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Presenting symptoms of children with cancer:

a primary-care population-based study

Abstract

Background

Knowledge of how children with cancer present in general practice is sparse. Timely referral from general practice is important to ensure early diagnosis.

Aim

To investigate the presenting symptoms and GPs' interpretations of symptoms of children with cancer.

Design and setting

A Danish nationwide population-based study including children (<15 years) with an incident cancer diagnosis (January 2007 to December 2010).

Method

A questionnaire on symptoms and their interpretation was mailed to GPs ($n = 363$). Symptoms were classified according to the International Classification of Primary Care (ICPC)-2 classification.

Results

GPs' response rate was 87% (315/363) and GPs were involved in the diagnostic process of 253 (80.3%) children. Symptoms were few (2.4 per child) and most fell into the category 'general and unspecified' (71.9%), apart from patients with tumours of the central nervous system (CNS), whose symptoms fell mostly in the category 'neurological' (for example, headache). Symptoms like pain, swelling/lump, or fatigue were reported in 25% of the patients and they were the most commonly reported symptoms. GPs interpreted children's symptoms as alarm symptoms in 20.2%, as serious (that is, not alarm) symptoms in 52.9%, and as vague symptoms in 26.9%. GPs' interpretation varied significantly by diagnosis ($P < 0.001$).

Conclusion

Children with cancer presented with few symptoms in general practice, of which most were 'general and unspecified' symptoms. Only 20% presented alarm symptoms, while 27% presented vague and non-specific symptoms. This low level of alarm symptoms may influence the time from symptom presentation in general practice to final diagnosis.

Keywords

childhood cancer; family practice; patients; signs and symptoms.

INTRODUCTION

The total incidence of childhood cancer varies little throughout the world. In Europe, approximately one in 500–600 children develops a malignant disease before they reach the age of 15 years.¹ In Denmark, general practice is the front line in the national healthcare system, and GPs have a core function in singling out the few children with serious disease among the many with less-threatening diseases. GPs' likelihood of encountering children with severe and life-threatening disease in the clinic is small, yet real.²

A fundamental problem in childhood cancer is that its early symptoms mimic those seen in common transient and harmless conditions.^{3,4} A UK study recently demonstrated that the positive predictive values (PPVs) of the presenting symptoms in childhood cancer are very low.⁵ Symptoms and symptom onset may be insidious and may vary according to cancer type, the size of the tumour, its anatomic location and rate of growth, and the child's age.^{6–9}

According to the Danish National Board of Health, the suspicion of leukaemia in childhood should be raised in the presence of pallor, fatigue, irritability, unexplained fever, persistent/recurrent upper respiratory tract infections, generalised lymphadenopathy, persistent/unexplained bone pain, and/or unexplained bruising. Further, specific recommendations for

children with suspected lymphoma, brain and CNS tumour, neuroblastoma, Wilms' tumour, soft tissue sarcoma and retinoblastoma has been described.¹⁰ The diagnostic process may be unduly prolonged if the GP adopts an expectant attitude to early symptoms. A heightened knowledge among GPs of the symptoms of early childhood cancer, and closer attention to such symptoms when they are seen for the first time in the clinic, may help to ensure a more timely referral of children with cancer for diagnostic work-up.¹¹

The aim of this study was to investigate the presenting symptoms of particular childhood cancers and GPs' interpretations of these symptoms.

METHOD

Overall design

The study was a nationwide population-based study using data from three national registries and from a GP questionnaire. The civil registration number, a unique 10-digit personal identification number assigned to every Danish citizen at birth, was used to link registers on an individual level.¹²

Participants

All children aged 0–14 years diagnosed with incident cancer between 1 January 2007 and 31 December 2010 were identified in the Danish Registry of Childhood Cancer (DCCR).¹³ The study included children

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How this fits in

Childhood cancer is rare and GPs have little experience in recognising presenting symptoms. GPs must suspect cancer when relevant to ensure the best prognosis for these children. Children with cancer often present with few symptoms, which are most often of a general and unspecified nature. Symptoms were interpreted as vague and non-specific in one-quarter of cases and as alarm symptoms in one-fifth of cases.

diagnosed with malignant cancer types and benign tumours of the central nervous system (CNS) according to the Danish version of the International Classification of Diseases (ICD-10):¹⁴ C00.0 to C96.9 (malignant) and D32, D33, D35.2 to D35.5, D42, D43, D44.3 to D44.5 (benign tumours of the CNS). A flowchart of participants included in the study is presented in Figure 1.

