Smeri gibanja pojavnosti cerebralne paralize v odvisnosti od razvoja perinatalne medicine in intenzivnega zdravljenja novorojenčkov v Mariboru (1988–2003)

Time trends in cerebral palsy incidence in correlation with development of perinatal and neonatal care in Maribor (1988–2003)

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Izvleček

Namen: *Raziskati smeri gibanja pojavnosti cerebralne paralize (CP) v Mariboru v populaciji otrok rojenih v obdobju 1988–2003 v povezavi s tehnološkim in farmakološkim razvojem perinatalne medicine in intenzivnega zdravljenja novorojenčkov.*

Metode: *V populacijsko študijo smo zajeli 52.450 živorojenih (1988–2003) na Oddelku za perinatologijo Univerzitetnega kliničnega centra Maribor in 1. januarja 2006 še bivajočih na področju regije Maribor. Uporabili smo več virov informacij. Pregledali smo nevropediatrično in drugo specialistično zdravstveno dokumentacijo otrok obravnavanih v cen-*

Abstract

Purpose: *To investigate time trends in cerebral palsy (CP) incidence in correlation with development of perinatal and neonatal intensive care in Maribor, Slovenia.*

Methods: *A population–based study covering the 52.450 live births (1988–2003) at the Department of Perinatology, University Clinical Center, Maribor and residents in one of the five communities of the Maribor region on January 1, 2006. Multiple sources were used. Neuropediatrician and other professional medical records were evaluated for all children at the rehabilitation units. The prevalence of CP was analyzed in yearly cohorts according to birth weight, gesta-*

trih za razvojno nevrologijo in habilitacijo otrok z motnjami v razvoju. Stopnjo pojavnosti CP smo analizirali v letnih kohortah z ozirom na porodno težo, gestacijsko starost, vrste CP in stopnjo prizadetosti in vse skupaj v povezavi z razvojem fetalne in neonatalne medicine.

Rezultati: *Izračunana srednja vrednost prevalence CP v raziskovani populacijski skupini je 3,7/1000 preživelih otrok, 2,7/1000 v skupini nedonošenih in 1/1000 v skupini donošenih. Prevladujoča oblika CP je spastična diplegija. 44% otrok s CP iz raziskovane skupine (1998–2003) je bilo po sistemu razvrščanja glede na grobo motoriko (Gross Motor Function Classification System) uvrščenih v skupini I in II (najlažjo in blago obliko prizadetosti). Povečanje stopnje CP v letih 1999, 2000 in 2001 lahko pojasnimo z izjemnim povečanjem števila živorojenih z zelo nizko porodno težo v zadnjem petletnem obdobju povezano z istočasno povečanim preživetjem nedonošenčkov gestacijske starosti 28–32 tednov. V zadnjih 10 letih se je v Mariboru stopnja umrljivosti novorojenčkov signifikantno zmanjšala od 6,6/1000 živorojenih v letu 1997 na 3,1/1000 v letu 2001 in na 1,8/1000 živorojenih v letu 2009.*

Zaključek: *Razvojne spremembe na področju perinatalne in neonatalne medicine v Mariboru od leta 1994 naprej so vodile do očitnega znižanja zgodnje umrljivosti novorojenčkov, kar je zaradi povečane stopnje preživetja nedonošenih prehodno povečalo tudi stopnjo CP.*

tional age, type of CP, and degree of disability.

Results: *Calculated crude mean prevalence of CP for this population group was 3.7/1000 infant survivors, 2.7/1000 for preterm CP, and 1/1000 for term CP, and 44% were Gross Motor Function Classification System levels I and II. Spastic diplegia was the most prevalent subtype of CP. The increase in CP rates in 1999, 2000 and 2001 could be explained by improved survival of preterm infants at 28–32 weeks gestation. The neonatal mortality rate has declined in Maribor significantly from 6.6/1000 live births in 1997 to 3.1/1000 in 2001 and 1.8/1000 in 2009.*

Conclusion: *Progressive changes in perinatal and neonatal intensive care in Maribor since 1994 have led to a fall in the early neonatal mortality rate, and this increase in survival of preterm infants has increased CP morbidity rate.*

INTRODUCTION

The frequency of cerebral palsy (CP), a major clinical marker of brain injury, increased during the early years after the introduction of neonatal intensive care, concomitant with the decreased mortality of very low birth weight (<1500 g) preterm infants (1). Treatment with steroids in the antenatal period and with surfactants in the postnatal period was introduced in the early 1990s and led to further reductions in neonatal mortality, particularly for less–mature infants of birth weight <1000 g.

