Eur J Pediatr (2009) 168:1081–1090
DOI 10.1007/s00431-008-0891-y

ORIGINAL PAPER

Prevalence of congenital heart defects in neuroblastoma patients: a cohort study and systematic review of literature

Klaartje van Engelen · Johannes H. M. Merks · Jan Lam · Leontien C. M. Kremer · Manouk Backes · Marieke J. H. Baars · Heleen J. H. van der Pal · Alex V. Postma · Rogier Versteeg · Huib N. Caron · Barbara J. M. Mulder

Received: 8 September 2008 / Accepted: 13 November 2008 / Published online: 17 December 2008

Abstract Data on the prevalence of congenital heart defects (CHD) in neuroblastoma patients are inconsistent. If CHD are more common in neuroblastoma patients than in the general population, cardiac screening might be warranted. In this study we used echocardiography to determine the prevalence of CHD in a single centre cohort of surviving neuroblastoma patients. In addition, we performed a systematic review of the literature. Echocardiography was performed in 119 of 133 patients (89.5%). Only two patients (1.7%) had CHD. The prevalence of CHD was not significantly different from a previously published control group of 192 leukaemia patients examined by echocardiography (P=0.49). Literature search revealed 17 studies, showing prevalence rates of CHD in neuroblastoma patients ranging from 0 to 20%. Prevalence was less than 3.6% in the majority of studies. Most studies lacked information on validity. We conclude that current evidence does not support standard cardiac screening in all patients with neuroblastoma.

Keywords Neuroblastoma · Congenital heart defects · Echocardiography · Association · Screening · Neural crest

Introduction

Neuroblastoma is an embryonal cancer of the postganglionic sympathetic nervous system, which mostly arises in the adrenal gland. It is the most common extracranial solid tumour in children, comprising 8% to 10% of all childhood cancers. The incidence is nearly one per 10,000 children under the age of 15 years [3].

K. van Engelen · M. Backes · B. J. M. Mulder
Department of Cardiology,
Academic Medical Centre,
Amsterdam, The Netherlands

K. van Engelen (✉) · M. J. H. Baars
Department of Clinical Genetics,
Academic Medical Centre,
Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands
e-mail: k.vanengelen@amc.uva.nl

J. H. M. Merks · H. N. Caron
Department of Paediatric Oncology,
Academic Medical Centre,
Amsterdam, The Netherlands

J. Lam
Department of Paediatric Cardiology,
Academic Medical Centre,
Amsterdam, The Netherlands

L. C. M. Kremer · H. J. H. van der Pal
Outpatient Clinic for the Late Effects of Treatment for Childhood Cancer, Academic Medical Centre,
Amsterdam, The Netherlands

L. C. M. Kremer
Cochrane Childhood Cancer Group, Academic Medical Centre,
Amsterdam, The Netherlands

A. V. Postma
Heart Failure Research Centre, Department of Anatomy and Embryology, Academic Medical Centre,
Amsterdam, The Netherlands

R. Versteeg
Department of Human Genetics, Academic Medical Centre,
Amsterdam, The Netherlands

B. J. M. Mulder
Department of Cardiology, University Medical Centre,
Utrecht, The Netherlands

Several case reports have been published of patients with coexisting neuroblastoma and congenital heart defects (CHD) [1, 8, 10, 17, 28]. Some studies of patients with neuroblastoma suggest a higher prevalence of CHD in neuroblastoma patients than in the general population [5, 6, 9, 11, 18], however, others did not find an association between neuroblastoma and CHD [2, 20–25]. An association between neuroblastoma and CHD is considered to be plausible as neuroblastoma originates from embryonal neural crest-derived cells [3], and neural crest-derived cells are essential in cardiogenesis as well [14]. Neural crest cells play an important role in the septation of the outflow tract of the heart and in the formation of the conotruncal part of the ventricular septum [14]. Abnormal development or migration of neural crest cells, possibly due to an underlying genetic defect, has been postulated as a mechanism that could contribute to both conditions [1, 11, 13, 28]. Indeed, neural crest-derived CHD have been reported to be more frequent in neuroblastoma patients than is expected when considering the normal distribution of subtypes of CHD [11, 13].

An association between neuroblastoma and CHD might have clinical consequences: if neuroblastoma patients have a higher risk of CHD, cardiac screening might be indicated for all neuroblastoma patients. Early detection of CHD could be important for the patient, in terms of bacterial endocarditis prophylaxis, choice of anti-cancer treatment and possible need for treatment of the CHD.

To assess the prevalence of CHD in neuroblastoma patients we conducted an echocardiographic study in a large single centre cohort of consecutive neuroblastoma patients. In addition, we systematically searched and critically appraised the literature to evaluate the existing evidence regarding the prevalence of CHD in neuroblastoma patients.

