	5	8	4	–	–
	Amp.	6	5.0	4	6.7	4	–	–
	Pen.+Chl.		–	–	–	–	4	11.7
	Cef.		–	1	7	–	4	10.8

* Pen. = Penicillin G; Amp. = Ampicillin; Chl. = Chloramphenicol; Cef. = Cefotaxime. Antibiotics were administered intravenously as follows: Penicillin 300 mg/kg/day divided every 4h; Ampicillin 300 mg/kg/day divided every 4h; Chloramphenicol 100 mg/kg/day divided every 8h; Cefotaxime 150 mg/kg/day divided every 8h.

Table 3: Clinical and laboratory findings at the time of termination of antibacterial therapy.

	Study group n = 26	Control group n = 49
Clinical feature:		
Temperature 37.5–38.5°C	1	11
No. of seizures	–	3
Negative meningeal syndrome	25	45
Laboratory findings:		
CSF WBC (10^{-6}/l)	45 (4–89)	59 (2–102)
CSF protein (g/l)	758 (305–1,388)	1,047
CSF glucose (mmol/l)	2.4 (2.1–2.8)	2.6 (2.2–3.6)
ESR (mm/h)	34 (18–46)	42
Total WBC (10^{-6}/l)	11.4	12.1

Table 4: Hospital course of patients studied.

	Study group n = 26	Control group n = 49
Duration of antibacterial therapy (days)	5.0	13 (7–43)*
Duration of hospitalisation	10.2 (7–18)	22.5 (9–116)*
Number of nosocomial infections	–	8*
Completely recovered (No.)	21	36
Mild disturbances (No.)	4	8
Severe disturbances (No.)	1	5
Deaths (No.)	–	1

*$p < 0.005$.

Table 5: Outcome of children after bacterial meningitis during the follow-up examination.

	Study group n = 23	Control group n = 48
Normal	21	37
Mild to moderate disturbances	2	8
Severely impaired	–	3
Motor abnormalities	2	7
Hearing impairment	1	3
Late seizures	–	5

the comparison group recovered completely. There were no relapses in either group. On the examination at discharge, abnormalities were still present in five children in the study group and 14 in the control group. They included three cases of ataxia in each group, three cases of other motor defects in the study group and eight cases in the control group. Three control group children were discharged using anticonvulsive drugs.

Long Term Follow-Up

There were 23 children examined in the study and 48 in the control group. During the follow-up examination, 79% of the children in the control group and 91% in the study group were normally healthy. Two of the children who had received 5 days of antibacterial therapy had sequelae: one

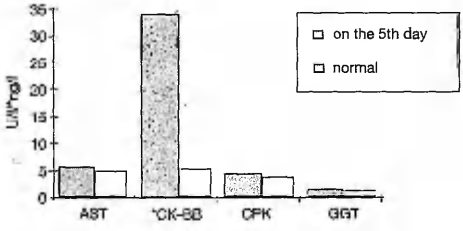


Figure 1: Activity of AST, CK-BB, CPK and GGT on the 5th day of therapy.

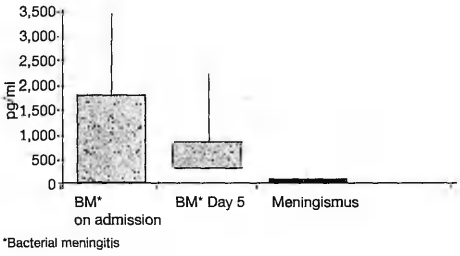


Figure 2: Concentration of IL-6 in the CSF on admission and on day 5.

Table 6: EEG findings on the 5th day of therapy (n = 29).

EEG abnormalities	No. of patients
Background dysrhythmia	16
Generalised delta waves	8
Generalised suppression	4
Epileptiform discharges	1

had ataxia in combination with one-sided moderate hearing impairment and the other slight hemiparesis (Table 5).

Activity/Concentration of Intracellular Enzymes in the CSF

The median activity of AST, CPK and γGT did not exceed the normal reference values at the time of the examination whereas the concentration of CK-BB was markedly increased (34.0 vs. 5.3 ng/l) (Figure 1).

Concentration of IL-6 in the CSF

The median level of IL-6 in bacterial meningitis patients decreased with therapy from 1,800 pg/ml (95% confidence interval [CI], 991–2,265 pg/ml) to 685 pg/ml, (95% CI, 178–1,811 pg/ml), nevertheless it remained significantly higher than in patients with meningismus even on day 5 ($p < 0.005$) (Figure 2).

Cerebral Ultrasound Picture

Abnormal patterns of cerebral ultrasound characterised as mild (n=11) or moderate (n=1) ventriculomegaly were seen in 12 out of 21 patients on days 5–6 of therapy. There were no statistically significant differences in outcome between those with or without ventriculomegaly.

EEG Findings

Slight changes of the EEG pattern, mostly characterised by background dysrhythmia were seen in all children studied on day 5 of therapy (Table 6). There were no focal abnormal findings. Only the child with epileptiform discharges had seizures and recovered with sequelae.

