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Neuroblastoma in Hungary ☆

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ABSTRACT

In a cohort study we investigated the incidence and distribution of the age and stage of neuroblastoma at diagnosis, and the outcome, in children aged 0–14 years during 1988–1998 in Hungary.

The proportion of neuroblastoma in age groups of 0 year old, 1–4 year old, 5–9 year old and 10–14 year old children was 30%, 53%, 12% and 5%, respectively. The proportion of stage 1–2, stage 3–4 and stage 4s cases was 30%, 65% and 3%, respectively.

Hungarian data were compared with data reported for other Western European countries. The distribution of age at diagnosis of Hungarian cases was significantly different from France and Germany ($p < 0.05$), but not different from that of the United Kingdom (UK). However, the proportion of stage 1–2 neuroblastoma was higher in Hungarian children (30%) than that reported in French, German and UK children.

The incidence and survival of neuroblastoma in Hungary is broadly comparable to that reported elsewhere in Europe.

1. Introduction

Neuroblastoma is one of the most common solid tumours found in children and the most common tumour found in infants, accounting for about 9% of all cases of paediatric cancer and it is a major contributor to childhood cancer mortality worldwide.[1] Approximately 90% of patients with neuroblastoma are diagnosed within the first 5 years of life. The incidence of neuroblastoma varies between different countries in Europe as does the distribution of stage and age at diagnosis.[2]

In this study we investigated the incidence and distribution of the age and stage of neuroblastoma at diagnosis, and the outcome, in Hungary over a period of 11 years, and compared the findings with those reported for other Western European countries.

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2. Materials and methods

2.1. Study population

Children diagnosed with neuroblastoma during 1988–1998 were considered. Registrations of first malignancies for children, diagnosed according to the International Neuroblastoma Staging System (INSS), aged under 15 years in Hungary between 1988–1998 were obtained from the Hungarian Paediatric Oncology Centres, of which there are ten. The ten contributing centres cover the whole of Hungary. All paediatric cancer patients are registered and followed in the Hungarian Paediatric Oncology Group data centre. The registry is updated every 3 months. Each child is followed-up until adulthood which provides a high level of completeness of ascertainment for a long time period.

For each case child, dates of birth and diagnosis, sex, and disease stage were recorded. Cases over the age of 15 years were omitted from the analysis. Because of the small number of cases, stages I and II were combined, as were stages III and IV. The vital status of each registered case was assessed on 31 December 2004.

The gender and year of birth and population for the study period by age and gender was obtained from the Demographic Yearbook.[3]

2.2. Statistical methods

Age-specific incidence rates and their 95% confidence intervals (CI) were calculated.[4] To enable comparison of the Hungarian neuroblastoma data with that reported for elsewhere in Europe by Powell et al.,[5] the appropriate age and stage categorisation were adopted and directly standardised incidence rates (world population) were calculated. Median and interquartile range were used to compare age at diagnosis between countries. Kruskal–Wallis tests were carried out to compare the age and stage differences between countries. Survival rates with 95% CI were calculated using Kaplan–Meier estimation. The statistical differences in survival among sex and stage subgroups were tested using logrank statistics for homogeneity. Five-year survival was compared for three diagnosis periods (1988–1991, 1992–1994 and 1995–1998) using Cox regression. Schoenfeld residuals were used to check model goodness of fit.[6] All analyses were performed using STATA Software (version 8.0). A p-value less than 0.05 was taken to be statistically significant.

3. Results

3.1. Characteristics of neuroblastoma

The total number of eligible neuroblastoma cases in Hungary identified for the study was 253 (147 (58%) boys and 106 (42%) girls). The median age at diagnosis was 25.8 months (IQR: 10.0–49.8 months). Seventy-five (30%) were younger than one year of age at diagnosis, 135 (53%), 30 (12%) and 13 (5%) cases were between 1–4 years old, between 5–9 years old and between 10–14 years old, respectively. Table 1 shows the distribution of cases by age, sex and stage. The proportion of stage 1–2, stage 3–4 and stage 4s cases were 30%, 65% and 3%, respectively. In the study group four cases (2%) had no stage classification. To compare the Hungarian data with data reported for some Western European countries the data were aggregated as shown in Table 2. Between 1987 and 1991, 1672 cases of neuroblastoma were diagnosed in the four European countries – 624 from France, 69 from Austria, 493 from Germany, and 486 from the United Kingdom (UK). There was significant variation in the median age at diagnosis ($p < 0.0001$), the UK having the highest median age and the smallest proportion of cases in children under 1 year of age. Disease stage was known in more than 95% of cases; the proportion of cases that were stage 4 was 61.5% in the UK, compared with around 40% in the other countries.