Materials and methods

Patients

The study group consisted of all patients diagnosed with neuroblastoma or ganglioneuroblastoma at the Emma Children's Hospital, Academic Medical Centre (AMC), the Netherlands, between June 1966 and September 2006, who were eligible for echocardiography, i.e. all living patients (surviving patients and patients more recently diagnosed with neuroblastoma). The Emma Children's Hospital-AMC is one of the five paediatric oncology centres in the Netherlands with a constant referral region. To minimise referral bias, we did not include patients who had been referred from another Dutch paediatric oncology centre to the Emma Children's Hospital-AMC for specialised cancer treatment. Patients referred from other countries were also excluded. We placed special emphasis on making the cohort as complete as possible to minimise

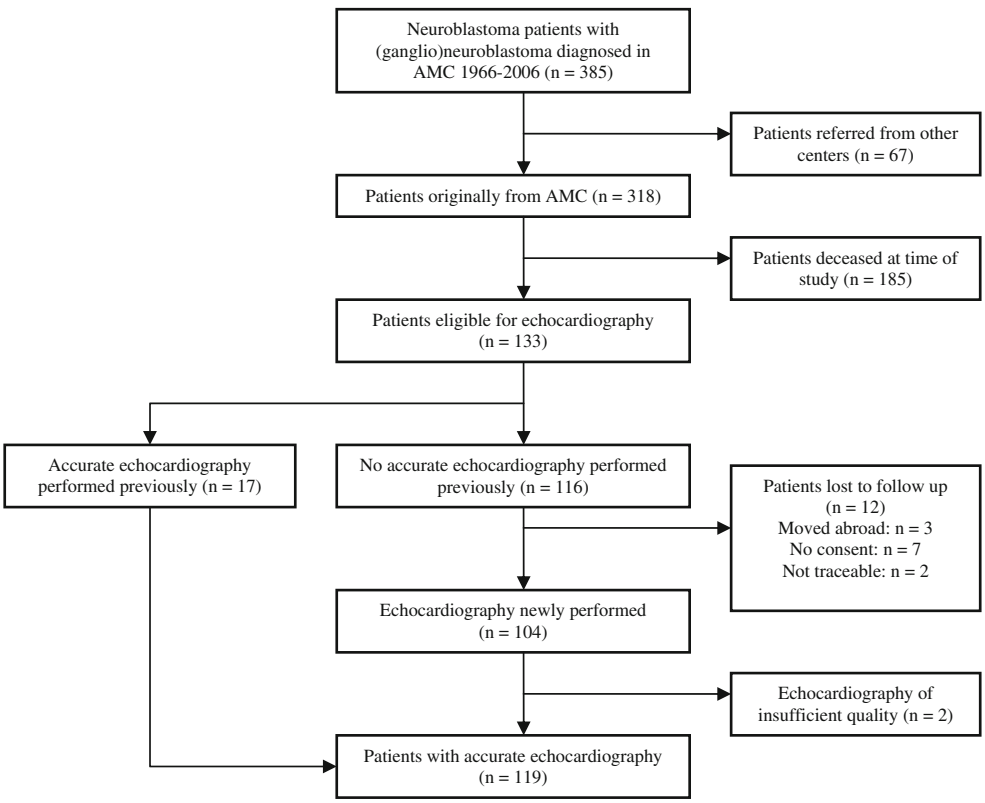

Fig. 1 Flow chart of inclusion and exclusion of patients

Table 1 Characteristics of the study group (n=119)

Male (%)		51 (42.9)
Median age at diagnosis of neuroblastoma in years (range)		0.8 (0.0–10.5)
Tumour stage (INSS)	I–III (%)	74 (62.2)
	IV (%)	45 (37.8)
Tumour MYCN amplification	Yes (%)	4 (3.4)
	Unknown (%)	49 (41.2)
Median age at echocardiography in years (range)		15.7 (0.8–41.4)

bias by selective follow-up. Patients who were deceased were not included in the echocardiography study; however, we reviewed medical charts of these patients to look for CHD.

Methods

One experienced paediatric cardiologist (JL) reviewed and performed all echocardiograms at the same laboratory in the AMC. First, we retrospectively analysed the echocardiographic images of patients who underwent echocardiography in the past before the start of this study. If the images were extensive enough to diagnose or exclude CHD, we used these in this study. If the images were not sufficient, or if echocardiographic data were not available, patients were invited to participate in this study. In the vast majority of patients, echocardiography was prospectively performed especially for this study. In those patients in whom accurate echocardiography could not be obtained we reviewed medical charts for evidence of CHD. Standard diagnostic definitions were used for CHD. Patent foramen ovale (PFO) at any age and atrial septal defect (ASD) or patent ductus arteriosus (PDA) at less than 2 months of age were regarded to be normal stages of cardiovascular development and therefore where not considered to be CHD.