Discussion

Our preliminary results showed that the short term as well as long term outcome in children treated for 5 days was similar to that when treated longer. The children treated for 5 days had a significantly shorter duration of hospitalisation ($p < 0.005$) and no case of hospital-acquired respiratory infection was registered. There were no relapses in either group, which is not surprising because the bacteria, especially in meningococcal meningitis, are usually eliminated from the CSF within 24–48 h of initiating parenteral antibacterial therapy [16].

The limitation of this study was that it was not a prospective double-blind study and a historical comparison group was used as a control. The recently decreasing number of bacterial meningitis cases in North America and in Europe due to the introduction of vaccination against *H. influenzae b* and nonepidemic period of meningococcal infection [17–20] makes it difficult to organise any trial with a sufficient number of patients. This would require, for example, approximately 1,400 patients to be randomly assigned to two treatment groups to be followed for 5 years in order to detect a 50% increase in sequelae with 80% certainty [21].

In this study penicillin was used for the therapy of meningococcal and pneumococcal meningitis while resistant meningococci and pneumococci are still uncommon in Estonia. *Tuncer* et al. [7] in a randomised study compared the effectiveness of 4-day therapy with ceftriaxone and penicillin in meningococcal infection and did not find any differences between the two drugs in the outcome. Intermediately resistant isolates are now being recognised and it is

Infection 23 (1995) No. 2 © MMV Medizin Verlag GmbH München, München 1995

likely that it will be an important factor influencing the selection of antibiotics in the future.

A shorter course of antibacterial therapy than recommended in the textbooks [22,23], has been reported to be highly effective in some previous studies. *Martin* et al. [24] used ceftriaxone monotherapy for 4 days in patients with meningococcal meningitis, for 6 days in cases of *H. influenzae b* meningitis and for 7 days in pneumococcal meningitis and showed that these regimens were as effective as longer periods of therapy. Repofts about meningococcal meningitis suggested that shorter treatment periods (4–5 days) are sufficient and safe in uncomplicated cases [6,7,25]. Although 5-day therapy in our study was effective also in *H. influenzae b* and pneumococcal meningitis, it has to be said that in five out of eight children, antibiotics had been administered before hospital admission and we agree that *H. influenzae b* and pneumococcal meningitis may require longer treatment [16,21,25].

Because an increased concentration of intracellular enzymes in body fluids is evidence of cytolysis and because IL-6 plays a central role in host defence mechanisms, we used these as additional parameters of CNS dysfunction. The activity of AST and γGT in the CSF, which was increased during the first days of bacterial meningitis, was almost normal [9]. However, it is interesting to mention that the concentration of CK-BB in the CSF was still high. This isoenzyme is highly specific for the brain tissue and its raised concentration probably shows that damage of the cell membranes is still present [10,11]. The concentration of IL-6 at the time of the termination of antibacterial therapy was still significantly higher in children receiving 5 days of therapy ($p < 0.001$). Persisting IL-6 activity during the first 5–6 days of bacterial meningitis was also shown by *Rusconi* et al. [22]. The exact role and source of IL-6 in the pathogenesis of bacterial meningitis is not clear; a local production of IL-6 in the CNS seems to occur [13,26].

Enlargement of the brain side ventricles was seen in 60% of infants on the 5th–6th day of therapy and was in all but one case mild. Mild to moderate ventriculomegaly, which developed mostly by the second week of acute bacterial meningitis, has also been seen in previous studies. It is believed to be caused by a decreased compliance of the brain tissue and is normally reversed within 6 months [14,15,27]. Despite the good general condition of patients on day 5, all children had slight changes in their EEG patterns, in that background dysrhythmias and generalised delta activity have been predominant findings. However, *Pike* et al. [28] described the above mentioned findings in most of their bacterial meningitis patients on the 7th–21st days of illness and showed that these were not connected with an unfavourable prognosis.

Thus, despite the fact that the patient has no fever and is already in a good general condition on day 5 of therapy, the processes in the brain tissue have not ended. Nevertheless, we believe that for patients with uncomplicated meningococcal meningitis, 5 days of antibacterial therapy is adequate, although due to the small number of patients we cannot recommend it for *H. influenzae b* and pneumococcal meningitis. Our preliminary results of 5 days of antibacterial therapy for bacterial meningitis in children are promising, but before changing the general rules controlled prospective trials with a larger number of patients are needed.

Acknowledgements

The authors would like to thank Prof. *George H. McCracken* Jr. for his review of the manuscript.

