Factors influencing time to diagnosis of childhood cancer in Ibadan, Nigeria

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Abstract

Background: Early diagnosis of cancer allows an opportunity for timely treatment while disease burden is in its earliest stages. Unfortunately, late presentation and delayed diagnosis of childhood cancers remains a problem in developing countries.

Objectives: To describe the pre-diagnostic symptomatic intervals and the factors influencing these time intervals in childhood cancer at the University College Hospital, Ibadan, Nigeria.

Methods: Information was obtained from the case notes of children seen between March 2006 and August 2008. Information included socio-demographic variables, stage of the cancer, duration of illness at diagnosis and other health seeking activities.

Results: Sixty-four children (40 males, 24 females) were studied. Median overall lag time was 13.1 weeks; median parent delay was 2 weeks and median health system delay was 8.8 weeks. Median lag times were shortest in acute leukaemia (8.1 weeks) and Wilms' tumour (8.7 weeks) and longest in Hodgkin lymphoma (101.7weeks).

Conclusion: Lag times were longer than those in developed countries. Factors contributing to delayed diagnosis included delayed referral by doctors, seeking health care from alternate sources and financial constraints. Education of parents and physicians on early presentation and early referral for early diagnosis is recommended.

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Introduction

During the past three decades, survival of childhood cancer has markedly improved particularly when appropriate protocols are used. In developed countries, the 5-year survival rate increased from 30% for children treated in the 1960s to over 70% for children treated in the 1990s.[1-3] In low income countries however, cure rates are at least 20-30% lower than in high income countries[4], reflecting an advanced stage of disease at diagnosis (usually due to delayed diagnosis) and higher rates of fatal toxicity and abandonment of therapy.[5] Similarly in Nigeria, childhood cancer survival is poor and frequently characterized by late presentation. [6,7]

Early diagnosis of cancer is a fundamental goal in oncology because it allows an opportunity for timely treatment while disease burden is in its earliest stages. Consequently, prognosis may improve, and a cure can be attained with minimal side or late effects.[8] Various researchers have carried out studies to find out the time to diagnosis of a variety of childhood cancers and the factors associated with delayed diagnosis. Some researchers have focussed on the time between a patient's first symptom recognition to a diagnosis of cancer. This time period, called diagnosis delay has also been designated as pre-diagnosis symptomatic interval, time to diagnosis, lag time or wait time by different authors.[8] Others have made a distinction between patient and physician delays.[9,10] The former was defined as the length of time between the onset of signs and symptoms and the patient's first visit to the health care system, whereas the length of delay between the first health care visit and the diagnosis was designated physician delay. The latter definition of physician delay may however not be strictly applicable in Nigeria where for a variety of social and cultural reasons, patients after entering the health care system may leave it for alternative medical practices for no fault of the physician.

A study in Nigeria is particularly important because of existing socio-cultural factors different from those in countries where previous studies have carried out.

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The objectives of this study were to describe the clinical stages of the tumours at diagnosis, the pre-diagnostic symptomatic intervals and the factors influencing these time intervals or diagnosis delays in cases of childhood cancer seen at the University College Hospital (UCH), Ibadan, Nigeria

Materials and Methods

This study involved all cases of childhood cancer seen between March 2006 and August 2008 at the Department of Paediatrics of the University College Hospital, Ibadan, Nigeria. Information was obtained from the patients' clinical notes and included socio-demographic variables, stage of the cancer, duration of illness at diagnosis and other health seeking activities embarked upon. The time between onset of symptoms and diagnosis was divided into two namely parent delay and health system delay. Parent delay also called patient delay by other authors was the interval between onset of symptoms and the first visit to the health care system. We used the term health system delay to represent what other authors called physician delay i.e. the interval between the first contact with the health care system and diagnosis. For the purpose of uniformity and ease of comparability, clinical staging was done using the SEER (Surveillance, Epidemiology and End Results)[11] clinical staging as follows:

Localized tumour: A malignancy limited to organ of origin with no spread beyond organ of origin

Metastasis (Distant): a tumour which has spread to areas of the body distant or remote from the primary tumour. This stage is also called remote or diffuse. Leukaemias are assumed to be diffuse at the time of diagnosis.