Table 1 – The incidence of neuroblastoma cases (per million) by age, stage and sex in Hungary (n = 253)

Age	Stage	Male	Female	Total
<1 year	1–2	31.27	25.62	28.45
	3–4	33.14	18.56	25.85
	4s	9.02	3.48	6.25
<1 year total		**73.43**	**47.66**	**60.55**
1–4 years	1–2	6.43	5.39	5.92
	3–4	21.96	17.21	19.59
1–4 years total		**28.39**	**22.61**	**25.5**
5–9 years	1–2	0.86	0.91	0.88
	3–4	2.86	3.75	3.31
5–9 years total		**3.72**	**4.66**	**4.19**
10–14 years	1–2	0.71	0.29	0.49
	3–4	1.43	0.75	1.09
10–14 years total		**2.14**	**1.04**	**1.59**
0–14 years	1–2	4.01	3.14	3.57
	3–4	8.71	6.8	7.75
	4s	0.51	0.21	0.37
0–14 years Total		**13.23**	**10.15**	**11.69**

The distribution of age at diagnosis of Hungarian cases was significantly different from those of France and Germany ($p < 0.05$), but not different from that of the UK. Austria was omitted from the comparisons because of the small number of cases. The Hungarian children were older (median age 25.8 months) at diagnosis than French (21.6 months) and German (17.3 months) children, but not UK children (24.8 months). However, the proportion of stage 1–2 neuroblastoma was higher in Hungarian children (30%) than that reported in French, German and UK children, 25%, 24% and 14% respectively.

3.2. Incidence of neuroblastoma

Age-specific incidence rates are shown in Table 3. The age-standardised incidence rate for Hungary was 12.8 per million children per year (95% CI: 10.5–15.0), which was comparable to that from Austria (11.7), France (12.5), Germany (11.4) but non-significantly higher than the UK (10.1).

The age-specific incidence rates per million children per year were lower for girls (age under 1 year: 47.7 (23.2–72.1); age 1–4 years: 22.6 (14.1–31.1); age 5–9 years: 4.7 (2.4–6.9) and

Table 2 – Characteristics of neuroblastoma cases in Hungary and four Western European countries[5]

	Hungary	Austria*	France	Germany	UK
Time period	1988–1998	1989–1991	1989–1991	1989–1991	1989–1991
Cases	253	69	624	493	486
Age at diagnosis					
<1 year	75 (30%)	29 (42%)	240 (39%)	209 (42%)	126 (26%)
1–4 years	135 (53%)	30 (43%)	299 (48%)	231 (47%)	289 (59%)
5–9 years	30 (12%)	7 (10%)	71 (11%)	42 (9%)	62 (13%)
10–14 years	13 (5%)	3 (4%)	14 (2%)	11 (2%)	9 (2%)
Stage					
1–2	77 (30%)	17 (25%)	157 (25%)	119 (24%)	70 (14%)
3–4	164 (65%)	45 (65%)	408 (66%)	310 (63%)	368 (76%)
4s	8 (3%)	7 (10%)	56 (9%)	45 (9%)	25 (5%)
Not known	4 (2%)	0 (0%)	3 (0%)	19 (4%)	23 (5%)

* Excluded from comparisons because of small number of cases.

Table 3 – Age-specific and directly age-standardised (world population) incidence rates (per million) for neuroblastoma in Hungary (1988–1998) and in four Western European countries (1987–1991)[5]