Zusammenfassung: 5-Tages-Therapie für die antimikrobielle Behandlung der bakteriellen Meningitis im Kindesalter? Die Wirksamkeit einer 5tägigen antibakteriellen Therapie wurde bei bakterieller Meningitis im Kindesalter geprüft. Die Studiengruppe umfaßte 26 Kinder im Alter von 2 Monaten bis 15 Jahren, die 1990–1993 mit mikrobiologisch gesicherter bakterieller Meningitis aufgenommen und 5 Tage lang behandelt wurden. 49 Patienten, die 8–15 Tage lang behandelt wurden, dienten als historische Vergleichsgruppe. Bei Meningokokken- und Pneumokokken-Meningitis wurde eine Monotherapie mit Penicillin (300 mg/kg KG) durchgeführt, die *Haemophilus influenzae*-Meningitis wurde mit Ampicillin (300 mg/kg KG) behandelt. Am Behandlungstag 5 wurden die Aktivitäten von Aspartataminotransferase (AST), Laktatdehydrogenase (LDH), Kreatinphosphokinase (CPK) und gamma-Glutamyl-Transpeptidase (γ GT) im Liquor fotokolorimetrisch bestimmt. Die Kreatinkinase BB-Konzentration (CK-BB) wurde mittels ELISA gemessen. IL-6 wurde mit einer EIA Technik bestimmt und zum Zeitpunkt des Therapieendes mit Antibiotika wurde eine zerebrale Ultraschalluntersuchung vorgenommen. Die mittlere Verlaufsbeobachtung betrug bei den Kindern der Studiengruppe 1,3 Jahre, bei der Kontrollgruppe 3,2 Jahre. Kinder, die die 5-Tages-Therapie erhielten, blieben kürzer in stationärer Behandlung ($p < 0,005$). Eine vollständige klinische Wiederherstellung war bei Kindern der Studiengruppe bei Therapieende in 81% und bei der Vergleichsgruppe in 66% der Fälle eingetreten. Rezidive ereigneten sich nicht. Am 5. Therapietag hatten sich AST, CPK, LDH und γGT im Liquor normalisiert, die Konzentration von CK-BB war noch fast 7fach erhöht. Die IL-6 Konzentration im Liquor nahm mit der Therapie von 1,800 pg/ml auf 685 pg/ml ab, blieb jedoch noch erhöht. Die Langzeit-Verlaufsbeobachtung zeigte keine Unterschiede zwischen den Gruppen. Wir folgern, daß eine antibakterielle 5-Tages-Therapie für die Behandlung der Meningokokkenmeningitis bei Kindern adäquat ist.