Until the late 1990s, CP was defined as a non–progressive disorder of movement, posture, or both, and there was no reliable measure of the severity of motor disability or consideration of other cognitive or neurosensory problems. In 1997, Pallisano and colleagues developed a reliable system to classify gross motor function quantitatively in children with CP (2).

The motor disorders of CP are often accompanied by disturbance of sensation, cognition, communication, perception and/or behavior, and/or by a seizure disorder. This definition of CP was put forward by the participants at an international workshop on the definition and classification of CP, held in Washington in 2004 (3). With this definition, more emphasis than before is placed on the accompanying impairments. Furthermore, the 2004 classification includes anatomical and radiological findings and causation of the lesion. This classification aids comparison of the frequency of CP and its correlates and enables

a multidisciplinary approach to treatment. For the sake of European cooperation, a common classification has been put forward by 14 centers throughout Europe: the Surveillance of Cerebral Palsy in Europe (SCPE 2002) (4). This classification is in accordance with the recently proposed definition and classification of Bax et al (3).

Neonatal special care for preterm infants was first introduced in Maribor in the late 1960s. Initially, it included the provision of intravenous fluids and special care in incubators. In the late 1980s, endotracheal assisted ventilation for infants with respiratory distress syndrome was first initiated. Technological advances in neonatal intensive care led to the development of infant monitors that allowed for continuous monitoring of heart rate, respiration, blood pressure and oxygenation. In addition, umbilical catheter placement facilitated the measurement of intra–arterial levels of oxygenation. This more aggressive therapy was extended to newborns with lower birth weight and shorter gestation in Maribor by the mid 1990s to mid 2000s. The majority of <1500 g birth weight infants received delivery room resuscitation and endotracheal assisted ventilation. Surfactant therapy was introduced to prevent or treat respiratory distress syndrome in the late 1990s to mid 2000s (31).

Concomitant perinatal obstetric interventions, which increased in the 1990s, included fetal monitoring and antenatal steroid therapy for all mothers with threatened preterm labor, to accelerate pulmonary maturity and prevent intraventricular cerebral hemorrhage. Indomethacin and magnesium sulfate were increasingly used as tocolytic agents for mothers with threatened preterm labor. In addition, there was an increase in the use of antibiotics for mothers with premature membrane rupture and the rate of cesarean section.

Additional neonatal therapies introduced in the 1990s included the administration of indomethacin to prevent or treat patent ductus arteriosus. Indomethacin had been proven also to decrease the rate and severity of periventricular hemorrhage. Postnatal dexamethasone was also used with increasing frequency in the late 1990s. Its use has been sharply reduced after a joint statement from the American Academy of Pediatrics in 2002 that postnatal steroid therapy is not recommended for routine use. The use of endotracheal assisted ventilation was curtailed in the early 2000s, and increasing numbers of immature infants are receiving trials of nasal constant pressure rather than endotracheal ventilator support. Oxygen administration has been relatively restricted. Nutrition has also been optimized. Increased protein is being provided parenterally, and oral intake of fortified breast milk or increased calorie and protein formula is being provided as early as possible (31).

Understanding the trends in CP incidence is important when evaluating primary preventive efforts and estimating the medical care and supportive services needed for the affected children and their families. The aim of our study was to estimate the trends in frequency, the changes in types of CP, and the frequency of combinations with other disabilities, based on changes in perinatal health care in the Maribor region of Slovenia.

MATERIAL AND METHODS

The study area comprised the districts of Maribor, Ptuj, Ormož, Slovenska Bistrica and Lenart, and had a total population of 319,530 inhabitants on January 1, 2006 (Figure 1). The geographical area was divided into three child rehabilitation districts (Maribor, Ptuj and Slovenska Bistrica) that offered services to the pediatric population with developmental disabilities. Neuropediatricians, physiotherapists and occupational therapists collaborate and offer all children with probable or defined CP participation in the follow–up program, with the main priority on prevention of hip dislocation and severe contractures and deformities.