Neuroblastoma staging was performed according to the International Neuroblastoma Staging System (INSS) criteria [4]. In patients who had been diagnosed with neuroblastoma before the introduction of the INSS, we converted the staging system that had been used into the INSS. MYCN oncogene amplification was analysed by southern blot analysis of tumour cells.

Data analysis

We compared the prevalence of CHD in our cohort of neuroblastoma patients who had echocardiography with the prevalence of CHD in the acute lymphoblastic leukaemia (ALL) cohort as presented by George et al. [11]. This cohort consisted of 192 children diagnosed with ALL in one hospital in Boston, USA, between 1990 and 2000, who all have had echocardiography screening. We also compared the prevalence of CHD in our cohort to data from EUROCAT Northern Netherlands (1981–2005), a network for the registration of congenital anomalies (European Registration Of Congenital Anomalies) [7]. Children with congenital anomalies are registered in EUROCAT since 1981, after report by midwives, general practitioners and specialists. We estimated prevalence of CHD in patients as a proportion. Significance of our findings was determined by use of two-tailed P-values calculated by comparing the proportion of patients with CHD in our cohort to the proportion of patients with CHD in the control group (Fisher exact test).

Results

Between June 1966 and September 2006, 385 patients had been diagnosed with (ganglio)neuroblastoma at the Emma

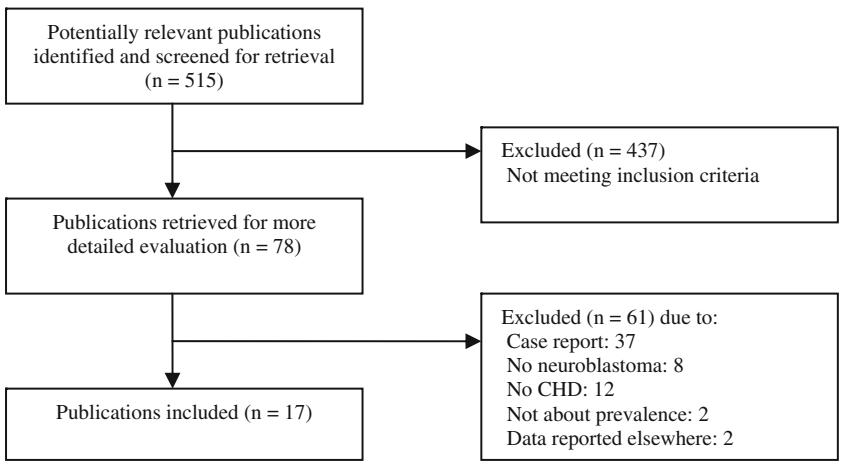

Fig. 2 Publications identified for study and exclusions

Table 2 Description of selected articles

Study	Miller et al. [21]	Miller et al. [20]	Berry et al. [2]	De la Monte et al. [6]
Country and time period	USA, different time periods within 1941–1964	USA, 1960–1966	UK, time period nm	USA, 1889–1982
Design and setting	Multicentre retrospective patient series	Multicentre (all USA) retrospective cohort study	Single centre retrospective patient series	Single centre retrospective cohort study
Patients and methods				
NB patients	Patients (<15 years) with NB listed in the diagnostic files of the hospitals and National Cooperative Leukaemia Survey (*n*=nm)	Patients (<15 years) who died of NB (*n*=2,093)	Patients with NB (*n*=nm)	Patients with NB listed in autopsy files with tumour present at autopsy (*n*=63)[a]
N of patients analysed (%)	504 (% unclear)	2,093 (100)	144 (% unclear)	63 (100)
NB stage	nm	nm	nm	nm
Control patients	–	–	–	A. Patients from remaining autopsy population minus peripheral neuroblastic tumours (*n*=43,149) B. Patients with malignant melanoma or central neuroblastic tumour in same autopsy population (*n*=135)
Method of review of cardiac status	Review of medical charts	Review of death certificates	Review of medical records	Review of autopsy files (in addition all available fixed heart specimens and post-mortem coronary angiograms of CHD were studied)
Results				
N of patients with CHD (%)	7 (1.4)	6 (0.3)	2 (1.4)	7 (11.1)
N of controls with CHD (%)	–	–	–	A. 2,081 (4.8) B. 0 (0)
Significance	–	–	–	nm

NB neuroblastoma, *CHD* congenital heart defects, *nm* not mentioned
[a]Neuroblastoma was detected incidentally at autopsy in all patients with CHD
[b]In six cases neuroblastoma was detected incidentally, of which three cases during evaluation of CHD
[c]In all patients with CHD neuroblastoma was detected in a screening programme using urine samples
[d]Odds ratio for neuroblastoma risk in patients with CHD

Children's Hospital-AMC. Sixty-seven patients were excluded from this study because they had been referred from other centres. One hundred eighty-five patients had deceased by the time of the start of this study. The study group therefore consisted of 133 living patients. Inclusion and exclusion of patients is illustrated in Fig. 1.