References

1. **Committee of Infections Diseases:** Treatment of bacterial meningitis. Pediatrics 81 (1988) 904–907.
2. **Klein, N. J., Heyderman, R. S., Levin, M.:** Antibiotic choices for meningitis beyond neonatal period. Arch. Dis. Child 67 (1992) 157–161.
3. **Feigin, R. D., McCracken, G. H. Jr.:** Diagnosis and management of meningitis. Pediatr. Infect. Dis. J. 11 (1992) 785–814.
4. **Klein, J. O., Feigin, R. D., McCracken, G. H. Jr.:** Report of the task force on diagnosis and management of meningitis. Pediatrics 78 (Suppl.) (1986) 959–982.
5. **McCracken, G. H. Jr.:** Current management of bacterial meningitis in infants and children. Pediatr. Infect. Dis. J. 11 (1992) 169–174.
6. **Pecco, P., Pavesio, D., Peisino, M. G.:** [Rational basis of current etiopathogenetic therapy of bacterial meningitis. Review of the literature and personal experience in 122 pediatric cases.] Minerva Pediatr. 43 (1991) 753–775 (Italian).
7. **Tuncer, A. M., Gür, I., Ertem, U., Ece, A., Türkmen, S., Deniz, B., Gurman, I., Tuncer, S.:** Once-daily ceftriaxone for meningococcemia and meningococcal meningitis. Pediatr. Infect. Dis. J. 7 (1988) 711–713.
8. **Lin, T. Y., Chrane, D. F., Nelson, J. D., McCracken, G. H. Jr.:** Seven days of ceftriaxone therapy is as effective as ten days' treatment for bacterial meningitis. JAMA 253 (1985) 3559–3563.
9. **Lutsar, I., Topman, M., Haldre, S., Talvik, T.:** Enzymatic changes in the cerebrospinal fluid in patients with infections of the central nervous system. Acta Pediatr. 83 (1994) 1146–1150.
10. **Worley, G., Lipman, B., Gewolb, L. H., Green, J. A., Schmechel, D. E., Roe, C. R., Gross, S. J.:** Creatine kinase brain isoenzyme: relationship of cerebrospinal fluid concentration to the neurologic condition of newborns and cellular localization in the human brain. Pediatrics 76 (1985) 15–21.
11. **Bödvarson, A., Franzson, L., Briem, H.:** Creatine kinase isoenzyme BB in the cerebrospinal fluid of patients with acute neurological diseases. J. Intern. Med. 227 (1990) 5–9.
12. **Rusconi, F., Parizzi, F., Garlaschi, L., Assael, B. M., Sironi, M., Ghezzi, P., Mantovani, A.:** Interleukin-6 activity in infants and children with bacterial meningitis. Pediatr. Infect. Dis. J. 10 (1991) 117–121.
13. **Waage, A., Halstensen, A., Shalaby, R., Brandtzaeg, P., Kierulf, P., Espevik, T.:** 13 Local production of tumor necrosis factor α, interleukin 1, and interleukin 6 in meningococcal meningitis. J. Exp. Med. 170 (1989) 1859–1867.
14. **Kim Han, B., Babcock, D. S., McAdams, L.:** Bacterial meningitis in infants: sonographic findings. Radiology 154 (1985) 645–650.
15. **Ilves, P., Lutsar, I., Mägi, M.-L., Beilmann, A.:** Brain ultrasonography for diagnosis of bacterial meningitis, ventriculitis and post-meningitic complications in the infants. Abstracts of the conference "Meningococcal infections and purulent meningitis". Novosibirsk 1990, p. 69 (Russian).
16. **Peltola, H., Anttila, M., Renkonen, O.-V.:** Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Lancet i. (1989) 1281–1287.
17. **Peltola, H., Kilpi, T., Anttila, M.:** Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunization with conjugate vaccines. Lancet 340 (1992) 592–594.
18. **Kostjukova, N. N., Korzhueva, N. A., Derkach, S. A., Bagirova, L. Sh., Merzeniuk, Z. A., Gulman, L. A., Niyakuya, V. N., Volkova, M. O.:** [The etiological structure of acute bacterial meningitis in different regions] Zh. Mikrobiol. Epidemiol. Immunobiol. 7 (1992) 14–17 (Russian).
19. **Adams, W. G., Deaver, K. A., Cochi, S. L., Plikaytis, B. D., Zell, E. R., Broome, C. V., Wenger, J. D.:** Decline of childhood *Haemophilus influenzae* type b (Hib.) disease in the Hib. vaccine era. JAMA 269 (1993) 221–226.
20. **Lutsar, I., Poder, A., Udras, M., Tamm, K., Olesk, A.:** [Epidemiology of bacterial meningitis in children in South Estonia in 1980–1991]. Estonian Doctor 6 (1993) 408–413 (Estonian).
21. **Helwig, H.:** Duration of treatment of bacterial meningitis. In: *Schönefeld, H., Helwig, H.* (eds.): Bacterial meningitis. Antibiot. Chemother. 45 (1992) 153–160.
22. **McGee, Z. A., Baringer, J. R.:** Acute meningitis. In: *Mandell, G. L., Douglas, R. G., Bennett, J. E.* (eds.): Principles and practice of infectious diseases. 3rd ed. Churchill Livingstone 1990, pp. 741–754.
23. **Feigin, R. D.:** Bacterial meningitis beyond the neonatal period. In: *Feigin, R. D., Cherry, J. D.* (eds.): Textbook of pediatric infectious diseases. 3rd ed. Saunders Company 1992, pp. 401–428.
24. **Martin, E., Hohl, P., Guggi, T., Kayser, F. H., Fernex, M., and Members of the Swiss Multicenter Meningitis Study Group:** Short course, single daily dose ceftriaxone monotherapy for acute bacterial meningitis in children. 1. Clinical results. Infection 18 (1990) 70–77.
25. **Viladrich, P. F., Pallares, R., Ariza, J., Rufi, G., Gudiol, F.:** Four days of penicillin therapy for meningococcal meningitis. Arch. Intern. Med. 146 (1986) 2380–2382.
26. **Chao, C. C., Hu, S., Close, K., Choi, C. S., Molitor, T. W., Novick, W. J., Peterson, P. K.:** Cytokine release from microglia: differential inhibition by pentoxyfylline and dexamethasone. J. Infect. Dis. 166 (1992) 847–853.
27. **Snyder, R. D.:** Ventriculomegaly in childhood bacterial meningitis. Neuropediatrics 15 (1984) 136–138.
28. **Pike, M. G., Wong, P. K. H., Bencivenga, R., Flodmark, O., Cabral, D. A., Speert, D. P., Farell, K.:** Electrophysiologic studies, computed tomography, and neurologic outcome in acute bacterial meningitis. J. Pediatrics 116 (1990) 702–706.

IV

Pediatr Infect Dis J 1995; 14: 624–625

Brief Reports

LONG TERM FOLLOW-UP OF ESTONIAN CHILDREN AFTER BACTERIAL MENINGITIS.

With the general accessibility of rapid clinical diagnosis, appropriate antimicrobial therapy and modern intensive care facilities, the mortality of bacterial meningitis (BM) has decreased dramatically during last decades to less than 5%[1,2]. A significant number of patients however develop sequelae, i.e. an average of 17% of survivors in developed countries and 26% in the developing world[3]. Hearing disturbances, motor abnormalities, late seizures and psychological problems are the most common sequelae. At least 45 studies characterising long term outcome of BM have been published in English[3] and various prognostically significant factors have been found.

The aim of the present study was to evaluate the late sequelae of BM in Estonian infants and children and to establish which features of acute illness predict long term outcome.

Materials and methods. The medical records of children treated for BM at the Tartu University Children's Hospital (Estonia) from 1983 through 1990 were retrospectively reviewed. In 123 cases at least one of the following diagnostic criteria had to be fulfilled: (1) bacteria grown from cerebrospinal fluid (CSF) culture, (2) bacteria grown from blood culture with more than 10 polymorphonuclear (PMN) white blood cells (WBC) per mm^3 of CSF, (3) no bacteria from CSF, but more than $500x10^6$ PMN WBC per mm^3.

At the time of hospital discharge children were retrospectively divided into three classes according to motoric functional capability as described by Talvik[4]: (1) mild changes of muscle tonus and elevated reflexes without functional disturbances, all activities possible without special aids; (2) function is acquired through special aids; (3) limited voluntary action, enable to walk, to sit without aid, often bedridden.