Regionalized tumour: Tumour extension beyond limits of the organ of origin but with no evidence of distant metastasis. Unknown: cases for which sufficient evidence is not available to assign a stage.

In this study, staging was done using at least clinical signs and diagnostic imaging (ultrasonography), in all patients, and when necessary surgery and cytology of bone marrow aspirate.

Data were recorded onto a case record form, entered into a computer and analysed using SPSS version 15.0. Frequency distributions of categorical variables were computed and continuous variables described with parametric tests. Since time lag was found to be skewed, median figures and ranges were presented. For the same reason, Mann-Whitney and Kruskal-Wallis tests, which are non-parametric statistics, were used in comparing time lag between different categorical variables and Wilcoxon Signed Ranks test in comparing paired time lag between parent delay and health facility delay. Statistical significance was set at $p < 0.05$.

Results

A total of 64 children were studied comprising 40 males and 24 females giving a male: female ratio of 1.7:1. Their ages ranged from 1 to 14 years with a mean (standard deviation) of 5.3 (3.3) years. Based on SEER staging, disease was localized in 14 (21.9%) patients, regionalized in 19 (29.7.0%), and metastatic in 31 (48.4%) of the children. Median overall lag time was 13.1 weeks (2.1-156.9 wk), median parent delay was 2 weeks (0.1-52.1wk) and median health system delay was 8.8 weeks (0.4-152.6 wk)[table 1]. Paired comparison of the parent delay and 'health system' delay revealed the latter to be significantly longer (Wilcoxon Signed Ranks tests, $p < 0.001$).

Table 1: Breakdown of lag time (weeks) between onset of symptoms and diagnosis

	Parent delay	Health system delay	Overall delay
Mean	5.9	18.3	24.2
Standard deviation	9.5	26.8	28
Median	2	8.8	13.1
Range	0.1-52.1	0.4-152.6	2.1-156.9

The lag time of patients with respect to demographic and clinical characteristics is shown in table 2. A significant difference in lag time was found among tumours types with the shortest lag times in acute leukaemia and Wilms' tumour and the longest in Hodgkin lymphoma (Kruskal-Wallis test, p 0.034). In analyzing the effect of the presence of metastatic disease at diagnosis on lag time, cases of Leukaemia and Burkitt lymphoma were excluded. This is because, cases of leukaemia are assumed metastatic at diagnosis and Burkitt lymphoma being multi-focal in nature may present with disease at multiple sites right from the onset (i.e. time zero). There was no association between overall lag time and presence of metastatic disease (Mann-Whitney U, p=0.296).

Table 2: Overall lag time of patients with respect to demographic and clinical characteristics

Patient characteristics		No of Patients	Lag time (weeks)	
			Mean(SD)	Median (range)
Sex	Male	40	20.7 (27.2)	13.1 (2.1-156.9)
	Female	24	30.0 (29.1)	16.6 (2.7-103.6)
Age (years)	1-4	36	25.8 (26.6)	13.9 (2.1-103.6)
	5-9	18	19.2 (35.5)	9.4 (2.6-156.9)
	10-14	10	27.5 (17.5)	28.9 (8.1-52.1)
*Stage (n= 38)	Metastatic	15	28.9 (41.2)	13.0 (2.3-156.9)
	Non-metastatic	23	31.82 (28.4)	17.8 (2.7-103.6)
Diagnosis	Burkitt lymphoma	17	16.9 (13.8)	9.7 (2.1-49.1)
	Retinoblastoma	9	50.7 (34.2)	51.4 (8.7-103.6)
	Rhabdomyosarcoma	11	25.1 (22.2)	14.3 (6.3-74.0)
	Non-Hodgkin lymphoma	2	10.9 (5.9)	10.9 (6.7-15.0)
	Hodgkin lymphoma	2	101.7 (78.1)	101.7 (46.5-156.9)
	Wilms' tumour	6	10.4 (9.2)	8.7 (2.3-27.3)
	Acute leukaemia	9	10.8 (10.6)	8.1 (2.6-36.6)
	Neuroblastoma	4	19.9 (21.7)	11.2 (5.0-52.1)
	Hepatoblastoma	1	8.1	8.1
	Germ cell tumour	2	20.0 (22.7)	20.0 (3.9-36.0)
	Osteogenic sarcoma	1	17.1	17.1
Father's education				
	> secondary	25	28.7(35.5)	13.0 (2.3-156.9)
	Below or equal to secondary	39	21.3(22.0)	13.4 (2.1-93.0)
Mother's education				
	> secondary	18	24.6(26.2)	14.1 (2.3-103.6)
	Below or equal to secondary	46	24.1 (29.0)	13.0 (2.1-156.9)
First health facility				
	Tertiary	11	34.3 (35.3)	25.4 (2.7-103.6)
	Non- tertiary	53	22.1 (26.2)	13.0 (2.1-156.9)