In the birth–year period 1988–2003, there were around 52,450 live births in the study area. A population group of 52,292 children aged 3–19 years was living in the Maribor region on January 1, 2006. Multiple sources of information about the child population were used during the study: the Slove-

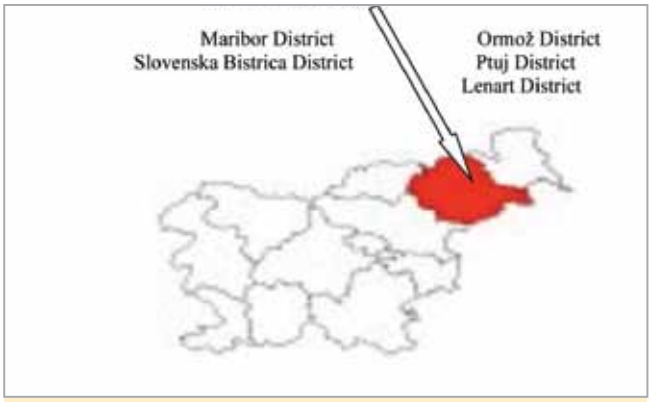

Figure 1. *Study area in the north–eastern part of Slovenia (Maribor region)*

nian population register, and diagnosis registers in hospitals/pediatric clinics, as well as those from rehabilitation centers.

CP and CP subtypes were classified according to the Swedish (Hagberg) classification system for the period 1988–1998, and the Pallisano classification system for 1998–2003 (2,5). The Swedish classification system includes three spastic syndromes: spastic hemiplegia, diplegia and tetraplegia. Spastic tetraplegia is defined as massive total motor disability involving all four limbs; the upper to at least the same degree as the lower ones. All cases in which the lower limbs are more affected than the upper ones are assigned to the spastic diplegic CP group. The dyskinetic subgroups are choreoathetosis and dystonia, and also include a third transitional group, dystonia plus choreoathetosis, in which neither dyskinetic sign is dominant. Capability and performance of gross and fine motor activities were evaluated for every child in 1998–2003. Children with CP were divided into five groups according to the Gross Motor Function Classification System (GMFCS) according to Pallisano et al. : 1, minimal CP (movement difficulties present but without significant functional impairment); 2, mild CP (movement difficulties causing milder functional impairment); 3, moderate CP (movement difficulties causing more severe functional impairment); 4, moderately severe CP (functions achieved by use of aids and/or by surgical corrections); and 5, severe CP (few useful intentional movements, although some function can be achieved) (2).

We determined the trends in the frequency of suspected CP in live births and 1–year survivor cohorts of children born at the Department of Perinatology, Maribor Teaching Hospital, who were living from birth to the end of our study in one of the three child rehabilitation districts (Maribor, Ptuj and Slovenska Bistrica) of the Maribor region in 1988–2003.

The Maribor region birth cohort was under effective surveillance and the appropriate diagnostic information was sought at regular yearly intervals. We were in a position to describe the cumulative incidence of CP within the cohort. Consistent with the view that the population at risk should be the denominator, we agreed with other authors that survivors of the neonatal period are the best denominator (6). The cumulative incidence of CP based on serial examinations of a cohort will always be higher than the prevalence of CP ascertained through registry work (7).

Children with CP were identified through three related studies over three birth–year periods, 1988–1993, 1994–1998, and 1998–2003. Children born between 1988 and 2003 were identified as candidates for CP at the age of 1 year, and then regularly followed up, and diagnosis was confirmed at the age of ≥3 years. The same neuropediatrician confirmed each case of CP. The epidemiological data on suspected CP or CP, epilepsy and mental retardation were obtained from the annual reports of the Center for Children with Developmental Disabilities (CCDD) at the Maribor Public Health Center, and from the CCDDs at Ptuj General Hospital and Slovenska Bistrica. The data were collected with the cooperation of pediatricians, child neurologists and child psychiatrists, clinical psychologists at Maribor Public Health Center and pediatricians at several other centers: Neonatology Unit of Division of Gynecology and Perinatology; and Intensive Care Unit and Unit of Child Neurology and Child Psychiatry of Division of Pediatrics, University Medical Center Maribor.

