SERVICE D'HEMATOLOGIE ET ONCOLOGIE PEDIATRIQUE

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RESIDANAT EN PEDIATRIE

MEMOIRE DE STAGE EN HEMATOLOGIE ET ONCOLOGIE PEDIATRIQUE

Pediatric cancer in Morocco: Latency to diagnosis and treatment

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Mai / 2017

ABSTRACT

Background: Early diagnosis is fundamental in pediatric oncology because it allows for timely treatment of the disease in its earliest stages. A few studies have assessed factors associated with cancer latency to diagnosis in children in Africa. To the best of our knowledge this is the first in Morocco.

Methods: We performed a prospective study of 65 cases of childhood cancer referred to the Pediatric Hematology and Oncology department of Rabat Children's Hospital between January 2017 and April 2017; patients' data were recorded through interviews with the parents and review of the medical records. We studied the time intervals between onset and final diagnosis and start of treatment and investigated associated factors with shorter intervals

Results: The median latency to diagnosis in our study was 34 days. The median physician interval was higher than median patient interval (24 vs. 5days); Gender, family size, residence and type of health insurance had no significant association with latency to diagnosis. There was no significant association between physician lag time and tumor type or health care system variables such as first attending doctor and type of health facility. Misdiagnosis was recorded in 35% of our patients, 8 of them had steroid intake prior to diagnosis of cancer.

Factors associated with a significantly shorter patient interval were mother's high level of education, age at presentation (patients aged between 5 and 10 years) and parents' employment (both parents working).

Our findings show that the index of suspicion for childhood cancers remains low in our country and mother's education level was a factor of shorter consultation delay.

Thus, increase in public awareness and continued medical education for general practitioner and pediatricians would reduce latency to pediatric cancer diagnosis in our country.

Keywords:

Cancer; diagnosis; latency; delay; children

INTRODUCTION

Childhood cancer is a leading cause of death in children despite the great progress in the field of pediatric oncology during the past two decades. [1]

Multidisciplinary approaches for treating cancer have allowed for increased survival rates around the globe. [2] However, lower survival rates are still reported in middle-and low-income countries. [3]

Pediatric cancer responds somewhat better to therapy than at older ages, but it also progresses faster in the absence of treatment. Early diagnosis is, therefore, fundamental, because it allows treatment of early stage disease, which results in better prognoses for these children and can also have a positive effect on their quality of life. [2]

Diagnosing cancer in children remains a complex process that includes related factors such as parental characteristics, the healthcare system factors, and the clinical presentation. [4]

Such factors may impact diagnostic process and lead to delays.

The term ‘’delay’’, widely used in medical literature about latency to cancer diagnosis, imply a negative and unclear connotation, as there is no established reference point for the delay in diagnosis, which leads to an arbitrary and individual reference point for every study. [5]

New definitions are currently used, the **latency to diagnosis** (also known as the wait time or lag time) is divided in to the **patient interval** (length of time between the onset of signs and symptoms and the patient’s first visit to a health care practitioner) and the **physician interval** (length of time elapsed from the first health care system contact to the definitive cancer diagnosis).

Recognition of these intervals and factors influencing them would be useful to form effective strategies to shorten delays and hereby potentially improve survival.

To date, few studies have assessed research on this topic in developing countries, particularly in Morocco. This research attempts to investigate the diagnostic process of childhood malignancies among a Moroccan population, with the focus on the time course from initial symptoms until diagnosis and start of treatment.

SUBJECTS & METHODS

▪ **Study design:** A prospective study was performed in the Pediatric Hematology and Oncology department of Rabat Children's University Hospital, the main tertiary referral center for treating childhood cancers nationwide, it is composed of two inpatient units and an outpatient clinic and serves large northern and central areas in Morocco (Tangier-Tetouan-Al Hoceima and Rabat-Sale-Kenitra).

We used a predesigned questionnaire to collect data from parents or legal guardians of children (0 ± 16 years) referred to our center for suspected or confirmed malignancy between January 2017 and April 2017.