* Burkitt lymphoma and leukaemia excluded

Although lag time was longer in female than in male children, this difference did not reach statistical significance (Mann-Whitney U, p = 0.185). Although, the lag time was least for the 5-9 year age group and longest for the 10-14 year age group, there was no significant difference in lag time across the different age groups (Kruskal-Wallis test p = 0.106). There was also no significant difference in lag time between children whose parents had post secondary education and those with lower educational levels (Mann-Whitney U , p= 0.496 for paternal educational level, p= 0.870 for maternal educational level). In addition, no significant difference was observed in the lag time between patients whose first health facility visit was tertiary and those who visited lower level facilities (Mann-Whitney U, p=0.455). Duration of illness when patients visited tertiary health facilities was significantly longer than duration of the illness when they visited non-tertiary facilities (Mann-Whitney U, p=0.005).

For most parents, 48 (75.0%), the first port of call for medical attention was a health facility; 13 (20.3%) administered drugs bought over the counter for their children and 1(1.6%) each consulted a patent medicine dealer, used herbal preparation and took the child to a church respectively. Among the 48 patients who visited health facilities first, 28 subsequently engaged in other health seeking behaviours as shown in table 3.

Table 3: Alternative health seeking practice of 28 parents who had first visited health facilities

Practice	Frequency	Percentage
Parental medication	17	60.7
Patent medicine dealer	9	32.1
Visit to a Nurse	2	7.1
Traditional healer	10	35.7
Church	9	32.1

Among those who sought alternative sources 14 (50%) of 28 had metastatic disease at diagnosis compared to 8 (40%) of 20 who only attended health facilities. Although there was a greater tendency for those who sough health care outside health facilities

to present with metastatic disease, this did not reach statistical significance (Fisher's exact significance p = 0.565).

When eventually each of the 64 patients presented at a health facility, 11 (17.2%) first presented to tertiary health facilities, 42 (65.6%) to secondary health facilities and 11 (17.2%) to primary health centres.

Seven children presented first at the UCH out of which 6 followed through to diagnosis and management whilst 1 was scheduled for surgery but defaulted for 67weeks before presenting again at the hospital. Of the remaining 57 children for whom the first health facility visited were other health facilities aside from UCH, 17 (29.8%) were referred to UCH within 2 weeks of presentation. The others were managed in the health facilities for periods ranging from 1 day to 156 weeks with a median of 6.0 weeks and mode of 8 weeks; they were either subsequently referred after a long time of treatment or taken away by parents due to unsatisfactory response to treatment.

Regarding sources of referral, eleven parents brought their children to the University College Hospital and the remaining children were referred by health facilities; details shown in table 4.

Table 4: Referral characteristics of children

		Frequency	Percentage
Source of referral	N=64		
	Parents	11	17.2
	Health facilities	53	82.8
Interval between referral and presentation at UCH	N=53		
	Less or equal to 1 week	42	79.2
	> 1 week	11	20.8
Reasons for delayed presentation	N=11		
	Financial constraints	5	45.5
	Referral from a distant town	3	27.3
	Others	3	27.3

Discussion

Late presentation has been reported to be associated with an increased risk of mortality in childhood cancer[12]. Our finding of metastatic or diffuse disease occurring in majority of children at diagnosis is in keeping with previous reports in our country.[13] This may ultimately result in poor prognosis in such cases. It is therefore important to find out factors that influence the time of presentation of children with cancer in order to design strategies aimed at facilitating early diagnosis.