All children still living in this area, who were at least 4 years old and had documented BM at least 3 years ago were recalled. Of 90 children 84 (94.3%) had follow-up examinations. The median age during the follow-up was 8 years (range, 4 to 18 years) and in average 6 years (range, 3 to 9) had passed since acute illness.

Standard neurologic examination was performed and estimated using above mentioned criteria. Pure tone audiometry with the audiometer MA-31 (DDR) was performed. The thresholds were determined at 500, 1000, 2000, 4000 and 8000 Hz. The four classes of hearing were defined in terms of hearing level for speech as: (1) < 30 dB- normal; (2) 30-55 dB-mild loss; (3) 55-70 dB- moderate loss; (4) > 70 dB-severe loss.

Speech development was estimated by a speech therapist by 8 classes scoring system as follows: (0) no vocalisation; (1) understanding of language; (2) babbling; (3) single words with meaning; (4) one word utterance; (5) two word utterance; (6) three words together; (7) normal speech. The children were divided as follows: normal or mild, Classes 6 and 7; moderate language disorders Classes 4 and 5; Classes 0 to 3, severe language disorders.

During the follow up examination all children were divided into the three groups: (1) normal or only mild disturbances, i.e. motor disturbances of first classes and/or one-sided hearing disturbances and/or mild speech disorders; (2) moderate disturbances, i.e. motor disturbances of 2nd classes and/or two-sided mild to moderate hearing disturbances and/or moderate speech disorders and/or seizures controlled by antiepileptic drugs (impairment corrected by rehabilitation); (3) handicapped children needing special aid- i.e. multiple disturbances not corrected with the rehabilitation: 3 third class motor abnormalities, deafness and/or severe speech disorders and/or seizures not controlled with antiepileptics.

Chi-square test were used to compare differences in proportions and the t-tests to compare the means in normally distributed continues data. Logistic regression was used to assess the relative importance of the various prognostic factors.

Results. The retrospective review of hospital charts showed that 42 children (50%) had meningococcal, 7 (8.3%) pneumococcal, 12 (14.2%) *Haemophilus influenzae* type b meningitis and in 23 cases (27.3%) etiology of BM remained unknown. The median age of patients on admission was 15.5 months (range, 1 to 144), 17 had seizures, 9 were unconscious and 8 patients were hospitalised with septic shock.

The most common therapy was penicillin G 400 mg/kg daily for meningococcal or pneumococcal meningitis and ampicillin 300 mg/kg daily for *H.influenzae* trype b meningitis. Mean duration of antibacterial therapy was 13.8 days. Dexamethasone as adjunctive therapy was used in 16 cases. The mortality rate of BM was 4%. Of 84 children 63 (75%) had no or only mild motor defects (Class 1), 14 (16.7%) had moderate (Class 2) and 7 (8.3%) severe (Class 3) damage at the time of hospital discharge. Demographics and neurologic status of children with (n=84) and without (n=31) follow-up examinations were similar.

Three children, died after hospital discharge. one had progressive hydrocephalus, one died due to respiratory infection complicated with brain oedema and the third child drowned.

The results of the long term follow-up of BM of 84 children are shown in Table 1: 68 (80%) of children were regarded as normal, 11(13.3%) had moderate disturbances and 5(5.9%) were handicapped during follow-up examination.

Motor abnormalities were the most common finding at that time, diagnosed in 10 children (12%); two patients had severe disturbances (third degree spastic quadriplegia); and moderate to mild abnormalities were seen in 8 cases. Ataxia was diagnosed in 3 (3.5%) of children studied, combined with hearing disturbances in 2 cases.

Of the 84 children 4 (4.7%) had nonfebrile seizures. They were clearly focal or had focal onset and started from half to 7 years after the acute illness. Good control of seizures was achieved in 3 of the 4 patients with a single anticonvulsant drug. Febrile seizures were registered in three cases. Moreover, history of breath-holding spells was found out in two children. One of them had those already before the BM, but after BM they occurred more often, in another child breath-holding spells were firstly diagnosed 3 months after BM.

Seven children (8.3%) had a sensoneural hearing deficit in speech area (from 1000 to 4000 Hz). There was bilateral impairment in 4 of them (4.7%). Two out of seven had profound hearing loss. Moderate unilateral hearing disturbances were found in two children and bilateral mild hearing deficit in three patients.

TABLE 1. Long term sequelae of BM in 84 Estonian infants and children.

Sequelae	No. of Patients	%
Motor disturbances	10	12
Ataxia	3	3.5
Hydrocephalus	1	1.1
Epilepsy	4	4.7
Hearing disturbances	7	8.3
Mental retardation	4	4.7
Speech delay	8	10

Speech delay was observed in nine (10.7%) children. It was diagnosed only in children who had BM during the first year

of life, before the speech development. There was no association between speech delay and hearing disturbances.

There was a significant correlation between seizures on admission and poor outcome ($p=0.018$). No other differences between late sequelae and age, sex, the severity of unconsciousness, CSF findings on admission, etiologic structure of BM or therapy used were statistically significant.