In 34 of 133 patients an echocardiogram had been performed in the past. The images of 17 of 34 patients were extensive enough for confirming or ruling out the presence of CHD and therefore were analysed retrospectively. The 17 patients with inaccurate echocardiography as well as 99 patients without echocardiography were approached to undergo cardiac evaluation. We obtained echocardiography in 104 of these 116 patients. In the remaining 12 patients, echocardiography could not be performed: three patients had moved abroad, two patients were untraceable and seven patients refused to undergo echocardiography. Two additional patients, children aged 12 and 24 months, were

Nakissa et al. [23]	Neglia et al. [25]	Mann et al. [16]	Mili et al. [19]	Foulkes et al. [9]
USA, 1965–1980	USA, 1969–nm	England, time period nm	USA, 1983–1988	Canada, 1977–1993
Single centre retrospective patient series	Multicentre retrospective patient series	Multicentre retrospective patient series	Multicentre (cancer registry) retrospective cohort study	Single centre retrospective cohort study
Patients (0–12 years) with NB visiting the centre within time period (n=nm)	Patients with NB newly diagnosed or seen in survey region and born in survey region (n=97)	Patients newly diagnosed with NB (n=nm)	Incident cases of NB registered in cancer registry and born in Iowa (n=34)	Patients newly diagnosed with NB (n=141)
32 (% unclear)	97 (100)	35 (% unclear)	34 (100)	141 (100)
nm	Stage 1, 8%; 2, 13%; 3, 18%; 4, 50%; 4s, 11%	nm	nm	Stage 1, 23.4%; 2, 9.2%; 3, 24.1%; 4, 31.9%; 4s, 11.3%
–	Birth certificates of age matched controls randomly selected from all live births in the same state (n=388)	Age- and sex-matched designated controls from general practitioner lists (n=555)	–	Live births in British Columbia Health Surveillance Registry 1979–1988 (n=419,646)
Review of radiographs and re-examination of patients	Review of birth certificates and supplemental information forms	Parental interview, verification of information in obstetric records and general practitioners' records	Review of records from birth defects registry after linkage with cancer registry	Patients: review of charts Controls: data in registry
0 (0)	0 (0)	1 (2.9)	1 (2.9)	6 (4.3)
–	0 (0)	0 (0)	–	Expected in patient cohort: 1.75
–	nm	nm	–	$P<0.01$

eventually excluded because echocardiography of sufficient quality could not be obtained due to unrest during the performance of the echocardiogram. Altogether, accurate echocardiography was available in 119 of the 133 eligible patients (89.5%), of which 102 were obtained prospectively and 17 retrospectively. Characteristics of these 119 patients are given in Table 1.

Two of 119 patients with echocardiography had CHD (1.7%, 95% CI 0.20–5.94). One patient was a 19-year-old male with a ventricular septal defect (VSD) at birth, which had spontaneously closed when he was 1 year old. In the other patient, a 19-year-old woman, echocardiography revealed a persistent left superior vena cava. Both patients were asymptomatic. No CHD was detected in any of the remaining 117 patients. In one patient, a 3-year-old boy with psychomotor retardation, hypertrophic cardiomyopathy was present, which had already been diagnosed before the start of this study and pre-existed before treatment for the neuroblastoma. The cause of the cardiomyopathy is unknown. In the control group of ALL patients, seven of 192 (3.6%) patients were reported to have CHD [11]. The proportion of CHD in our cohort of surviving neuroblasto-

Table 2 (continued)

Study	Narod et al. [24]	Friedman et al. [10]	Nishi et al. [26]	George et al. [11]
Country and time period	England, Scotland, Wales, 1971–1986	USA, in parts 1965–1994	Japan, 1969–1996	USA, 1990–2000
Design and setting	Multicentre (national cancer registry) retrospective cohort study	Single centre retrospective patient series	Multicentre (national cancer registry) retrospective cohort study	Single centre retrospective cohort study
Patients and methods				
NB patients	Patients (<15 years) diagnosed with NB in registry (n=1208)	Patients with NB listed in autopsy files (n=58)	Patients (<=14 years) with NB in registry (n=nm)	Patients newly diagnosed with NB (n=158)[b]
N of patients analysed (%)	1208 (100)	58 (100)	323 (>95)	70 (44)
NB stage	nm	nm	nm	INSS stage 1–3, 31%; stage 4, 69%
Control patients	–	–	–	Consecutive patients with acute lymphoblastic leukaemia from the same centre, same period (n=192)
Method of review of cardiac status	Information from hospitals and family doctors, postal questionnaire to family doctors (in part of patients)	Review of data in computerised autopsy databank	Cancer registry data	Retrospective review of echocardiographic reports
Results				
N of patients with CHD (%)	7 (0.6)	2 (3.5)	2 (0.6)	14 (20.0)
N of controls with CHD (%)	–	–	–	7 (3.6)
Significance	–	–	–	P=0.0001

