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Delay and Causes of Delay in the Diagnosis of Childhood Cancer in Africa

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Background. Although a few studies have investigated delays in diagnosis and treatment among children and adolescents with cancer, this has never been subject of study in South Africa. Early diagnosis is fundamental as it allows timely treatment and prevents unnecessary complications. ***Procedures.*** Combined prospective and retrospective study of 194 children with cancer at Tygerberg Hospital, Cape Town, diagnosed between 2000 and 2009: 126 patients were included through review of the medical charts and 68 through interviews with the parents. ***Results.*** The median total diagnosis delay was 34 days (2–1,826). The median patient delay was 5 days (0–457). The median physician delay was 20 days (0–924). Gender, age or ethnicity of the children, as well as parental level of education did not have a significant influence on the total time to diagnosis. Initial misdiagnoses were frequent (58%). ***Conclusions.*** There is considerable delay in diagnosing childhood cancer in the area served by Tygerberg Hospital, due mostly to a physician delay of 20 days on average. The findings of our unit should be correlated with other South African centers. There is a clear need to increase parental awareness of childhood cancer and to intensify the education of nurses and doctors with regard to the warning signs of the disease. Pediatr Blood Cancer. 2011;56:80–85. © 2010 Wiley-Liss, Inc.

Key words: Africa; cancer; children; delay

INTRODUCTION

Cancer occurs less frequently in childhood than in the later stages of life. Nevertheless, it constitutes the main cause of death from disease in children, in the developed countries. One approach to reducing the mortality from malignancies in this age group would be to diagnose them as early as possible, when the treatment has greater chance of success. Pediatric cancer responds somewhat better to therapy than at older ages, but it also progresses faster in absence of treatment.

A number of retrospective studies, done mainly in developed countries, addressed the question of length and determinants of the time interval from the onset of symptoms to the diagnosis of childhood cancers. Their findings were last reviewed by Dang-Tan and Franco [1]. The review used the term "delay" when referring to the time interval mentioned above.[1] The median length of delay in the papers reviewed was found to depend on the type of malignancy and varied from 2.5 to 29.3 weeks. The median length of time from the onset of symptoms to the initial presentation to the doctor (patient-related delay) ranged between 0.4 and 15 weeks. It depended on the type of malignancy, was significantly longer in older children and slightly longer for males. Better educated parents tended to consult the doctor earlier. While mothers who either stayed at home or had academic professions sought medical advice earlier, the father's profession did not influence the delay; however, the father's ethnicity and religion did.

Cancers presenting with rare clinical signs, in advanced stage or fast-growing were brought for consultation earlier. Easily detectable cancers or those triggering a deterioration of body functions also prompted the parents to seek help sooner.

The health care system-related (or physician-related) delay was measured from the first visit of the patient to the moment when the diagnosis was established. Its length depended on the type of malignancy and also on the characteristics of the first point of contact with the healthcare system. When the children were brought to the emergency rooms the delay was shorter than when seen first by pediatricians and shorter for pediatricians versus other specialties. In general, the median health-care related delay was longer than the patient-related delay.

The same group of researchers published subsequently two further studies analyzing the determinants of delay in children's cancer diagnosis in Canada [2] and the delay in diagnosing leukemias and lymphomas in Canada [3], respectively. Their findings are aligned along the same lines as those of the previous review; however, they found that the health care-related delay was much shorter than the patient-related delay. The diagnostic delays decreased significantly from 1995 to 2000.

Another recent study from Singapore [4], while generally reinforcing the above data, found no progress towards earlier diagnostic between 1997 and 2007. In this study too, the physician delay was shorter than the parent/patient delay.

To date, there are no studies published on the length and determinants of delay in childhood cancer diagnosis in Africa. This research attempts, for the first time, an analysis of the data from a South African pediatric oncology service.