The number of births and data on infant mortality for the region of Maribor for the periods of interest were obtained from the database of the Institute of Public Health of the Republic of Slovenia. One–year

survivors, who were defined as those born alive and who survived their first birthday in the Maribor region in 1988–1993, 1994–1997 and 1998–2003, were determined by subtracting the number of infant deaths from the number of live births.

Birth weight groups were defined as follows: normal, >2500 g; low, 1500–2499 g, and very low, <1500 g. Gestational age groups were defined as follows: extremely preterm, <28 weeks; very preterm, 28–31 weeks; moderately preterm, 32–36 weeks; and birth at term, ≥37 weeks.

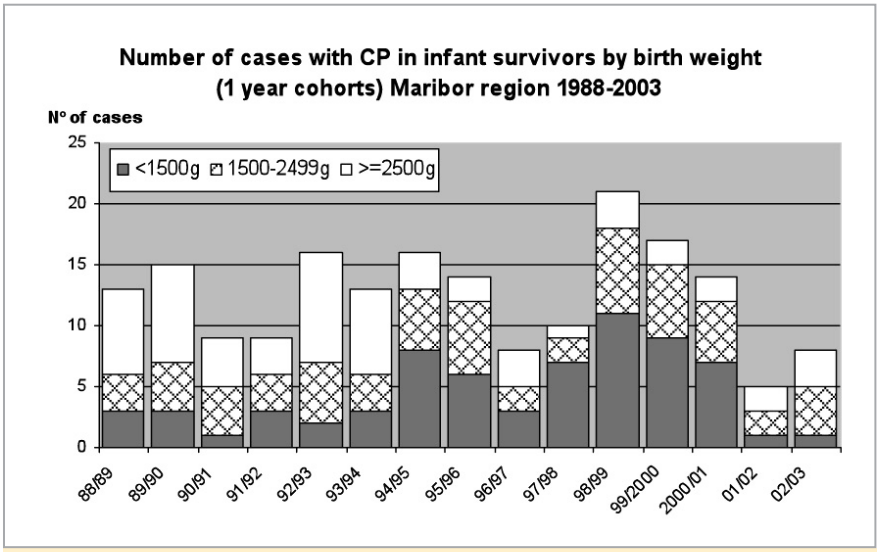

Figure 2. *Number of cases with CP in infant survivors by birth weight (1 year cohorts) Maribor region (1988–2003)*

Data were also analyzed by: trends in incidence of suspected CP in 1-year survivor cohorts by birth weight and gestational age; trends in type of CP (5); and trends in degree of disability (2).

Epilepsy was diagnosed if the child had recurrent epileptic attacks that were not caused by increased body temperature or acute brain injury (8). Mental retardation was evaluated by clinical psychologists using standard psychometric tests, and was diagnosed if the child's basic intellectual capacity was at least two standard deviations under the average in children of the same age (9).

RESULTS

Prevalence and incidence of CP in the whole study group

The present series comprised 196 children with CP born in 1988–2003: 61 cases in 1988–1993, 62 in 1994–1998, and 73 in 1998–2003. The crude mean prevalence of CP was 3.7/1000 infant survivors, 2.7/1000 for preterm infants, and 1/1000 for term infants. In Figure 2, the incidence of CP in 1-year cohorts according to birth weight is presented. For CP at all birth weights, the overall impression was of stability in 1988–1995, with the largest increase in incidence in 1999, 2000 and 2001, followed by decline in the next few years. CP incidence per 1000 survivors with birth weight <1500 g exhibited a sharp increase in the 1999, 2000 and 2001, but seemed to decline in the last 2 years of our study. A similar, but slightly less pronounced trend was found for infants who weighed 1500–2499 g at birth. Finally, the time trend for CP in infants who weighed >2500 g at birth showed an up-and-down pattern until 1999 and then a sharp decrease in the following years.

Birth characteristics of the present series of 73 children with CP born in 1998–2003

Six children (8.5%) were born extremely preterm, 31 (42%) very preterm, 23 (31%) moderately preterm, and 13 (18.5%) at term. Thirty-three children (45.5%) had a birth weight of < 1500 g; 27 (36.5%), 1500–2499 g; and 13 (18%), ≥2500 g.