ma patients (two of 119, 1.7%) did not differ significantly from the proportion of CHD in this control group (seven of 192, 3.6%) (P=0.49). EUROCAT Northern Netherlands reported 2,526 patients with CHD in 404,790 live births between January 1981 and January 2006, which corresponds to a prevalence rate of 62.4 per 10,000 (0.62%). The proportion of CHD in our neuroblastoma cohort was not significantly higher than the proportion of CHD reported by EUROCAT (P=0.17).

Review of the medical charts of the 14 surviving patients in whom echocardiography could not be obtained (n=12) or echocardiography was inaccurate (n=2), did not reveal evidence of CHD. Medical records were still available of 176 of 185 deceased patients (95.1%). Review of these records showed CHD in one patient (coarctation of the aorta and bicuspid aortic valve). In the remaining 175 patients no evidence of CHD was observed. When we considered all survivors and non-survivors together, echocardiography or medical records were available in 309 patients (133 survivors and 176 non-survivors). If we assumed that all patients without evidence of CHD have normal hearts, three of 309 patients (1.0%, 95% CI 0.20–2.81) had CHD.

Menegaux et al. [18]	Yanai et al. [29]	Chow et al. [5]	Munzer et al. [22]	Current study
USA/Canada, 1992–1994	Japan, 1990–2002	USA, 1980–2004	France, 2003–2004	Netherlands, 1966–2006
Multicentre (139 hospitals) retrospective cohort study	Two-centre retrospective patient series	Multicentre (national cancer registry) retrospective cohort study	Multi-centre (National Registry of childhood solid tumours) retrospective cohort study	Single centre retrospective/ prospective cohort study
Patients (<19 years) newly diagnosed with NB (n=741)	Patients newly diagnosed with NB (n=nm)[c]	Patients (<20 yrs) newly diagnosed with NB and born in Washington (n=240)	Patients (<15 years) newly diagnosed with NB, surviving and not terminally ill (n=235)	Patients newly diagnosed with NB, alive at time of study (n=133)
538 (73)	156 (% unclear)	240 (100)	191 (75)	119 (89.5)
nm	nm	Localised, 12.9%; regional, 20%; distant metastatic, 40.8%; unspecified, 26.3%	nm	INSS stage I–3, 62.2%; stage 4, 37.8%
Age matched controls selected through a random digit dialling method (n=504)	–	Birth certificates of age matched controls from the same area (n=2,400)	Age and sex matched controls selected through a random digit dialing method (n=1,681)	Consecutive patients with acute lymphoblastic leukaemia ontrol group presented by George et al. [11] (n=192)
Standardised telephone interview with mother	Review of charts	Review of birth certificates and hospital discharge records database after linkage with cancer registry	Standardised telephone interview with mother	Prospective echocardiography in 102 patients; review of echocardiography images in 17 patients
15 (2.0)	4 (2.6)	5 (2.1)	0 (0)	2 (1.68)
3 (0.6)	–	9 (0.4)	5 (0.3)	7 (3.6)
Odds ratio 4.27 (95% CI 1.22–15.0)[d]	–	Odds ratio 5.84 (95% CI 1.93–17.66)[d]	Odds ratio 0[d]	P=0.49

Systematic review of literature, methods and results

To evaluate the existing evidence regarding the prevalence of CHD in neuroblastoma patients, we searched the electronic databases of PubMed (January 1966 to December 2007) and Embase (1980 to December 2007), as well as references of eligible papers. The main search terms were neuroblastoma and congenital heart defects. We collected all studies of neuroblastoma patient series that reported on the proportion of CHD. The study cohort should at least include 20 neuroblastoma patients. The number of 20 was arbitrarily chosen, as we estimated that smaller cohorts or case series might introduce uncontrollable bias. Information about study design, study group and results were abstracted by two independent reviewers (KVE and JHM). The two independent reviewers also critically appraised internal and external validity of each study. The validity assessment was based on the guidelines proposed by Hayden et al. [12]. Details about the search strategy and validity assessment can be obtained from the authors.