The patients' data, included age at onset, sex, sibling rank, family size, parental age and educational level, socioeconomic status and type of health insurance; characteristics of the latter are detailed in Table 1. [6] Disease first symptoms, first diagnosis by a health care professional, first doctor's notes, and any prescription given before the final diagnosis were also recorded.

Medical data were collected from medical records of the patients: diagnosis, date of diagnosis, and date of start treatment.

During the study period, all the types of heamatologic malignancies and solid tumors were included; five children were excluded because their tumors could not be classified as malignant (except for brain tumors). Six children were also excluded as their medical data were incomplete; that left 65 patients in the study group.

▪ **Definitions** (Figure 1): [7] a child with cancer was considered to be symptomatic starting at onset of unrelieved symptoms that were directly attributed to the malignancy.

The term **patient interval** referred to the interval of time measured in days that elapsed between the onset of cancer-related symptoms and the patient's first visit to a physician.

The term **physician interval** was defined as the interval of time that elapsed between the patient's first contact with a physician and the cancer diagnosis.

Latency to diagnosis is the sum of the patient interval and the physician interval.

The term **time of referral** was defined as the time it took to complete the administrative paper work for a patient's transfer from a primary or secondary care center to our hospital. Some patients were referred to our department prior to confirmation of cancer diagnosis, the referral time was included in the diagnosis time, and for other patients it was included in the treatment interval since they were referred after confirmation of diagnosis

The **treatment interval** was defined as the lag time between the cancer diagnosis and the start of treatment.

The term "misdiagnosis" was used when the malignant disease was not the first diagnosis and another benign disease was suspected.

The term "patient factors" used to describe factors associated with ''delay'' attributed to the patient such as age, sex, family size, parental education, residence, and socioeconomic level. "Tumor factor" denotes the type of tumor.

- **Statistical analysis:**

For assessment of relationship of the patient, physician and total intervals, respectively, as a function of the variables (tumor; age group; sex; parent's employement; age and level of education; type of health care insurance; place of residence, type of physician initially consulted), we performed non-parametric tests instead of ANOVA analysis given the non-normal nature of the data.

Non-parametric tests included the Mann–Whitney *U*-test (comparing two groups) or the Kruskal–Wallis test for more than two groups. We then carried out post hoc test to compare medians of patient interval, physician and total intervals respectively between different group pairs.

A *P* value of 0.05 was used to indicate the level of statistical significance. All analyses were performed using SPSS software (version 20.0).

- **Ethical considerations:** Oral consent of the parents/guardians was obtained prior to the participation in the study. To ensure uniformity and confidentiality, the interview was conducted in a private room and confidentiality safeguards were implemented in order to protect patients' names, medical record numbers, and diagnoses.

RESULTS

- **Demographic characteristics:**

A total of 65 children diagnosed with different malignancies were included in this study, sex ratio was 0.9 (34 females and 31 males). Age at onset ranged from 4 months to 15 years with a mean of 3.2 years, 46% of the cases was aged less than 5 years.

The majority of patients (67%) lived in urban areas; parents were both illiterate and jobless in respectively 24% and 7% of the cases; family was large sized (>7) in 20% of the cases and more than half (66%) had the RAMED health insurance system (cf. Table 1).

- **Clinical presentation:**

Clinical presentations at onset were various including: pain (34%), mass (27%), fever (12%), Signs of compression (6%), Leucocoria (4%), bleeding (1.5%), seizure (1.5%) and others (13%). In one patient with neurofibromatosis, asymtomatic glioma of optic pathway was revealed by MRI screening.

Hematologic malignancies: 46% of the cases, diagnosis interval ranged from 4- 288 days with a median of 35 days. Solid tumors were diagnosed 54% of cases, diagnosis interval ranged from 6-367 with a median of 42 days. Table 2 describes the distribution of tumor types in our study.