Incidence of CP (1998–2003)

The incidence of CP according to gestational age in yearly cohorts is presented in Figure 3. The gestational-age-specific prevalence of CP is presented in Figure 4. For the last 5-year study period, it was 18.7% (6/32) for <28 weeks gestation, 29.1% (30/110) for 28–31 weeks, 3.3% (22/695) for 32–36 weeks, and

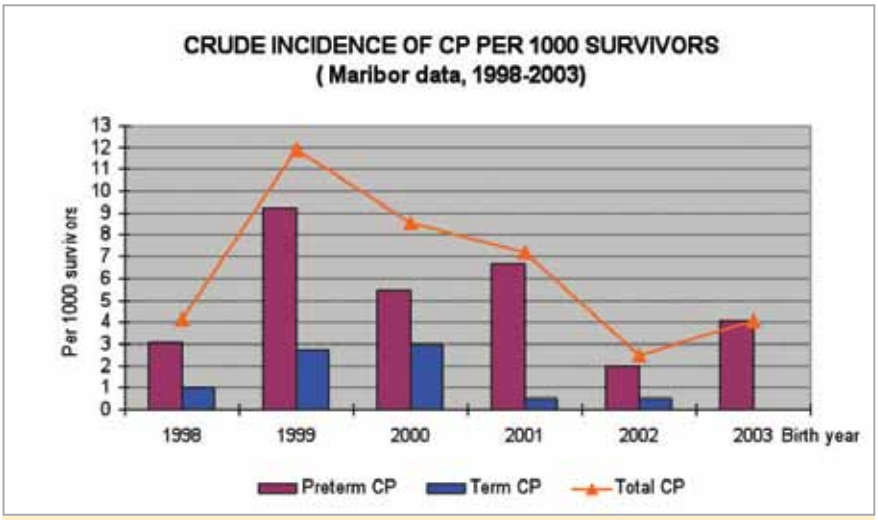

Figure 3. *Incidence of CP per 1000 survivors by gestational age (Maribor data, 1998–2003)*