Register data

The DCCR is a nationwide register that holds information on all types of malignant

cancer, as well as benign tumours of the CNS diagnosed in children under the age of 15 years. For each child, apart from those with a temporary civil registration number, for example due to recent arrival in the country ($n = 6$), the study cohort was linked with The Danish Civil Registration System,¹² which holds updated information on the residence and vital status of all residents in Denmark, and with the Danish National Health Service Registry,¹⁵ which provided the names and addresses of the GPs.

Questionnaire data

Collection of data from GPs was conditional on the parents' approval, which was requested by mail before a questionnaire was sent to the GP questionnaire with whom the child was listed at the date of diagnosis. The GP questionnaire asked if the GP had been fully or partly involved in the diagnostic process toward the child's cancer diagnosis (yes/no), and it requested a detailed description of the patient's first symptom presentation and the diagnostic pathway. The latter information could be extracted from GPs' electronic medical records and discharge letters from hospitals and specialists. GPs were also asked how they had interpreted the presenting symptoms at the time the child was examined in general practice. They were invited to base their assessment on their clinical judgement and any records in the patient's files, and to categorise their assessment of the symptoms as either 'alarm' (red flag signs), indicating cancer disease; 'serious', indicating severe disease; or 'vague', not indicating severe disease.

A thorough literature search revealed no appropriate questionnaires for the present study. The GP questionnaire was therefore designed by the research group, and the choice of items was informed by literature studies, preceding interviews, clinical experience, and studies on time intervals in the diagnosis of adult cancers performed at the Research Unit for General Practice, Aarhus University. The questionnaire was pilot tested twice (among researchers at the department and in a test sample of GPs) and adjusted accordingly. Questionnaire data were collected between December 2009 and September 2011. Non-responders received a reminder after 3 weeks. GPs received a £28 fee for their participation.

Statistical analysis

The children were categorised into five diagnostic groups according to the ICD10 diagnosis. For example, Leukaemia: C91–95; Lymphoma: C81–85; CNS tumour:

Figure 1. Flowchart of inclusion of study participants.
CRN = civil registration number (Danish identification number). DCCR = Danish Childhood Cancer Registry (DCCR). Q (GP) = GP questionnaire.

Table 1. Frequencies of GP-reported ICPC-2 symptoms (total 427) at first presentation in general practice for all children and according to sex and diagnosis

ICPC-2 classification	All, n = 253		Leukaemia, n = 83		Lymphomas, n = 37		CNS tumours, n = 51		Bone tumours, n = 19		Other solid tumours, n = 63	
	n	%	n	%	n	%	n	%	n	%	n	%
A: general and unspecified ^a	182	71.9	66	79.5	34	91.9	14	27.5	18	94.7	50	79.4
B: blood, blood-forming organs, and immune mechanism ^{a,b}	44	17.4	32	38.6	3	8.1	5	9.8	1	5.3	3	4.8
D: digestive ^{a,b}	37	14.6	7	8.4	2	5.4	20	39.2	0	0.0	8	12.7
F: eye ^a	13	5.1	1	1.2	0	0.0	7	13.7	0	0.0	5	7.9
L: musculoskeletal ^a	28	11.1	15	18.1	1	2.7	3	5.9	7	36.8	2	3.2
N: neurological ^a	52	20.6	5	6.0	0	0.0	37	72.5	0	0.0	10	15.9
R: respiratory ^a	19	7.5	14	16.7	3	8.1	0	0.0	1	5.3	1	1.6
S: skin	14	5.5	8	9.6	2	5.4	0	0.0	0	0.0	4	6.3
T: endocrine/metabolic and nutritional	30	11.9	10	12.0	5	13.5	5	9.8	0	0.0	10	15.9
Other ICPCs ^c	8	3.2	1	1.2	1	2.7	4	7.8	0	0.0	2	3.2

^aSignificant difference between diagnostic groups ($P < 0.05$). ^bSignificant difference between sexes ($P < 0.05$). ^cOther ICPCs: H = ear, K = cardiovascular, P = psychological, U = urological, and X = female genital. CNS = central nervous system. ICPC-2 = International Classification of Primary Care-2.