	Annual incidence rate (95%CI) per million children									
	Hungary		Austria		France		Germany		UK	
Age-specific										
< 1 year	60.9	(40.6–81.1)	65.8	(44.1–94.5)	63.7	(55.7–71.8)	61.6	(53.2–69.9)	33.7	(27.8–39.5)
1–4 years	25.5	(19.8–31.2)	17.0	(11.4–24.2)	19.9	(17.6–22.1)	18.0	(15.7–20.3)	19.9	(17.6–22.2)
5–9 years	4.2	(2.6–5.8)	3.1	(1.2–6.4)	3.7	(2.8–4.5)	2.7	(1.9–3.5)	3.6	(2.7–4.4)
10–14 years	1.7	(0.8–2.4)	1.3	(0.3–3.9)	0.7	(0.3–1.1)	0.7	(0.3–1.2)	0.5	(0.2–0.9)
Age-standardised	12.8	(10.6–15.0)	11.7	(9.0–14.5)	12.5	(11.5–13.5)	11.4	(10.4–12.4)	10.1	(9.2–11.0)

age 10–14 years: 1.1 (0.1–2.1)) than boys (age less than 1 year: 60.6 (43.3–77.8); age 1–4 years: 25.5 (20.2–30.8); age 5–9 years: 4.2 (2.7–5.7) and age 10–14 years: 1.6 (0.8–2.4)).

3.3. *Survival rates*

Of 126 deaths, 121 occurred within 5 years of diagnosis. Four children aged 1–4 years and one child aged 5–9 years at diagnosis died following the 5 year period after diagnosis. The distribution of the 126 deaths by age, stage and gender are shown in Table 4. The age-standardised mortality rate was 5.7 per million children (95% CI: 4.2–7.2).

Overall survival rate (Kaplan–Meier estimation) was 52% (46–58%). The gender specific survival rates were 50% (42–58%) and 55% (45–64%) for boys and girls, respectively ($p = 0.59$).

The 5-year survival rates were 87% (76–92%), 39% (31–47%), 40% (23–57%) and 23% (6–47%) for those aged under 1 year, between 1–4 years, 5–9 years and 10–14 years, respectively. Survival was significantly higher in younger children ($p < 0.001$).

Children aged under 1 year with stage 1–2 neuroblastoma had the highest survival rate (94%). The 5-year survival rates by stage of 88%, 82% and 36% were found for stage 4s, stage 1–2 and 3–4 cases, respectively. Survival was significantly lower for stage 3–4 ($p < 0.001$). Children aged under 1 year with stage 1 neuroblastoma had a high survival rate (97%).

The 5-year survival rates for the diagnosis periods of 1988–1991, 1992–1994 and 1995–1998 were 38% (28–49%), 64% (51–74%) and 56% (46–65%), respectively. Survival was significantly lower during the period 1988–1991 ($p < 0.001$). The

Table 4 – The distribution of deaths from neuroblastoma by age, stage and gender in Hungary (n = 126)

Age	Stage	Total cases	Number of deaths			Percent deaths of all cases
			Male	Female	Total	
<1 year	1–2	36	0	1	1	(3%)
	3–4	31	4	5	9	(29%)
<1 year	**Total**	**75**	**5**	**6**	**11**	(15%)
1–4 years	1–2	31	5	4	9	(29%)
	3–4	102	48	29	77	(75%)
1–4 years	**Total**	**135**	**53**	**33**	**86**	(64%)
5–9 years	1–2	6	1	1	2	(33%)
	3–4	22	9	7	16	(73%)
5–9 years	**Total**	**30**	**10**	**8**	**18**	(60%)
10–14 years	1–2	4	2	0	2	(50%)
	3–4	9	6	3	9	(100%)
10–14 years	**Total**	**13**	**8**	**3**	**11**	(85%)
0–14 years	1–2	77	8	6	14	(18%)
	3–4	164	67	44	111	(68%)
	4s	8	4	5	1	(13%)
	Unknown	4	0	0	0	(0%)
0–14 years	**Total**	**253**	**79**	**55**	**126**	(50%)

Table 5 – Five-year survival rates and 95% confidence intervals (95%CI) for children 0–14 years, stratified by age, sex, stage and time period