PATIENTS AND METHODS

Definitions

As in previously published studies, the word "delay" means here merely "a time interval," without reference to its adequacy in terms of disease management or good outcome. For the purposes of this research, the delay was measured in days. The total diagnostic delay was defined as the time interval from the detection of manifestations of disease to the diagnosis. The patient delay was the length of time between the onset of signs and symptoms and the patient's first visit to a health care practitioner, whereas the time elapsed from the first

[1] Here the term "delay" has its less frequently encountered meaning of "time gap" and does not imply the exceeding of any optimal deadline for diagnosis.

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Conflicts of interest: Nothing to declare.

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health care system contact to the diagnosis constituted physician delay [2]. For the analysis of the influence of age of the patient on delay, the age at the start of the symptoms was used in all cases.

Setting

The study was conducted at Tygerberg Children's Hospital, Cape Town, an academic pediatric healthcare unit which serves a large multi-ethnic community.

Data Collection

Data were collected retrospectively for 126 cases, from the medical records. A further 68 parents or legal guardians were interviewed directly and the data thus collected were completed with selected information from the patient records (such as the diagnostic). Informed consents were obtained for the interviews. None of the parents/guardians approached refused to participate in the study.

One single datasheet/questionnaire was created to collect data for both components of the study. Within this datasheet/questionnaire, patient identification data, ethnicity, level of education of parents, type of tumor, dates of diagnosis, onset of symptoms and first visit to healthcare, first symptoms, information about investigations, alternative diagnoses and other information were registered. When the patient delay exceeded 7 days, the reasons for not presenting to the doctor earlier, as well as the reasons for eventually seeking help, were recorded. When malignant disease was not the first diagnosis, the alternative first diagnosis and corresponding treatment were recorded.

Study Population

Three hundred forty-four patients ranging in age from 0 to 15 years, diagnosed with a malignancy from January 2000 to July 2009, were identified by means of the tumor registry of the Tygerberg Children's Hospital. Due to reorganizing of the registry, access could not be gained in due time, to a number of files, especially of deceased patients. The study population, consisting of 194 subjects, included only 8 deceased children.

One interview was included in the study, despite the fact that the patient was later found to have been diagnosed already in 1997. Two interviews were aborted as the too distant relatives or foster parents were not able to provide accurate information. One further interview had to be abandoned due to a language barrier; in two similar cases, an interpreter was used. Thirteen patients did not keep their appointment for follow up at the clinic and four patients left before being interviewed, because of miscommunication. The data for all above cases were thus collected exclusively from the files. Six patients had to be excluded from the retrospective data collection, as the information recorded in their files was insufficient.

Data Entry and Analysis

A data-entry form was developed in Epidata 3.1. From there the data was exported to Statistica 8.0, which was the program used for the analysis in this study. Because of missing data, the total number of patients included in the different calculations varies.

For certain parts of the analysis, the different types of tumors were grouped together. The group of lymphomas included Hodgkin, non-Hodgkin and Burkitt lymphomas. The leukemias consisted of acute lymphatic leukemia, acute myeloid leukemia and chronic myeloid leukemia. The blastomas comprised neuroblastoma, nephroblastoma, retinoblastoma, hepatoblastoma and pleuropulmonal blastoma. The sarcomas consisted of bone- and soft tissue sarcomas. Other groups were brain tumors, histiocytosis and teratomas. The less common tumors were grouped under "other tumors."

For statistical analysis the following methods were used: Continuous measurements/ordinal variables were compared using the non-parametric Spearman correlation. Comparison of continuous measurement/ordinal variables were done using the Mann–Whitney *U*-test (comparing two groups) or the Kruskal–Wallis test for more than two groups. Categorical variables were compared using cross tabulation and the Chi-square test. The above methods are all non-parametric, and this was deemed necessary due to the non-normal nature of the data. Specifically delay times will not be normally distributed. When indicated, the data extracted from the files were analyzed together with those obtained from the interviews.

TABLE I. Length of Delay in Days

Type of delay	N[a]	Median	Minimum	Maximum
Total diagnosis delay	183	34	2	1,826
Patient delay	143	5	0	457
Physician delay	149	20	0	924

[a]Number of patients included in calculation.

Ethical Approval

This study was approved by The Health Research Ethics Committee of the Stellenbosch University.