All but one child of those who developed either hearing disturbances or motor defects had been discharged with neurological sequelae ($p\leq0.0001$). A significant correlation between motor and hearing disturbances during the follow-up was also seen as 5 of 7 children with hearing impairment had also motor defect and 4 of 10 with motor abnormalities had also hearing impairment ($p<0.0001$). No correlation was found either between late seizures and other abnormalities at the follow-up or between late seizures neurological defects of the patients at the time of hospital discharge.

Discussion. Our data are consistent with published results[3,5-7] indicating, that the long term prognosis of BM may not be as gloomy as initially thought. We found abnormalities in 20% of the children studied, but 13% were considered to have mild to moderate sequelae.

We found that severe neurological deficits at the time of hospital discharge are good predictors of other long term sequelae but epilepsy ($p<0.0001$).

Hearing impairment is the most common complication of BM in children[5,8]. Our study did not confirm the opinion that hearing disorders after BM are mostly unassociated with the brain damage[9]. Like Dodge et al.[10] we observed a significant correlation between hearing disturbances and motor defects during the follow up examinations. We, as others,[11-13] suggest that hearing disturbances are in association with labyrinthitis, since some of the patients had ataxia and hearing deficit. Speech disorders with the frequency of 7-23% in previous studies are thought to be connected to hearing deficit [6,7,14]. On the contrary no association between hearing impairment and speech delay was found by us.

The overall prevalence of nonfebrile seizures in this survey (4.7%) was similar to the data of meta-analysis made by Baraff et al.[5]. Like other authors[15] we found the highest risk of unprovoked seizures during first five years after BM. In agreement to previous reports[15-17] we found seizures on admission being risk factors for the development of late sequelae. In contrast to Pomeroy et al.[16] no correlations between other abnormalities and late seizures was found during the follow-up.

In conclusion only children with severe neurological deficits at the time of hospital discharge after BM seem to have a high risk for permanent neurological sequelae and hearing disturbances. Those showing no or only mild disturbances have an excellent chance of being normal or having only mild sequalae or late seizures on follow-up.

Acknowledgements. The authors would like to thank Prof.Bengt Björksten for his kind help in preparing and reviewing the manuscript and Mrs.Terje Reiter for English reviewing.

Irja Lutsar
Toomas Siirde
Tiiu Soopõld
Departments of Infectious Diseases
Otorhiholaryngology and
Pediatric Neurology
Tartu University Children's Hospital
Tartu, Estonia

Key words: Bacterial meningitis, child, sequelae

Address for reprints: Irja Lutsar, Department of Infectious Diseases, University Children's Hospital, Lunini 6, EE2400 Tartu, Estonia.

1. Salwen K.M., Vikerfors T., Olcen P. Increased incidence of childhood bacterial meningitis: a 25-year study in a defined population in Sweden. Scandinavian Journal of Infectious Diseases. 1987;19:1-11.
2. Lutsar I., Põder A., Olesk A., Udras M., Tamm K. [Epidemiology of bacterial meningitis in children in South Estonia 1980-1991] Estonian Doctor 1993;6:408-413 (Estonian).
3. Baraff L.J., Lee J., Schriger D.L. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatric Infectious Diseases Journal. 1993;12:389-394.
4. Talvik T. Hypoxic-ischemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Acsdemic dissertation. Tartu 1992:29.
5. Jadavij T., Biggan W.D., Gold R. Sequalae of acute bacterial meningitis in children treated for seven days. Pediatrics 1986:78:21-25.
6. Lebel M.H., McCracken G.H.Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161-167.
7. Gary N., Powers N., Todd J.K. Clinical identification and comparative prognosis of high-risk patients with Haemophilus influenzae meningitis. American Journal Diseases of Childhood. 1989;143:307-311.
8. Fortnum H.M. Hearing impairment after bacterial meningitis: a review. Archives of Diseases in Childhood. 1992;67:1128-1133.
9. Feigin R.D., McCracken G.H.Jr., Klein J.O. Diagnosis and management of meningitis. Pediatric Infectious Diseases Journal. 1992;11:785-814.
10. Dodge P.R., Davis H., Feigin R.D. Prospective evaluation of hearing impairment as a sequalae of acute bacterial meningitis. New England Journal of Medicine. 1984;311:869-874.
11. Harada T., Semba T., Suzuki M., Kikuchi S., Murofushi T. Audiological characteristics of hearing loss following meningitis. Acta Otolaryngologica.(Stockh.) Suppl. 1988;456:61-67.
12. Kaplan S.L., Hawkins E.P., Kline M.W., Patrick G.S., Mason E.O. Invasion of the inner ear by Haemophilus influenzae type b in experimental meningitis. Journal of Infectious Diseases. 1989;159:923-930.
13. Bhatt S., Halpin C., Hsu W., Thediger B.A., Levine R.A., Tuomanen E., Nadol J.B. Hearing loss and pneumococcal meningitis: an animal model. Laryngoscope 1991;101:1285-1292.
14. Salih M.A., Khaleefa O.H., Bushara M., Taha Z.B., Musa Z.A., Kamil I., Hofvander Y. (1991). Long term sequalae of childhood acute bacterial meningitis in a developing country: a study from the Sudan. Scandinavian Journal of Infectious Diseases. 1991;23:175-182.
15. Annegers J.F., Hauser W.A., Beghi E., Nicolosi A., Kurland T. The risk of unprovoked seizures after encephalitis and meningitis. Neurology, 1988;38:1407-1410.
16. Pomeroy S.L., Holmes S.J., Dodge P.R., Feigin R.D. Seizures and other neurologic sequalae of bacterial menngitis in children. New England Journal of Medicine. 1990;323:1651-1657.
17. Letson G.W., Gellin B.G., Bulkow L.R., Parks D.J., Ward J.I. (1992) Severity and frequency of sequalae of bacterial meningitis in Alaska native infants. Correlation with a scooring system for severity of sequalae. American Journal Diseases of Childhood. 1992;146:560-566.