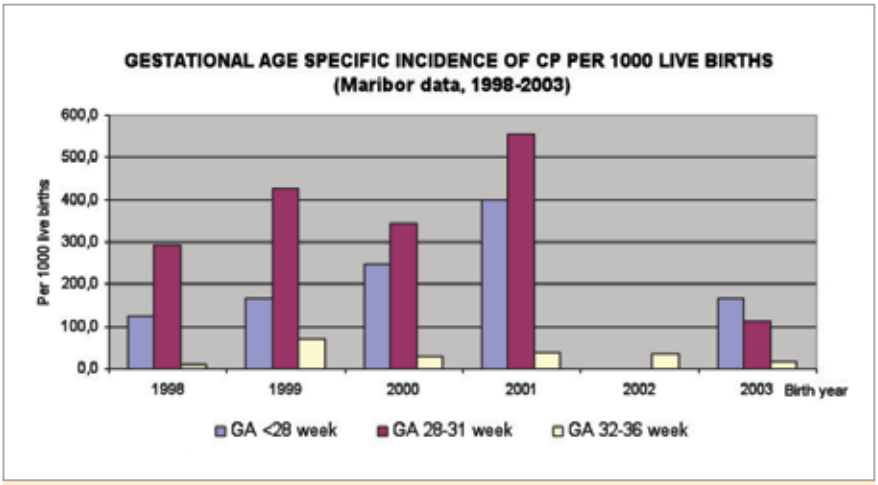

Figure 4. *Gestational age specific incidence of CP per 1000 live births*

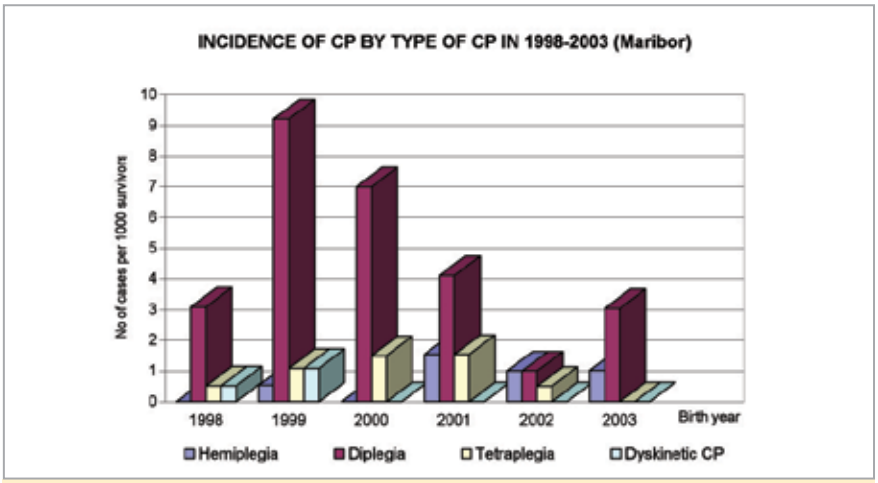

Figure 5. *Incidence of CP by type of CP in yearly cohorts (Maribor, 1998–2003)*

for 0.1% (16/11,711) for >37 weeks. The birth-weight-specific incidence of CP was 18% for <1000 g, 24% for 1000–1499 g, 3.5% for 1500–2499 g, and 0.1% for >2500 g.

The incidence per 1000 survivors in yearly cohorts according to CP type is shown in Figure 5. Spastic diplegia, hemiplegia and tetraplegia accounted for 68.4%, 12.2% and 14.8%, respectively, and dyskinetic CP for 4.6% in the whole 15-year period. In the last 5-year period (1998–2003), diplegia, hemiplegia, tetraplegia and dyskinetic CP accounted for 71%, 11%, 13% and 4%, respectively.

Gross motor function ability in the different CP subgroups as defined in the GMFCS is presented in Figure 6. Almost half the children with CP (44%) in 1998–2003 had minimal or mild functional impairment and were classified as GMFCS level I and II, 16% were level III, 21% were level IV, and 19% were level V.

DISCUSSION

CP epidemiology is important as an indicator of hazards relevant to maternal, perinatal and neonatal care. This ongoing epidemiological study of CP in Maribor region now comprises 196 children with CP from the birth-year period 1988–2003. During these years, perinatal mortality has decreased steeply (Figure 7), and maternal and peri/neonatal care has undergone major changes, accom-

panied by significant variations in CP prevalence. The neonatal mortality rate declined in Maribor significantly from 6.6/1000 live births in 1997 to 3.1/1000 in 2001 and 1.8/1000 in 2009. Children who were born very or extremely prematurely comprised 54% of those with CP in the last part of our study. During recent decades, the survival of very preterm infants has improved due to the introduction of antenatal steroids, surfactant replacement therapy, and postnatal steroids.

In the last 10 years of our study, the Neonatal Unit, University Hospital Department of Gynecology and Perinatology, and Intensive Care Unit, University Hospital Department of Pediatrics, both at University Clinical Center Maribor, have assumed responsibility for tertiary care. With these responsibilities have come greater perinatal morbidity, more premature births and more newborns with low birth weight. The change in perinatal care in recent years was expected to have an impact on the frequency of CP. All perinatal improvements in the management of maternal complications, more intensive surveillance of fetuses during labor, and improved ventilatory management of premature newborns have been translated into much better neonatal survival, especially in very premature infants. The pronounced decrease in perinatal mortality in the Maribor region in 1999 (Figure 7) coincided with an enormous rise (Figure 8) in predominantly preterm bilateral spastic CP, especially in 28–31 weeks gestational age