RESULTS

Length of Delay

The total delay and its components, as identified in our patients, are presented in Table I The median total diagnosis delay found in this study was 34 days, the median patient delay was 5 days, while the median physician delay was 20 days.

The median total diagnosis delay and its components according to gender are presented in Table II. Gender did not have a significant influence on the total diagnosis delay (Mann–Whitney *U*, $P = 0.73$), patient delay (Mann–Whitney *U*, $P = 0.29$) or physician delay (Mann–Whitney *U*, $P = 0.32$).

The mean age at the start of the symptoms was 5.9 years (SD = 4.00). The age at onset of the symptoms did slightly influence the delays. There was a trend of decreased total diagnosis

TABLE II. Gender and Length of Delay

Type of delay	Gender	Median	Minimum	Maximum
Total diagnostic delay	Male	33	2	605
	Female	34	2	1,826
Patient delay	Male	5	0	457
	Female	5	0	153
Physician delay	Male	22.5	0	442
	Female	17	1	924

TABLE III. Length of Delay and Age at Clinical Onset by Types of Tumors

Type of tumor	Number of patients	Percentage of total number of patients	Median total diagnosis delay	Median patient delay	Median physician delay	Age at start of symptoms (mean)	Age at start of symptoms (SD)
Lymphoma	42	22	31.5	5	24	7.84	3.96
Leukemia	63	32	31	4	22	6.23	3.69
Blastoma	38	20	28	5	14	2.16	1.74
Sarcoma	18	9	56	13	23.5	6.98	4.71
Brain tumor	16	8	42	5	8.5	6.19	3.61
Teratoma	2	1	36	16.5	19.5	10.21	2.43
Hystiocytosis	5	3	168	1	6	4.10	2.21
Other tumors	10	5	104	5	40	5.78	3.79

delay (Spearman, r = 0.13 $P = 0.08$) and decreased patient delay (Spearman, r = 0.15 $P = 0.07$) with increased age.

The ethnicity was recorded for 103 patients: colored[2] (N = 77; 76%), black (N = 18; 17%) and white (N = 8; 8%). The median patient delay for colored patients was 5 days and for black and white patients 6 days. Patients' ethnicity did not have a significant effect on the total diagnosis delay (Kruskal–Wallis, $P = 0.90$), patient delay (Kruskal–Wallis, $P = 0.86$) or physician delay (Kruskal–Wallis, $P = 0.73$).

The level of education of the parents/guardians was only available from the interviews and out of these 68 cases, only 8 parents/guardians (12%) were educated beyond secondary (high school) level. Of the other 59 parents/guardians, 1 (2%) had no education at all, 16 (24%) had a primary level education and 43 (63%) had a secondary level education. The level of education of the parents/guardians did not have a significant influence on the total diagnosis delay (Spearman, $P = 0.92$), patient delay (Spearman, $P = 0.69$) or physician delay (Spearman, $P = 0.88$). The number of different tumors diagnosed and the respective median delays, as well as the mean age at the onset of the symptoms are reported in Table III.

The type of tumor did not significantly influence the total diagnosis delay (Kruskal–Wallis $P = 0.26$), the patient delay (Kruskal–Wallis $P = 0.49$) or the physician delay (Kruskal–Wallis $P = 0.16$). There is however a significant relationship between the type of tumor and whether the initial diagnosis was correct (Chi-square, $P = 0.03244$). Of the 35 cases diagnosed with a blastoma, 21 cases (60%) were correctly diagnosed from the onset. This is in contrast with the other types of tumors recorded, where more than 50% of the cases were misdiagnosed at first. Misdiagnosed most often was the category sarcoma, of which only 3 cases (19%) were correctly diagnosed and 13 cases (81%) were misdiagnosed (Fig. 1).

In most of the 194 cases recorded, the first diagnosis was not that of malignant disease. Only in 66 cases (34%) was the malignancy the first diagnosis. Out of the remaining cases, 112 (58%) were misdiagnosed and of the remaining 16 cases (8%) there was no information available.