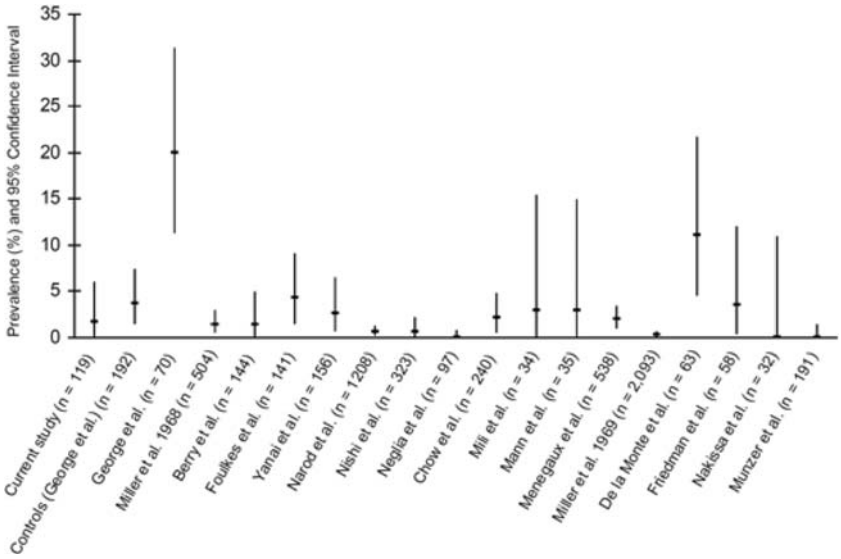

Fig. 3 Overview of prevalence rates (%) of CHD in the selected studies with 95% Confidence Interval. The prevalence rate in the control group (George et al.) is also shown

The literature search identified 515 unique articles. Reasons for exclusion are detailed in Fig. 2. Seventeen articles were eligible for our review. Table 2 presents descriptive characteristics and results of all studies, including the present one. The studies differed largely in terms of patient characteristics and methodology. The study of George et al. [11] was the only study in which patients had undergone echocardiography; the authors reviewed the echocardiographic images that had been recorded previously. In all other articles, it was not mentioned which cardiac assessment was used. The reported prevalence rates of CHD in neuroblastoma patients ranged from 0 to 20%, although the majority of the studies (14 out of 17) found a prevalence of less than 3.6% [2, 5, 10, 16, 18–26, 29]. In the echocardiographic review study, the prevalence was 20%. Figure 3 is an illustration of the prevalence rates of CHD with 95% confidence interval of proportion as calculated by us. A statistically higher prevalence of CHD in patients as compared to controls was present in six of eight studies that included a control group [5, 6, 9, 11, 16, 18]. However, all studies lacked information on different items of validity.

In conclusion, several studies have evaluated the prevalence of CHD in neuroblastoma patients, with little information on validity. Echocardiography had been performed in only one study. The majority of the studies reported a prevalence of less than 3.6%, however, a prevalence of 20% was found in the echocardiographic review study.

Discussion

In this single centre cohort of consecutive neuroblastoma patients, the prevalence of CHD was 1.7%, which was not significantly different from two control groups [11].

The prevalence of CHD found in our study was much lower than the prevalence of 20% reported in the only other study in which echocardiography was used for detection of CHD, the study by George et al. [11]. Both studies have some limitations, however. In both studies it was not possible to evaluate the patients who died before echocardiographic assessment and this might have led to underestimation of prevalence of CHD in both studies. George et al. [11] did not perform echocardiography in all surviving neuroblastoma patients. Instead, the authors retrospectively analysed echocardiographic records and echocardiography was available in only 43% of neuroblastoma patients. This might have led to an over-estimation of the prevalence of CHD, since patients with CHD are more likely to have had echocardiography. In our study, we prospectively performed echocardiography in almost all eligible patients, regardless of symptoms or need for specific treatment. Another explanation for the difference in outcome of our study and the study by George et al. might be that patients in our study were older at time of echocardiography. Because some types of CHD can resolve spontaneously over time, such as spontaneous closure of septal defects [27], CHD might have been missed in our study. One patient in our study indeed had a VSD that had spontaneously closed. However, most CHD do not disappear over time and would have been detected if present. An additional explanation for the high prevalence rate found by George et al. as compared to our study could be referral bias in their tertiary care centre study [11]. An important potential source of bias that may have led to overestimation of CHD in the study of George et al. as well as in other studies and case reports, is surveillance bias: patients with neuroblastoma are investigated thoroughly, during which (asymptomatic) CHD might be detected. Likewise, neuroblastoma can be detected during workup of CHD patients.