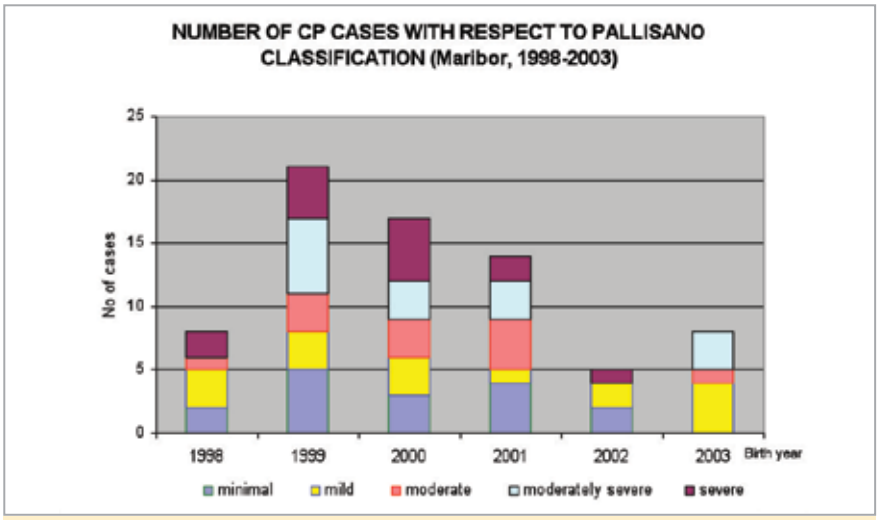

Figure 6. *Number of CP cases with respect to Pallisano classification (Maribor 1998–2003)*

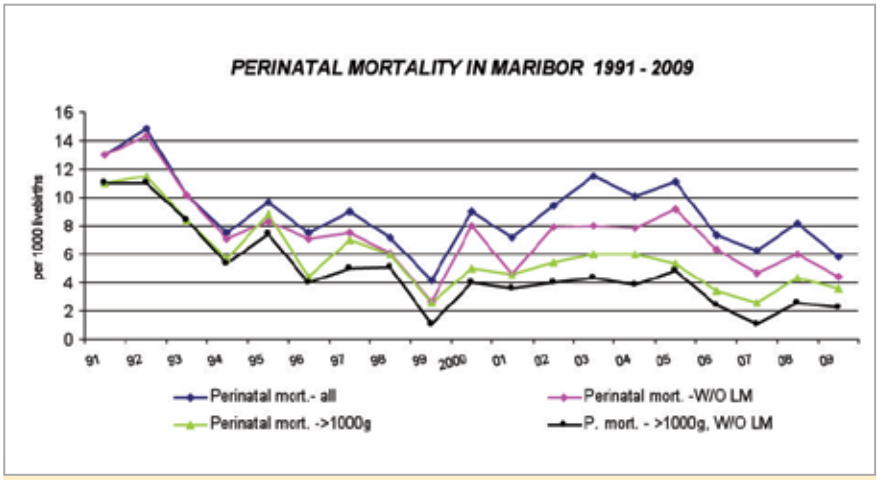

Figure 7. *Perinatal mortality in Maribor 1991–2009*

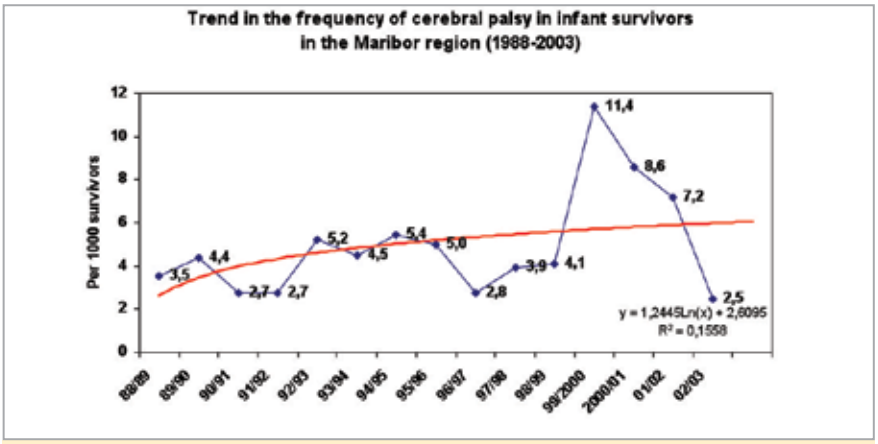

Figure 8. *Trend in the incidence of CP in infant survivors in the Maribor region (1988–2003)*

group, but there was also a decrease in CP incidence in the term group.

This higher survival rate has led to increased interest in the long–term outcome of low birth weight infants. In the late 1990s, the first publications about the adverse effect of postnatal corticosteroids (especially dexamethasone) on neurodevelopmental outcome were reported by Yeh and Shinwell (10,11). In the study of Vohr et al., postnatal steroids were associated with higher incidence of CP (12).