Age	Stage	1988–1991		1992–1994		1995–1998		1988–1998					
		Total		Total		Total		Male		Female		Total	
		SR	95%CI	SR	95%CI	SR	95%CI	SR	95%CI	SR	95%CI	SR	95%CI
<1 year	1–2	88%	(39–98%)	100%	–	100%	–	100%	–	93%	(61–99%)	97%	(82–99%)
	3–4	57%	(17–84%)	81%	(45–95%)	75%	(41–91%)	80%	(55–92%)	60%	(25–83%)	73%	(54–86%)
	4s	100%	–	100%	–	67%	(5–95%)	83%	(27–97%)	100%	–	87%	(39–98%)
<1 year total		78%	(51–91%)	92%	(72–98%)	87%	(69–95%)	89%	(76–95%)	81%	(61–92%)	87%	(76–92%)
1–4 years	1–2	75%	(31–93%)	50%	(11–80%)	76%	(49–90%)	71%	(43–87%)	71%	(41–88%)	71%	(52–84%)
	3–4	19%	(9–34%)	50%	(31–67%)	21%	(10–35%)	22%	(13–33%)	37%	(23–51%)	28%	(20–38%)
1–4 years total		29%	(17–43%)	51%	(34–66%)	39%	(27–52%)	34%	(24–44%)	47%	(33–59%)	39%	(31–47%)
5–9 years	1–2	100%	–	0%	–	75%	(13–96%)	67%	(5–95%)	67%	(5–95%)	67%	(19–90%)
	3–4	9%	(1–33%)	40%	(5–75%)	50%	(11–80%)	10%	(1–36%)	42%	(15–67%)	28%	(11–46%)
5–9 years total		29%	(9–52%)	33%	(5–68%)	60%	(25–83%)	29%	(8–52%)	50%	(25–71%)	40%	(23–57%)
10–14 years	1–2	0%	–	–	–	100%	–	33%	(1–77%)	100%	–	50%	(6–85%)
	3–4	0%	–	0%	–	0%	–	17%	(1–52%)	0%	–	11%	(1–38%)
10–14 years total		0%	–	0%	–	40%	(5–75%)	22%	(3–51%)	25%	(1–67%)	23%	(6–47%)
0–14 years	1–2	74%	(48–88%)	79%	(53–92%)	87%	(72–94%)	82%	(67–90%)	82%	(64–91%)	82%	(71–89%)
	3–4	21%	(12–32%)	55%	(40–68%)	34%	(22–46%)	33%	(23–42%)	40	(28–51%)	36%	(28–43%)
	4s	100%	–	100%	–	67%	(5–95%)	83%	(27–97%)	100%	–	88%	(39–98%)
0–14 years total		38%	(28–49%)	64%	(51–74%)	56%	(46–65%)	50%	(42–58%)	55%	(45–64%)	52%	(46–58%)

distribution of 5-year survival rates stratified by age, stage, gender and diagnosis period are summarised in Table 5. There was a decreasing trend for mortality rate overall across the three time periods (hazard ratio 0.74 (95% CI: 0.60–0.91; $p = 0.004$). This model had a good fit.

4. Discussion

4.1. *Summary of the results*

In our study which covered a time period of 11 years, we examined the incidence of neuroblastoma among children aged under 15 years in Hungary.

The proportion of neuroblastoma in age groups of 0 year old, 1–4 year old, 5–9 year old and 10–14 year old children were 30%, 53%, 12% and 5%, respectively. The proportion of stage 1–2, stage 3–4 and stage 4s cases were 30%, 65% and 3%, respectively.

The age-standardised incidence rate of neuroblastoma was 12.8 per million per year for children aged 0–14 years and the age standardised mortality rate was 5.7 per million children. A significant increase in 5-year survival rates over the time periods was found. The highest 5-year survival rate was for children aged under 1 year and diagnosed with 4s neuroblastoma. In contrast, for older age groups, the 5- year survival rates were under 50%.

4.2. *Strengths and weaknesses*

The Hungarian Paediatric Oncology Group (HPOG) standardised the diagnosis and staging procedure with collaboration of all ten regional centres.[7,8] All paediatric cancer patients are registered and followed in the HPOG data centre which provides a high level of completeness of ascertainment for a long time period.

4.3. *Comparison with other studies*

The age-standardised incidence rate of neuroblastoma in children aged 0–14 years in Hungary was similar to that reported for Germany, Austria, France but non-significantly higher than that in the UK.[5] However, the proportion of children presenting under 1 year was significantly lower than that reported for France and Germany, but similar to the UK. This could reflect a delayed diagnosis in Hungary which was suggested as an explanation for the pattern of presentation in the UK.[5] However, the proportion of stages 1–2 at diagnosis is higher rather than lower than reported for these countries, which does not support the hypothesis of diagnostic delay in this population. Nevertheless, the proportion of stages 3–4 at diagnosis was comparable to that in Austria, France and Germany. The age-standardised mortality rate of neuroblastoma in children aged 0–14 years in Hungary was similar to that in the UK (5.5 95% CI: 4.8–6.1)[9] but higher than that reported in Germany (4.2 95% CI: 3.6–4.8).[5]

Hence the pattern of neuroblastoma cases at presentation in Hungary has characteristics of France, Germany and the UK.