Figure 2. Figure 1. GP-reported symptoms (total 601) with a frequency of $\geq 2\%$ (n = 253 children). International Classification of Primary Care-2 codes are marked for each symptom.

C70-72, C75.1-3, D32-33, D35.2-4, D42-43, D44.3-5; Bone tumour: C40-41; and other solid tumour: remaining ICD10 codes, chapter II. GP-reported symptoms were categorised into categories according to the International Classification of Primary Care second edition (ICPC-2).¹⁶ A (general and unspecified), B (blood, blood-forming organs, and immune mechanism), D (digestive), F (eye), L (musculoskeletal), N (neurological), R (respiratory), S (skin), T

(endocrine/metabolic and nutritional), and, finally, a group of symptoms belonging to other ICPC-2 chapters: H (ear), K (cardiovascular), P (psychological), U (urological), and X (female genital). In the ICPC-2, fatigue is coded as weakness/tiredness general (A04).

Various symptoms within the same ICPC-2 chapter counted as a single registration within the individual ICPC-2 chapter. Descriptive analyses were performed on GPs' involvement in the diagnostic process. Analyses of symptom frequency, symptom interpretation, and combinations of ICPC-2 chapters were restricted to diagnostic pathways involving the GP. Analyses of symptom frequency were performed according to cancer type (leukaemia, lymphomas, CNS tumours, bone tumours, and other solid tumours) and for the entire study population.

χ^2 -tests were used to test whether the symptom interpretation was influenced by diagnostic groups or age groups. P -value of 0.05 or less was defined as statistically significant. Data were analysed using Stata 11.2 software.

RESULTS

Permission to send a GP questionnaire was given by 96.3% [363/377] of the parents. GPs' response rate was 87%, which allowed 315 children to be included (Figure 1). GPs were involved in the diagnostic pathways of 253 children (80.3%), of whom 104 (41.1%) were aged 0-4 years at diagnosis, 77 (30.4%) were 5-9 years, and 72 (28.5%) were 10-14 years. These children were included in the analyses (Table 1).

Figure 3. The 10 most commonly reported symptoms for children with leukaemia, lymphoma, central nervous system (CNS) tumour and bone tumour, and for children with other solid tumours.

Table 2. GPs' interpretation of symptoms according to cancer type and age

	Alarm		Serious		Vague	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
All	48	20.2	126	52.9	64	26.9
Cancer type^a						
Leukaemia	14	18.2	49	63.6	14	18.2
Lymphomas	16	44.4	11	30.6	9	25.0
CNS tumours	5	10.9	30	65.2	11	23.9
Bone tumours	1	5.6	8	44.4	9	50.0
Other solid tumours	12	19.7	28	45.9	21	34.4
Age, years						
0–4	15	15.0	59	59.0	26	26.0
5–9	13	19.4	37	55.2	17	25.4
10–14	20	28.2	30	42.3	21	29.6

^aStatistically significant difference between cancer types ($P < 0.001$). CNS = central nervous system.

GP involvement

Differences in the GPs' involvement in the various subgroups of children with cancer were small and insignificant. GPs were most frequently involved in the diagnostic work-up of children subsequently diagnosed with bone tumours (86.4%) and least frequently (75.0%) in children subsequently diagnosed with malignancies classified as 'other solid tumours' ($P = 0.67$).

Reported symptoms

Overall, GPs reported 2.4 symptoms per child (Figure 2). Monosymptomatic symptoms were reported in 97 (38.3%) children, whereas two or more symptoms were reported in 153 (60.5%) children. Clinical symptoms at first presentation were absent in three patients (1.2%).

Almost three in four symptoms and signs were symptoms classified as 'general and unspecified' (ICPC-2 A symptoms), whereas one-fifth were classified as neurological (N) and one-sixth as (B) symptoms from the blood-forming system (Table 1). Overall, symptoms like pain (A01), swelling/lump (A08), or weakness/tiredness in general (A04) were reported for every fourth patient (Figure 2). Headache (N01) was reported in 13% and was the most frequently reported neurological symptom. The remaining ICPC chapters were infrequently used; for example, specific symptoms like weight loss (T08) and bleeding tendency (B83) were reported for only a few children.