Advances in maternal health care and obstetric and neonatal care have resulted in changes in the prevalence of CP in preterm infants, a decrease in children born at low gestational age in some countries, and in an increase in others (13–16). At the same time, more fragile children of all gestational ages survive than before, with chronic morbidity of various kinds, such as lung disease and neurodevelopmental impairment other than CP (17). Spastic CP types are by far the most common, constituting 80–91% of the CP panorama (16,18). In more than half the children with CP, there are accompanying impairments, which may override the motor impairment in some cases (16). Epilepsy, learning disability, severe visual and hearing impairments may be detected at an early age, whereas more subtle sensory and cognitive problems become apparent at school age (19). Screening for these conditions should be a part of the evaluation of a child with CP (1).

The new preterm survivors constitute a very high–risk population for various kinds of disability and CP. A similar trend has been observed in Western Australia, where an increase in CP incidence has been seen in children born very and extremely prematurely, although the overall trend in CP frequency is decreasing (15). In Western Sweden, in the birth–year period 1995–1998, a decrease in CP incidence has taken place in preterm and term infants (20, 21).

The risk in infants born before 28 weeks gestation is about 100/1000 survivors (19), whereas among infants born at term, the risk is about 1/1000 (22,23). In our study (Maribor 1998–2003), the age–specific prevalence of CP for <28 weeks gestational age was 187/1000 survivors, and among infants born at term, the risk was 1/1000. Despite this strong association, CP is not the most prevalent adverse outcome among extremely premature infants; mental retardation occurs twice as frequently (24). The SCPE Collaboration has reported that 31% of children with CP have severe intellectual disability, 11% have severe visual disability, and 21% have epilepsy (25). The strength of this association between prematurity and CP in Maribor is presented in Figure 3.

Interest in secular trends has gained importance with the advent of modern obstetric and neonatal practices. In developed countries over the past two decades, CP rates have been stable, increasing or decreasing (26–28). The results of changes in perinatal health care in Slovenia and in Maribor region have shown a significant improvement in 1988–2003, and survival among neonates with birth weight <1500 g increased to 80%. The present study showed a slightly increasing trend in CP incidence from 3.7 /1000 in the 1980s to 4.3/1000 in the 1990s and >5/1000 1–year survivors in the last observed 5–year period, and to 2.5/1000 in the year 2003 (Figure 8). The data from eight European countries presented by the SCPE network reported an increasing trend in CP from 1.7/1000 live births in the 1970s to 2.4/1000 live births in the 1990s (25). The SCPE reports that the proportion of low birth weight infants among all children with CP is rising: 32% of all cases in 1966 and 50% in 1989. In the present study, the proportion of premature infants among all children with CP increased to 82% in 1998–2003. In addition, the SCPE reports that there is a strong association between socioeconomic status and the occurrence of CP. In the United Kingdom, the prevalence of CP is 3.3/1000 live births in the poorer quintile compared with 2.08 in the more affluent quintile. This association between socioeconomic status and occurrence of CP was also found in our study.

Wilson Costello et al. have assessed two cohorts of infants born with birth weights <1000 g during 1982–1989 and 1990–1998 (30). They found that survival increased from 49% in 1982–1989 to 67%

in 1990–1998, but that the rate of overall neurodevelopmental impairments at 20 months increased from 26% in 1982–1989 to 36% in 1990–1998. In a subsequent study that has compared the outcomes of infants born in 2000–2002, the same authors have found improved neurodevelopmental outcome without further change in survival.

CONCLUSION

The evolution of neonatal intensive care in Maribor since the 1980s, with increasing efforts to help high–risk babies survive at birth and in the neonatal period, has resulted in increased survival in the late 1990s. The dramatic increase in infant survival in 1999 was especially evident in the group born at 28–32 weeks of gestation. This increase indicates good prospects, i.e. many healthy survivors, as well as disadvantages, such as a slowly increasing group of children who have sustained brain injuries, some of them with serious impairments, including CP. Since 2001, there has been little change in survival. There is also evidence of a lower rate of neonatal morbidity, and in the last 3 years of our 15–year study, we can report of a decrease in the rate of CP. All of these results are associated with changes in perinatal and neonatal practice, including increased use of antenatal steroid therapy, a decrease in postnatal use of dexamethasone, curtailed use of endotracheal assisted ventilation, restricted oxygen administration, and optimized nutrition of high–risk newborn infants.

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