Information about the mistaken diagnosis that was made initially was available in 98 cases. The most common misdiagnoses found in this study are presented in Table IV. The most frequently prescribed initial treatment in the 112 misdiagnosed cases was antibiotics (56 patients, 50%).

Para clinical testing was done after most of the initial visits to the healthcare system. Out of the 111 patients whose information about testing was available, 66 (59%) had one or more tests done after the first visit. The different investigations were: blood tests (N = 36), radiographs (N = 17), CT-scans (N = 14), ultrasound (N = 8) and a tuberculosis skin-test (N = 4). A MRI-scan was done in just 1 of the 66 cases.

The median physician delay when investigations were done was 16.5 days. The median physician delay when no testing was done was 25.5 days. Although a trend is noticeable, the positive correlation between testing being done and shorter physician delays is not statistically significant (Mann–Whitney U, $P = 0.08$).

In 52 cases (46%) of the 112 cases misdiagnosed at first, the eventual diagnosis of malignancy was made by the same health practitioner that saw the patient initially. Another 38 patients (34%) were seen by another health practitioner where the eventual diagnosis of a malignancy was established. For the remaining 22 patients (20%), there was no information available about how the eventual diagnosis was made.

The most common reasons why the same health professional eventually thought of the final diagnosis were: treatment for the first diagnosis failed (N = 20; 38%), the symptoms changed (N = 12; 23%), further diagnostic testing was done (N = 10; 19%) or that the symptoms worsened (N = 5; 9%). The most common reasons why patients consulted another health practitioner were that the parents/guardians looked for another doctor at their own initiative (N = 18; 47%), decided to go to the hospital at their own initiative (N = 11; 29%) or that the first doctor referred them to another doctor although he did not think of the diagnosis of cancer at that time (N = 6; 16%).

In 47 cases of the total of 194 cases included, the patient delay exceeded 7 days. The reasons for not visiting the healthcare system earlier were available in 26 of these 47 cases. The different reasons mentioned were that the symptoms did not seem very important or the patient was not very sick (N = 17), no financial means were available (N = 3), the parents/guardians did not notice the symptoms (N = 2), the symptoms were intermittent (N = 2) and the parents/guardians thought the symptoms were caused by a preexistent condition (N = 2). The reasons to eventually seek help from the healthcare system were available from 20 of these 47 cases. These were that the symptoms worsened (N = 17) or that the symptoms changed (N = 3).

[2] The Cape Coloreds: official designation, largely used in South Africa, also in governmental or scientific statistics of historical descendents of couples of mixed ethnicity. They constitute the major ethnic group in the Western Cape province of South Africa, as well as in the area served by Tygerberg Hospital.