Symptoms and cancer types

Patients with bone tumours, in particular, had A symptoms and pain (A01) was reported in 78.9% of patients (Figure 3). Musculoskeletal (L) symptoms were reported among one-third of the patients with a bone malignancy. Leukaemia patients had musculoskeletal symptoms,

too, such as limping in 12.5% of cases (Figure 3). In children with leukaemia, pain was reported as frequently as the classic symptoms weakness/tiredness, fever, and paleness, and almost twice as often as 'susceptibility to infection'. Among patients with CNS tumours, headache and vomiting were the main symptoms, followed by other neurological (N) symptoms such as disturbances in gait.

Combined symptoms

A total of 118 children (46.6%) had symptoms within two or more ICPC-2 chapters. The combinations were: A and L symptoms (22.1%) followed by A and B symptoms (16.9%), or A and T symptoms (10.4%). No further combinations of ICPC chapters or specific symptoms were found.

Symptom interpretation and diagnosis

GPs' symptom interpretations were reported in 238 (94.1%) cases (Table 2). The interpretation varied according to the diagnosis ($P < 0.001$). The proportion of alarm symptoms was higher for patients with lymphoma (44.4%) than for those with bone tumour (5.1%). The proportion of alarm symptoms tended to increase with increasing age at diagnosis, albeit not statistically insignificantly.

DISCUSSION

Summary

GPs reported having been involved in the diagnostic process in 80% of the early diagnostic pathways of children subsequently diagnosed with malignant cancers and benign CNS tumours. At their first presentation in general practice, children had few symptoms. The most frequently reported symptoms were pain, swelling/lump, and weakness/tiredness. Symptoms varied significantly with cancer type.

In one-quarter of the cases, the symptoms were interpreted as vague and non-specific, while in one-fifth they were interpreted as alarming. Although belonging to the category of general and unspecific (A), the majority (53%) of symptoms were interpreted by the GPs as serious. GPs' symptom interpretations varied according to cancer type. For children subsequently diagnosed with a bone tumour, only one in 20 was deemed to have alarm symptoms, whereas almost half of symptoms presented by lymphoma patients were characterised as alarm symptoms. Thus, some cancers may produce a more pronounced symptomatology, and some symptoms (for example, pain and headache)

may cause less alarm than others (lump and paleness).

The finding that most symptoms belonged to the ICPC-2 'A symptoms' (general and unspecified) may, apart from the nature of symptoms, also stem from the ICPC classification and the way GPs recorded and reported the symptoms. Further research should strive to focus on how to ensure a more precise registration of symptoms in general practice.

Strengths and limitations

This study was population based and included children from a whole nation for 4 years. Its main strength is its completeness. Selection bias was reduced by using complete registry data to identify all potential incidences of childhood cancer, their parents, and GPs. The sampling of children with cancer from the DCCR had several advantages. The DCCR is updated several times a year, it holds the child's civil registration number and information on treatment start, and it offers a quick and patient-related interchange of data.¹³ GP response rate was high (87%). The distribution of sex, age groups, and diagnostic groups in the study population was in keeping with incidence rates for childhood cancers.^{1,17,18} Although the study was nationwide, its statistical precision was small in some subgroup analyses.

The retrospective nature of the questionnaire-based study makes it prone to recall bias. Nearly all Danish GPs have electronic patient files,¹⁹ and the GPs were encouraged to consult their files when completing the questionnaire to reduce recall bias. Other sources of bias may pertain to GPs' actual symptom interpretations. The GPs were asked to retrospectively report their interpretation of the child's symptoms during the initial presentation to the GP. This reporting may to some degree be biased because the GP knew the child's diagnosis at the time of filling in the questionnaire. This 'hindsight bias' may, for example, arise if GPs tended not to report symptoms that were actually present at an earlier consultation, because they did not give rise to a cancer-specific investigation. It may also arise if a child presented with both a main symptom that was recorded by the GP and with a number of less indicative symptoms (like fatigue) that were not entered into the patient's file. If this is the case, potential 'alarm' symptoms like weight loss or swelling/lump would be more likely to be recorded and reported than vague symptoms. On the other hand, GPs may remember the clinical

trajectory well, because a GP rarely encounters a child with cancer in the clinic, and on reflection the GP could have added symptoms that were not initially recorded in the patient's file.