Diagnostic delays in our study population were much longer than reported by Haimi *et al* in Israel.[10] While the latter reported median parent's delay of 1 week, doctor's delay of 4 weeks and overall delay of 7 weeks, the corresponding values in our study were 2, 8.8 and 13.1 weeks respectively. The delays in our patients appear to be twice as long as those in Israel. This may be due to differences in the health seeking attitudes which may in turn be related to socio-cultural factors and the challenges of access to health services in a developing country like Nigeria.

The health service delay in diagnosis (interval between first contact with the health care system and diagnosis) was significantly longer than the parent delay in our study in keeping with findings by Haimi *et al.*[10] However, unlike in the latter study, we have refrained from calling it doctor's delay since in our setting; multiple factors including parental decisions and not exclusively the doctor contribute to delay in diagnosis after the first contact with the health services. Important factors include delayed referral of children to centres where appropriate management can be provided. These patients were kept for a median of 6.0 weeks but in an extreme case for three years being managed for a wrong diagnosis before referral. This contrasts with a country like Canada where half of children under 15 years of age wait less than one month from the onset of symptoms to their first anti-cancer therapy .[9] Parental factors contributing to delayed diagnosis after contact with the health system include seeking health care through alternative means such as "parental self medication", patent medicine dealers, traditional healers and churches. Other factors that contributed to the health system delay were financial constraints faced by the parents and the need to travel to a referral centre that is far from the city of residence of the family.

The habit of seeking alternate sources of care after initial contact with the health care system

suggests a lack of confidence in the system. It is also a reflection of the socio-cultural factors influencing health seeking behaviour in the country. Unfortunately, higher educational level of parents did not seem to confer any advantage with regard to diagnosis delay in our study. Persons of higher educational levels in Nigeria, tend to patronize private hospitals and deliberately avoid government owned specialist centres because of the series of diagnostic tests often requested and the processes involved in seeing a doctor which are often longer than those in private hospitals. Consequently, persons with higher educational levels often suffer delayed diagnosis despite being frequently more economically empowered.

Our finding of significant difference in lag time with regard to tumour types confirms previous observations by Pollock *et al*[14] and Haimi *et al*.[10] Apart from hepatoblastoma in which only one case was seen, the shortest delays in diagnosis in our patients were seen in acute leukaemia and Wilms' tumour with median times of 8.1 and 8.7 weeks respectively. This is in keeping with findings by Fajardo-Gutierrez *et al* [15] who also observed that, leukaemias had the shortest time to diagnosis in Mexican children but with a median time of 1 month. Further corroborating our findings, Haimi *et al* [10] observed the shortest delays in children with kidney tumours in Israel but with a median time of 2.5weeks. In our patients, acute leukaemia and Wilms' tumour which had the shortest times to diagnosis were closely followed by Burkitt lymphoma (median time 9.7 weeks). The longest delays in our patients were in retinoblastoma and Hodgkin lymphoma with median times of 51 weeks and 101 weeks respectively. This is also in keeping with findings by Fajardo-Gutierrez *et al* [15] in Mexican children in whom Hodgkin disease and retinoblastoma had the longest time to diagnosis but with a median time of 5 months. With leukaemia having the least delay and Hodgkin disease and retinoblastoma having the longest delays our finding are also similar to those in Mexican children.

However, the median times in Nigerian children seem to be at least twice as much as those in Mexican children just as it was in comparison to children in Israel. The delay in the diagnosis of Hodgkin lymphoma in our patients is probably due the indolent course of some forms of Hodgkin lymphoma; Miettinen reported an 80 percent 10 year survival for untreated nodular lymphocyte predominant Hodgkin lymphoma.[16] In addition, one of our two patients spent about 3 years in the source of referral receiving various treatments for infections probably due to the clinical similarity between Hodgkin lymphoma and infections in the tropics like tuberculosis.