It is well known that lower stage neuroblastoma can regress spontaneously over time and therefore these neuroblastoma might never have come into clinical attention without the thorough investigations after detection of CHD. This may artificially increase the difference between prevalence of CHD in neuroblastoma patients and controls. Indeed, in the study of George et al. [11] neuroblastoma was detected during workup for CHD in three patients.

George et al. found a relatively high proportion of patients with neural crest-derived CHD. Five of 14 (36%) patients with CHD had neural crest-derived CHD, which is more than expected when considering the normal distribution of CHD [13]. This seems in favour of a possible association between the two conditions, with its source in the common neural crest origin. However, numbers were very small in the study of George et al.

The 16 other studies on CHD in neuroblastoma patients reviewed here, showed prevalence rates much lower than the 20% reported by George et al. In these studies it was not mentioned how patients were evaluated for the presence of CHD, but it is unlikely that the majority of patients underwent echocardiography or other imaging techniques. CHD might thus have been missed. In all of these studies information was lacking on other items of validity as well. The validity of a study addresses the issue of whether the researcher actually measures what is said to be measured. It concerns the extent to which the results of a study can be interpreted adequately and the extent to which we can trust these results. A lack of information on validity items might lead to invalid results; the studies reviewed here might have been subject to various types of bias. For example, a well-defined definition of CHD was not given in the studies, which led to difficulties in interpretation of what exactly had been considered as CHD. The use of a non-representative sample of patients from the original study group may have led to either over- or under-estimation of the true prevalence of CHD, depending on whether patients with a higher or a lower risk profile were selected for the study. In addition, cancer registries, birth certificates and medical charts might not contain all medical information and therefore CHD could be under-reported. In studies were data from these registries served as control data, the significance of a higher prevalence of CHD in neuroblastoma patients might have been overestimated [7, 9, 15]. In studies based on parental interviews, recall bias may have led to overestimation of CHD in neuroblastoma patients. In addition, studies in tertiary care centres might have been subject to referral bias.

Non-accuracy of the control group can be a source of bias as well. We used the consecutive ALL cohort presented by George et al. as a control group [11]. We chose this control group because all consecutive children in this cohort had undergone echocardiography, like the patients in our study group. A concern might be that the control group comprises patients from another country. We therefore also compared the prevalence of CHD in our cohort to data from EUROCAT Northern Netherlands, with non-significant results. As mentioned above, use of data from a health registry for comparison may lead to bias as well. However, because data in health registries might be prone to under-representation of anomalies in the general population [7, 9, 15], this would imply that the significance of the difference is even less than described.

In conclusion, although several studies have addressed the prevalence of CHD in neuroblastoma patients, only the present study and the study of George et al. [11] used adequate methodology and had reasonable validity to determine the prevalence of CHD in these patients. However, the results differed largely between these two studies. The difference may in part be explained by differences in methodology and patient characteristics, but may be due to chance as well. Therefore, the association between neuroblastoma and CHD remains unclear. To confirm or reject the true existence of such an association, further research in a large and complete cohort of neuroblastoma patients is needed. Our study and systematic review have shown, however, that clear evidence of an association between neuroblastoma and CHD is lacking. Standard cardiac screening in all patients with neuroblastoma is therefore not supported by current evidence.

Acknowledgements We thank Edith Leclercq for her support in the construction of the search strategies and Jeroen Vis for help in the arrangement and performance of the cardiologic examinations.

Conflicts of interest statement The authors declare that they have no conflict of interest.

References

1. Bellah R, D'Andrea A, Darillis E et al (1989) The association of congenital neuroblastoma and congenital heart disease. Is there a common embryologic basis? Pediatr Radiol 19:119–121. doi:10.1007/BF02387900
2. Berry CL, Keeling J, Hilton C (1970) Coincidence of congenital malformation and embryonic tumours of childhood. Arch Dis Child 45:229–231
3. Brodeur GM, Maris JM (2006) Neuroblastoma. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology. 5th edn. Lippincott Williams and Wilkins, Philadelphia, pp 933–970
4. Brodeur GM, Pritchard J, Berthold F et al (1993) Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 11:1466–1477