The 5-year survival rate of 38% for the period of 1988–1991 was lower than the 53% reported for this period for Western Europe.[10] However, the 5-year survival rate of 64% for period 1992–1994 was similar to that reported for Western Europe for this time period (61.3%),[10,11] demonstrating a significant improvement in outcome for children with neuroblastoma in Hungary such that it is now comparable to that elsewhere in Western Europe.

Stage 4s neuroblastoma has been reported to represent around 5% of cases and occurs by definition in infants aged under 1 year.[12] Stage 4s is associated with a high rate of spontaneous maturation and involution of disease with survival rates of 70–90%.[13] In our study, stage 4s neuroblastoma estimated 3% of all cases and the 5-year survival rate was

87.5%. Thus our study confirms the favourable biologic features and excellent survival of infants with stage 4s neuroblastoma.

We did not find gender specific difference in survival, but the incidence of neuroblastoma was higher in boys than girls, similar to findings reported elsewhere.[14]

5. Conclusion

There is no evidence for delayed diagnosis for neuroblastoma in Hungary since the proportion of stage 1–2 and stage 3–4 at diagnosis is similar to that reported from elsewhere in Europe. However, the median age at diagnosis is older than those reported for some Western European countries. The incidence and survival of neuroblastoma in Hungary is broadly comparable to that elsewhere in Europe.

Conflict of interest statement

None declared.

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REFERENCES

1. Douglas NM, Dockerty JD. Population-based survival of children in New Zealand diagnosed with cancer during 1990–1993. *Eur J Cancer* 2005;**41**:1604–9.
2. Spix C, Aareleid T, Stiller C, Magnani C, Kaatsch P, Michaelis J. Survival of children with neuroblastoma. time trends and regional differences in Europe, 1978–1992. *Eur J Cancer* 2001;**37**:722–9.
3. Demographic Yearbook 1988–1998, KSH, Budapest (1973–1998).
4. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J, editors. *Cancer Incidence in Five Continents*. **Volume VI**, Lyon, IARC, 1992.
5. Powell JE, Esteve J, Mann JR, Parker L, Frappaz D, Michaelis J, et al. Neuroblastoma in Europe, differences in the pattern of disease in the UK. *Lancet* 1998;**352**:682–7.
6. Schoenfeld D. Residuals for the proportional hazards regresssion model. *Biometrika* 1982;**69**:239–41.
7. Schuler D. Systemizing childhood cancer care in Hungary, twenty-five years of progress. *Med Pediatr Oncol* 1999;**32**:68–70.
8. Jakab Zs, Balogh E, Kiss Cs, Oláh É. Epidemiologic studies in a population-based childhood cancer registry in Northeast Hungary. *Med Pediatr Oncol* 2002;**38**:338–44.
9. Cotterill SJ, Parker L, More L, Craft AW. Neuroblastoma, changing incidence and survival in young people aged 0–24 years. A report from the North of England Young Persons' Malignant Disease Registry. *Med Pediatr Oncol* 2001;**36**:231–4.
10. Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M, et al. Childhood cancer survival trends in Europe, a EUROCARE Working Group study. *J Clin Oncol* 2005;**23**:3742–51.
11. Viscomi S, Pastore G, Mosso ML, Terracini B, Madon E, Magnani C, et al. Childhood Cancer Registry of Piedmont, Italy. Population-based survival after childhood cancer diagnosed during 1970–98: a report from the Childhood Cancer Registry of Piedmont, Italy. *Haematologica* 2003;**88**:974–82.
12. Nickerson HJ, Matthay KK, Seeger RC, Brodeur GM, Shimada H, Perez C, et al. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy, a Children's Cancer Group study. *J Clin Oncol* 2000;**18**:477–86.
13. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. *Am J Epidemiol* 2004;**159**:843–51.
14. Hale G, Gula MJ, Blatt J. Impact of gender on the natural history of neuroblastoma. *Pediatr Hematol Oncol* 1994;**11**:91–7.