CURRICULUM VITAE

Irja Lutsar
citizenship: Estonia
born: 20. July 1954, Estonia, Räpina
married, two children
address: Kungla 14–3, EE2400 Tartu
Telef. +372–7–428927
Fax. +372–7–449503

Education:

1961–1972	Secondary School of Räpina
1972–1978	University of Tartu
1989–1991	All Union Institute of Epidemiology, postgraduate student
1993–	University of Tartu, postgraduate student

Professional employment:

1978–1979	Tallinn First Children's Hospital, internship
1979–1982	District Hospital of Võru, head of the pediatric department
1982–	Tartu University Children's Hospital, head of the infectious diseases department

Scientific work:

Most studies are connected to the infections of the central nervous system, their epidemiology, diagnostics and therapy. Recent studies deal with the investigation of the role of cytokines in the pathogenesis of bacterial and aseptic meningitis.
38 scientific publications and more than 10 reports in the international meetings.
Member of European Society for Pediatric Research, European Society for Pediatric Infectious Diseases, Baltic Child Neurology Association; board member of the Estonian Pediatric Association and Estonian Society for Infectious Diseases.

ELULOOKIRJELDUS

Irja Lutsar
kodakondsus: Eesti
Sünd: 20. juuli 1954, Eesti NSV, Räpina
abielus, 2 last
aadress: Kungla 14–3, EE2400 Tartu
Telef. +372–7–428927
Fax. +372–7–449503

Haridus:

1961–1972	Räpina Keskkool
1972–1978	Tartu Riiklik Ülikool
1989–1991	Üleliiduline Epidemioloogia Instituut mittestatsionaarne aspirant
1993–	Tartu Ülikool, doktorant

Ametikäik:

1978–1979	Tallinna I Lastehaigla, internatuur
1979–1982	Võru Rajooni Keskhaigla, lasteosakonna juhataja
1982–1993	Tartu Linna Kliiniline Lastehaigla, peaarsti asetäitja
1993–	Tartu Ülikooli Lastekliinik, nakkusploki juhataja

Teaduslik tegevus.

Põhilised uuringud on seotud kesknärvisüsteemi põletike epidemioloogia, diagnostika ja ravi probleemidega. Praegune uurimustegevus hõlmab tsütokiinide osatähtsuse hindamist bakterjaalsete ja aseptiliste meningiitide patogeneesis.
38 teaduslikku publikatsiooni, rohkem kui 10 ettekannet rahvusvahelistel konverentsidel.
Kuulub mitmetesse erialastesse teaduslikesse seltsidesse
Euroopa Pediaatriliste Uuringute Selts (ESPR), Euroopa Laste Infektsionistide Selts (ESPID), Balti Lasteneuroloogide Selts. Eesti Lastearstide Seltsi ja Eesti Infektsionistide Seltsi juhatuses.

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos.** The natural course of gastric ulcer in connection with chronic gastritis and Helicobacter pylory: A longitudinal long-term case-control study. Tartu, 1991.
2. **Mihkel Zilmer.** Na-pump in normal and tumorous brain tissues: Structural functional a. tumorigenesis aspects. Tartu, 1991
3. **Eero Vasar.** Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik.** Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation) Tartu, 1992.
5. **Ants Peetsalu.** Vagotomy in duedenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and Helicobacter pylory. Tartu, 1992.
6. **Marika Mikelsaar.** Evaluation of the gastrointestinal microbial ecosystem in health and disease. Tartu, 1992.
7. **Hele Everaus.** Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar.** Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm.** On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross.** Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
11. **Oivi Uibo.** Childhood coeliac disease in Estonia: occurrence, screening, diagnosis and clinical characterisation. Tartu, 1994.
12. **Viiu Tuulik.** The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
13. **Margus Viigimaa.** Primary haemostasis, antiaggregative and antico-agulant treatment of acute myocardial infarction. Tartu, 1994.
14. **Rein Kolk.** Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar.** Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi.** The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.

Vabandus

Trükitehnilistel põhjustel on joonistel 2, 3 ja 8 erinevad halltoonid kokku sulanud.
Toome siinkohal ära nende õiged variandid.