The late presentation of tumours is a cause for concern and particularly so for retinoblastoma considering the loss of vision that may occur even if the patient gets cured eventually. A delay in the diagnosis of retinoblastoma is not uncommon particularly in unilateral cases presenting with subtle signs like strabismus or masquerading features such as hyphaema, uveitis or secondary glaucoma [17, 18]. In a study by Wirix *et al* in Belgium, a child was found to have been followed up for strabismus for four years without any proper fundus examination, in whom a diagnosis of retinoblastoma was later made.[17] The presence of leukocoria itself, though present in up to 60% of patients, denotes a large tumour and may not even be noticed by the parents as it depends on the direction of light entering the eye to produce the characteristic cat's eye reflex.[17] Patient's presenting with a squint particularly suffer longer delays before diagnosis as compared with other symptoms.[17] This therefore underpins the need to emphasize to parents, physicians and ophthalmologists alike, the need to promptly and exhaustively evaluate any child presenting with a squint to exclude an occult intraocular tumour.

Some researchers have reported an increase lag time to diagnosis of cancers with increasing age.[14,19] Although our study similarly observed the longest delay in the 10-14 year age group, a trend of consistent increase from infancy upwards was not noted. The shortest lag time in our study was in the 5-9 year age group probably due to the high proportion of Burkitt Lymphoma which is highly proliferative and peaks at that age in our environment[20]. We also observed no difference in lag time between male and female in keeping inconsistent gender differences observed in various studies. In a review by Dang-Tan, only 2 out of 9 studies observed significant differences in diagnosis delay between male and female patients.[8]

We found no difference in lag time between cancers diagnosed at different stages in keeping with findings by Saha *et al*.[19] On the contrary, some other researchers have observed an association between shorter time at presentation and improved stage at diagnosis.[21] The relationship between diagnosis delays and disease stage is complex. It is rational to think

that longer delays would lead patients to be diagnosed at a more advanced stage of the disease. However, more aggressive, fast-growing tumours may lead parents to seek medical attention for their child early exemplified by the findings of Halperin and Friedman who observed that meduloblastoma patients with advanced stage exhibited shorter lag times compared with early stage disease patients.[22] Therefore aggressiveness of disease and the attendant severity of symptoms likely play a role in the relationship between diagnosis delay and cancer stage.

Haimi and colleagues observed that lag times were shorter for children first examined by Paediatricians in comparison to family physicians and other specialists. [10] We did not examine the lag time in relation to specialists first seen by the patient but rather by the level of health care facility first visited by the patient. We expected that children seen at tertiary centres are more likely to be attended to by Paediatricians and therefore be diagnosed earlier. We observed no difference in lag time for patients first seen at a tertiary health facility compared to those first seen at lower level facilities. This however was not a surprise since the duration of illness at presentation in tertiary centres was significantly longer than those at presentation at lower level health facilities. It seems therefore that parents take their children directly to tertiary centres when the illness has been protracted and the disease probably more advanced.

Conclusion

Diagnosis delay of childhood cancer in Ibadan, Nigeria, tends to be longer compared to more developed countries. Education of physicians on the need for a high index of suspicion of cancer and prompt investigation of suspicious clinical features for early referral is strongly indicated. In our study, following referral (although late in most instances), most parents immediately complied and took their children to the referral centres. This suggests that if children are referred early, parents may also comply, resulting in early diagnosis. Education of parents on the importance of early presentation at health facilities and continuing within the system until a diagnosis is established and management started is necessary. This may be further enhanced by
improved operation of the newly instituted National Health Insurance Scheme in the country.[23]

This is a scheme whereby an agreed amount of a worker's salary is deducted from source on a monthly basis and paid to enable the insured and dependants access health care without having to pay at the point of need. Some of the objectives of the Scheme are to ensure that every Nigerian has access to good health care services, to protect families from the financial hardship of huge medical bills and to ensure equitable distribution of health care costs among different income groups. Successful shortening of the diagnosis period may ultimately improve prognosis of childhood cancer in Nigeria.

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