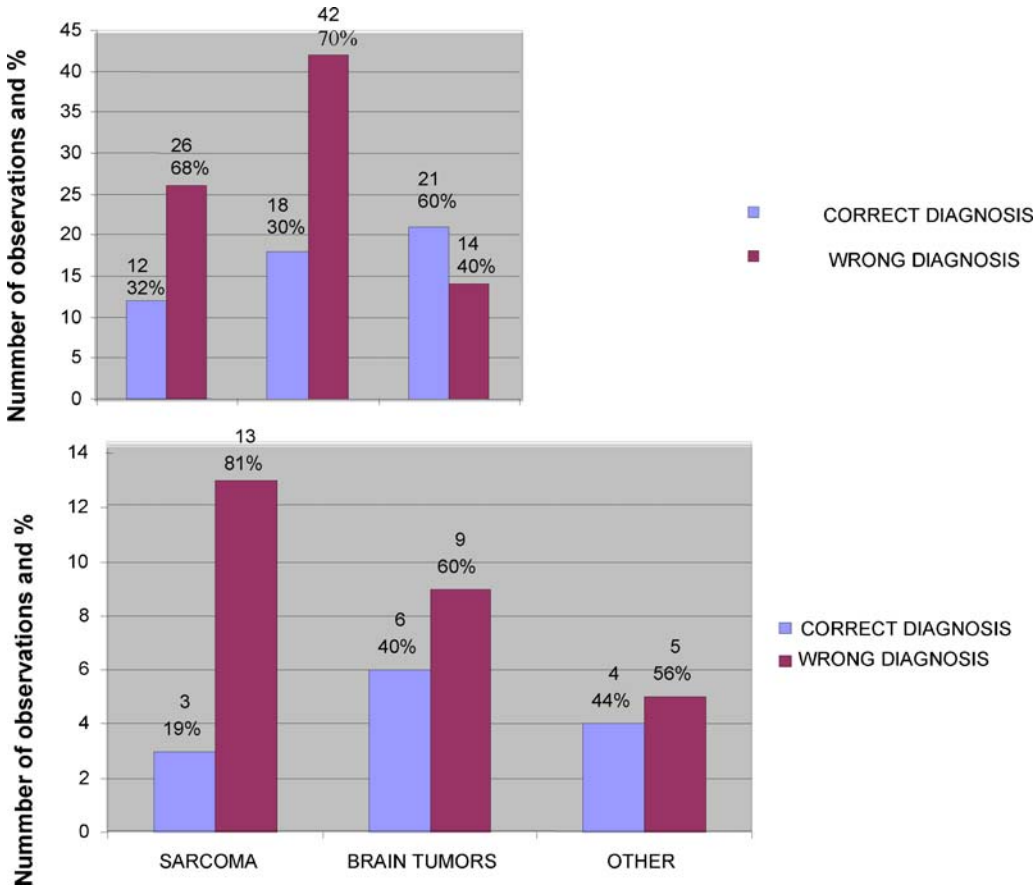

Fig. 1. Association between type of tumor and first diagnosis.

DISCUSSION

The median total diagnosis delay was 34 days. The median patient delay was 5 days and the median physician delay was 20 days. The total diagnosis delay is quite similar to the 30-day delay found in the Canadian study of Dang-Tan et al. [2] The median patient delay in Canada was almost twice as long (5 days vs. 9 days) as at the Tygerberg Hospital. This could be simply the consequence of the location of the present study, in a large urban center where the health services are readily accessible, while the Canadian study contained data from rural communities as well. The greater distances to health facilities, the possibly limited availability of transport and the sometimes unfavorable weather may have contributed to a longer delay.

TABLE IV. Common Misdiagnoses

Misdiagnosis	N[a]
Infections	51
Gastro-enteritis	6
Tuberculosis	8
Pneumonia	4
Tonsillitis	4
Sinusitis	3
Pharyngitis	3
Unspecified infection	23
Constipation	10
The flu/virus	9
Juvenile arthritis	4
Worms	4
Anemia	3
Total	81

[a]The number of times observed.

On the other hand, the median physician delay recorded here was a lot longer than in the cited study (20 days vs. 8 days), which suggests that physicians in this study have more difficulties diagnosing childhood cancer than in Canada. This finding is partly explained by the high rate of wrong first diagnoses, the delay in performing para clinical testing and by the relatively long wait for a histopathology result. The published review of the literature, however, found the same tendency for physician delays to be longer than patient delays [1].

It was decided to use the median values in order to describe the delay, since the outliers significantly influenced the mean. When these outliers are reviewed, the long total diagnosis delays appear to consist mainly of very long physician delays.

Gender did not significantly influence the delays. This outcome is similar to most previous studies. Differences in diagnosis delay between males and females were observed only for females with Non-Hodgkin lymphoma [5], while another study found a slightly higher risk for delayed diagnosis in males [4].

The mean age at start of the symptoms was 5.9 years old, while in previous studies the mean age at disease onset was 7.7 years old

[1,2,4]. However, in previous studies, by the age at disease onset was meant the age at diagnosis, while in this study the age at the start of the symptoms was calculated. It seemed more appropriate to consider the influence of the age at the start of the symptoms on patient delay, in order to assess the effect of age on the perception of symptoms by the parents. The negative correlation of age with total diagnosis delay and patient delay found here was not statistically significant. This finding is contrary to the results of most previous studies addressing this issue, but similar to the findings of Klein-Geltink et al. [6].