Tartu Ülikooli Kirjastus

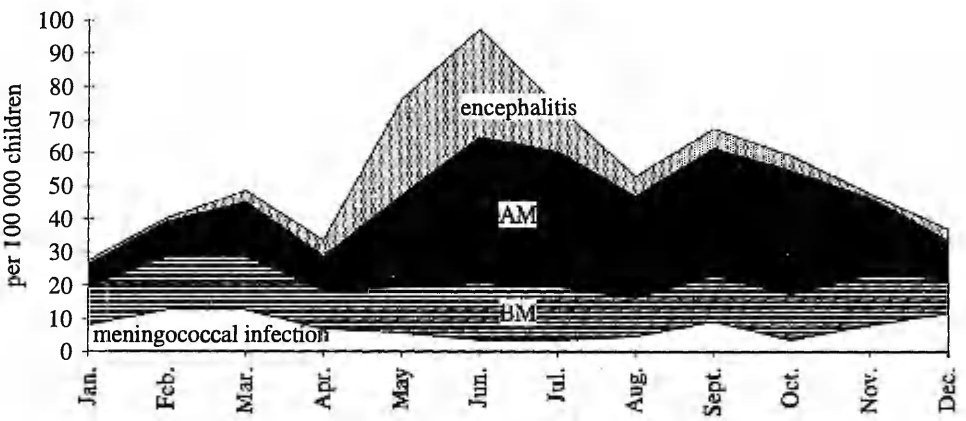


Figure 2. Monthly distribution of encephalitis, aseptic and bacterial meningitis and meningococcal infection in children in South-Estonia in 1980–1989.

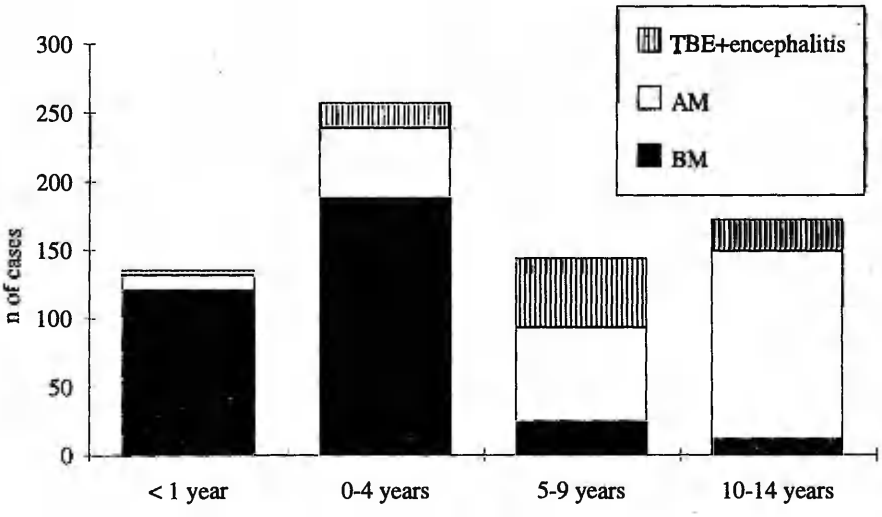


Figure 3. Age distribution of BM, AM and TBE+encephalitis in South-Estonia in 1980–1989.

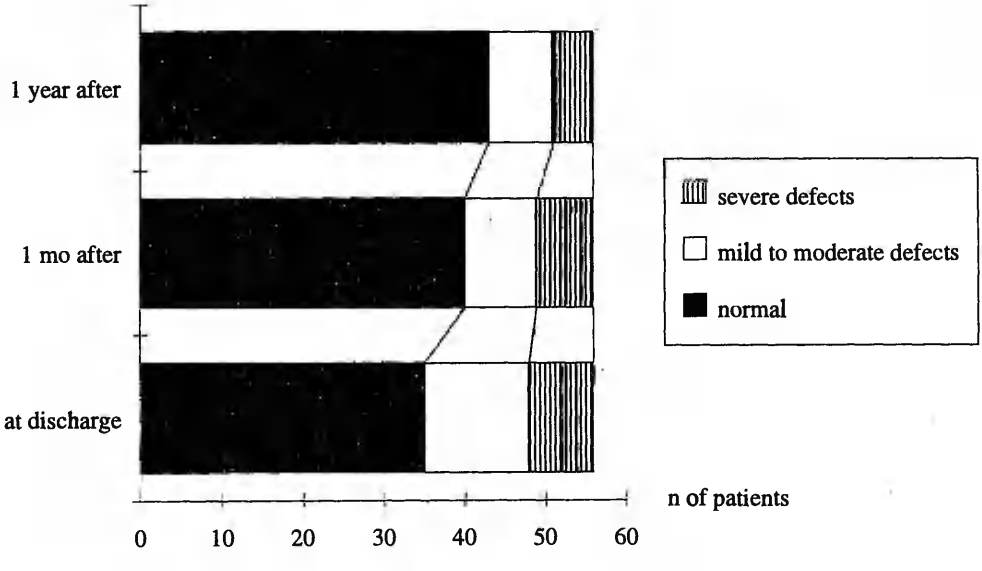


Figure 8. General condition of children at discharge, one months and one year after BM

ISSN 1024–395X
ISBN 9985–56–119–8