The choice of a questionnaire survey involves certain limitations in the precise identification of multiple time points,²⁰⁻²² and the collection of clinical information on issues that have not been written down; for example, information on the GP's 'gut-feeling'. An interview study might have shed more light on the use of important diagnostic tools and granted a deeper insight into diagnostic processing in general practice. Audits and thorough scrutiny of the children's medical records could also have been useful. However, such study designs demand high resources. Prospective collection of information on daily symptoms and diagnostic processes in a large follow-up study is needed to solve problems related to recall. However, it would be a major challenge to obtain a sufficient sample size and a sufficiently long follow-up time in any study of rare diseases like childhood cancers.

In the present study, the distribution of sex, age groups, and diagnostic groups in the study population of patients was overall in accordance with the incidence rates for childhood cancers.¹⁷ However, general practice was not involved in the diagnostic pathway of 62 children. These children could have had more aggressive tumours with perhaps a more pronounced symptomatology than children with a pathway involving general practice. However, the population-based approach with complete inclusion of patients with a diagnostic route involving general practice, means the present study has the potential of being generalisable to other healthcare systems in highly developed western countries where general practice serves at the front line of medical advice and health care.

Comparison with existing literature

This study found that most children presented with just a single or a few symptoms — a result that is in line with a recent study on adult cancer, which showed that almost 60% of cancer patients presented with only a single symptom in general practice.²³ Primary care is a key player in the diagnostic cancer pathway among adults and was recently reported to be involved in 85% of cancer diagnoses among adults,²⁴ which is consistent with the present findings. In Sweden, a country organised with no strict gatekeeper in the

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Ethical approval

The study was approved by the Danish Data Protection Agency (J.no. 2008-41-2956) and by the Multipractice Study Committee under the Danish College of General Practitioners and the Organisation of General Practitioners in Denmark, who recommended GPs to participate in the study. Data collection from GPs was approved by the National Board of Health, conditional on the parents' approval. According to the Scientific Committee for the Region of Central Jutland, the Biomedical Research Ethics Committee System Act did not apply to this project.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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healthcare system, a small study on childhood cancers showed that the GPs were involved in the diagnostic pathway in two-thirds of the cases — less for children with brain tumours (50%) than for children with leukaemia (80%).⁹

A review showed that children diagnosed with a tumour in the CNS most often had headache (33%), vomiting (32%), and abnormalities of gait and coordination (27%) at diagnosis.²⁵ A roughly equal range of presenting symptoms in patients with CNS tumours was also found in the present study, which is of particular interest, as the time from the first symptom presentation to diagnosis may last several weeks or even months for these children.^{9,26–29} It should be noted that most studies report the number and nature of symptoms that were present at diagnosis. The number of symptoms at the first presentation could thus be lower than at diagnosis because symptoms may progress,³⁰ and they may be more unspecific at first presentation. In the present study, the presenting symptoms among children with cancer were overall in line with the symptoms that should raise suspicion of cancer according to the prevailing guideline.¹⁰

Implications for research and practice

The study emphasises the need to ensure

that patients, including children without classic signs of cancer, can be seen without undue delay by specialists when requested by their GP. The development of effective strategies to shorten this time span requires an understanding of the factors that shape the diagnostic interval. Future research should aim to investigate how symptoms and symptom interpretation influence the time interval from the first symptom presentation to diagnosis, and further investigate how the GP may improve the diagnostic process with a view to discovering these diseases with low prevalence, while still maintaining a high-quality gatekeeper and gate-advisor function with acceptable rates of referral to the secondary healthcare sector.

Children with cancer presented with few symptoms in general practice. Only one-fifth presented alarm symptoms, while one-quarter presented vague and non-specific symptoms. Parents may continue to return to the GP, even though the GP is unable to identify a specific problem. This study emphasises the need to obtain a detailed medical history of children presenting with vague symptoms or persistent symptoms like pain, fatigue, and swelling, and in case of doubt or concern, to initiate further investigation for vague or unspecific symptoms.

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