In this study, ethnicity did not have a significant influence on the total diagnosis delay patient delay or physician delay. The reason for this finding could be that the majority of patients included in this study were colored, so that the study population was a very homogenous group.

It was expected to find longer delays with patients whose parents/guardians have a low level of education [4]. But this was again a very homogenous group, since only a few parents/guardians ($N = 8$; 12%) were educated beyond secondary (high school) level. This could have resulted in the statistically insignificant differences.

Leukemia, lymphoma and blastomas were the most frequent malignancies in this series. Among leukemias, acute lymphatic leukemia was the most common diagnosis. The median total diagnosis delay for leukemia in this study was 31 days, while the median diagnosis delay in Canada was 18 days. Leukemia had the shortest median physician delay in Canada, which was 3 days [2], while in this study the median physician delay for leukemia was 22 days. Reasons for this big difference could be that physicians may have difficulties to recognize the onset symptoms of leukemia or that leukemia investigation might not be as easy to perform in the study area as in Canada.

In this study, the type of tumor did not have a significant influence on any of the delays, while the diagnosis delay in most previous studies conducted did differ significantly among tumor types [1,2,4]. Leukemia had the shortest diagnosis delay (1 month) and retinoblastoma the longest (5 months) in Mexico City [7] whereas in this study, blastomas had the shortest total diagnosis delay (28 days). It is notable, though, that retinoblastomas, some cerebral tumors and hystiocytosis had the longest total diagnosis delays. Similar findings were reported in the literature; the numbers of cases included in this study are too small to add significant support to those data.

When para clinical testing was done at the first visit, the physician delays were slightly shorter. This underscores the importance of maintaining a high index of suspicion for childhood cancer and of performing investigations without delay.

It is clear from this study that many concurrent factors influence the diagnosis of childhood cancer and the diagnosis delay. This multi-factorial effect is supported by the work of Haimi et al. [8], in which the regressions performed for each prognostic factor group explained no more than 16% of the variance in delay times; this suggested that the nature, genetic and biological profiles and epidemiological characteristics of the tumor and individual factors are all important determinants for the length of delay.

The study has several limitations. The interviews used to collect data in this study may have been affected by reporting biases. The parents/guardians who were interviewed had to recall details that had usually happened a long time ago. Remembering those hectic and emotional periods may have influenced the answers given in various ways. Some subjects would change the information they had provided, a few times during the interview, before coming to a final version. Some would find it hard to remember the exact dates, although they would usually remember how much time elapsed from the start of the symptoms to the first visit to the healthcare system and final diagnosis. To minimize these biases, the information provided by the parents/guardians was corroborated with the medical chart.

The information collected retrospectively from the patient records had its specific drawbacks. At times, the notes and letters in the medical files contained contradicting informations. Some medical charts were disorganized and some data were missing. Another drawback of this study is the number of deceased patients included. For reasons mentioned above, only 4% of the study population consisted of deceased patients. Longer diagnostic delays may have contributed to the mortality risk of those patients which were not included.

CONCLUSIONS

The median delay in the diagnosis of childhood cancer in this study at the Tygerberg Children's Hospital in Cape Town in South Africa was 34 days. The median patient delay was 5 days while the median physician delay was found to be 20 days. These data are comparable with findings published in other studies. None of the causative factors investigated, such as gender, the age at the onset of symptoms, ethnicity, parental education level, and type of malignancy influenced the length of the diagnosis delay significantly.

More than half of the malignancies were misdiagnosed initially, which led to postponement of the para clinical investigations and contributed to the total delay. The main event leading to the correction of the diagnosis was the failure of the first treatment instituted. It follows that a sustained effort should be made to raise the level of awareness of the early signs of cancer among medical practitioners and nurses, as well as among the parents.

There is a need to corroborate our data with those of other South African centers in order to obtain an accurate image of the extent of delay in diagnosing cancer in childhood across the whole country. Such an extended study could also reveal if there are any ethnic determinants of delay, which could not be identified in the present research.

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