5. Chow EJ, Friedman DL, Mueller BA (2007) Maternal and perinatal characteristics in relation to neuroblastoma. Cancer 109:983–992. doi:10.1002/cncr.22486
6. de la Monte SM, Hutchins GM, Moore GW (1985) Peripheral neuroblastic tumors and congenital heart disease. Possible role of hypoxic states in tumor induction. Am J Pediatr Hematol Oncol 7:109–116
7. Northern Netherlands EUROCAT (2007) Prevalence of congenital malformations in the Northern Netherlands, 1981–2005. Updated 2007, June 30th. Available via EUROCAT. http://www.rug.nl/umcg/faculteit/disciplinegroepen/medischegenetica/eurocat. Accessed 15 Dec 2007
8. Faingold R, Babyn PS, Yoo SJ et al (2003) Neuroblastoma with atypical metastases to cardiac and skeletal muscles: MRI features. Pediatr Radiol 33:584–586. doi:10.1007/s00247-002-0858-5
9. Foulkes WD, Buu PN, Filiatrault D et al (1997) Excess of congenital abnormalities in French-Canadian children with neuroblastoma: a case series study from Montreal. Med Pediatr Oncol 29:272–279. doi:10.1002/(SICI)1096-911X(199710)29:4<272::AID-MPO7>3.0.CO;2-J
10. Friedman DM, Dunnigan A, Magid MS (1998) Coarctation of the aorta associated with neuroblastoma. Pediatr Cardiol 19:480–481. doi:10.1007/s002469900364
11. George RE, Lipshultz SE, Lipsitz SR et al (2004) Association between congenital cardiovascular malformations and neuroblastoma. J Pediatr 144:444–448. doi:10.1016/j.jpeds.2003.12.032
12. Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 144:427–437
13. Holzer R, Franklin RC (2002) Congenital heart disease and neuroblastoma: just coincidence? Arch Dis Child 87:61–64. doi:10.1136/adc.87.1.61
14. Hutson MR, Kirby ML (2003) Neural crest and cardiovascular development: a 20-year perspective. Birth Defects Res C Embryo Today 69:2–13. doi:10.1002/bdrc.10002
15. Larsen H, Nielsen GL, Bendsen J et al (2003) Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. Scand J Public Health 31:12–16. doi:10.1080/14034940210134194
16. Mann JR, Dodd HE, Draper GJ et al (1993) Congenital abnormalities in children with cancer and their relatives: results from a case-control study (IRESCC). Br J Cancer 68:357–363
17. McElhinney DB, Reddy VM, Feuerstein BG et al (1997) Intraoperative discovery of neuroblastoma in an infant with pulmonary atresia. Ann Thorac Surg 64:1827–1829. doi:10.1016/S0003-4975(97)01067-9
18. Menegaux F, Olshan AF, Reitnauer PJ et al (2005) Positive association between congenital anomalies and risk of neuroblastoma. Pediatr Blood Cancer 45:649–655. doi:10.1002/pbc.20263
19. Mili F, Lynch CF, Khoury MJ et al (1993) Risk of childhood cancer for infants with birth defects. II. A record-linkage study, Iowa, 1983–1989. Am J Epidemiol 137:639–644
20. Miller RW (1969) Childhood cancer and congenital defects. A study of U.S. death certificates during the period 1960–1966. Pediatr Res 3:389–397. doi:10.1203/00006450-196909000-00001
21. Miller RW, Fraumeni JF Jr, Hill JA (1968) Neuroblastoma: epidemiologic approach to its origin. Am J Dis Child 115:253–261
22. Munzer C, Menegaux F, Lacour B et al (2007) Birth-related characteristics, congenital malformation, maternal reproductive history and neuroblastoma: the ESCALE study (SFCE). Int J Cancer 122:2315–2321. doi:10.1002/ijc.23301
23. Nakissa N, Constine LS, Rubin P et al (1985) Birth defects in three common pediatric malignancies; Wilms' tumor, neuroblastoma and Ewing's sarcoma. Oncology 42:358–363
24. Narod SA, Hawkins MM, Robertson CM et al (1997) Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet 60:474–485
25. Neglia JP, Smithson WA, Gunderson P et al (1988) Prenatal and perinatal risk factors for neuroblastoma. A case-control study. Cancer 61:2202–2206. doi:10.1002/1097-0142(19880601)61:11<2202::AID-CNCR2820611113>3.0.CO;2-7
26. Nishi M, Miyake H, Takeda T et al (2000) Congenital malformations and childhood cancer. Med Pediatr Oncol 34:250–254. doi:10.1002/(SICI)1096-911X(200004)34:4<250::AID-MPO3>3.0.CO;2-W
27. Perloff JK (1971) Therapeutics of nature—the invisible sutures of "spontaneous closure". Am Heart J 82:581–585. doi:10.1016/0002-8703(71)90325-5
28. Rosti L, Lin AE, Frigiola A (1996) Neuroblastoma and congenital cardiovascular malformations. Pediatrics 97:258–261
29. Yanai T, Hasegawa D, Kosaka Y et al (2006) Congenital cardiovascular malformations are complicated in neuroblastomas identified by mass screening but not by clinical examination in Japan. J Pediatr 149:145–146, letter. doi:10.1016/j.jpeds.2005. 03.046