Misdiagnosis was reported in 23 patients (35%). Of the children diagnosed with hematological malignancies and solid tumors, 14/23 and 9/23 respectively, were initially misdiagnosed. Incorrect initial diagnoses included rheumatoid arthritis (8/23), bone or joint infections (5/23), other Infections (7/23) and cholesteatoma (1/23); 2 patients out 23 were mislabeled as having somatization disorder.

The most common alternative therapies were antibiotics and analgesics in respectively 52% and 39% of the misdiagnosed patients. While steroid intake was noted in 34% of them (3 patients had ALL).

- **Latency to diagnosis and treatment:**

Our study demonstrated a median total lag time of 42 days as detailed in table 3.

Non parametric tests were performed to identify the factors that were significantly associated with cancer latency to diagnosis and management (Table 4).

- **Patient interval:** There was no statistically significant association between the patient interval and sex, geographical residency, family size, health insurance, type of tumor or health care facility. Factors associated with a significantly shorter patient interval ($P < 0.05$) were the age at presentation (patients aged between 5 and 10 years), mother's level of education (high school level), parents' employement (both parents working). Reasons of patient delay given by parents were various including financial issues, beliefs and mis-interpretation of the symptoms, parental self-medication was noted in 9 cases and two patients were initially treated by an alternative medicine practitioner. In some cases, delay in consultation was related to more than a reason.
- **Physician interval:** There was no significant association between physician lag time and tumor type or health care system variables (first doctor and type of health facility); of the demographic data, only father's education level (high school level) was associated with a significant shorter physician delay.

DISCUSSION

Only few studies have investigated factors associated with cancer latency to diagnosis in children in Africa. [8, 9, 10] To the best of our knowledge this is the first in Morocco.

We decided in this study to use the median values in order to describe the lag time, since the outliers significantly influenced the mean.

Our study shows a median total interval of 42 days. This was comparable to reports from African countries, such as Egypt (47 days); [10] and shorter compared to report from Asian low- and middle-income countries, such as Indonesia (70 days), [7] Nigeria (110 days), [9] and Turkey (60 days). [11]

The median latency to diagnosis in our study was quite similar to the 34-day interval found in a South African study.[8] The median physician interval was higher than median patient interval (24 vs. 5days); this is consistent with many reports. [4, 8]

First attending doctor had no significant relationship with physician interval in our study.

Median physician interval was higher than the interval reported in a Canadian study (24 days vs. 8days). [4] That suggests that physicians in our study had more difficulties to diagnose cancer. It has been suggested that increased vigilance and awareness of cancer may decrease delay times. [12, 13] However, the severity of disease and symptoms on presentation at the physicians' office likely influences this relation. [4]

Physician delay in our study may be partly explained by the high rate of wrong first diagnoses which was recorded in 35% of our patients; this rate was a lot lower than in South Africa (58% of patients). [8] Furthermore, the extensive use of steroids before diagnosis in our series (8/65 patients) may have affected the diagnosis process as steroids can mask the disease in some cases.

This underscores the importance of maintaining a high index of suspicion for childhood cancer and excluding malignancies before initiation of steroid therapy.

Thus, efforts to further educate young physicians, general practitioners and general pediatricians about the presenting signs and symptoms of cancer in children will undoubtedly improve the diagnostic skills of the physicians. [10]

Our study found that median patient interval (5 days) was shorter than median HCS interval (33 days). This is in line with a study from Indonesia which reported a HCS interval of 49 days and a patient interval of 5 days. [7] Our findings contrast with a report from Uganda and Kenya, which reported significantly longer patient delays (30 and 63 days, respectively) compared to HCS delays (14 and 18 days, respectively). [14] In both African countries, low socioeconomic backgrounds were the major barriers to care and predictors of delay. [7,14]

Socioeconomic level was determined to be an important factor in suspecting and interpreting symptoms and signs of malignancies. [10] In our study, shorter patient intervals were noted in patients with both parents working.

Moreover, in rural areas, the greater distances to health facilities and the possibly limited availability of transport may contribute to a longer delay. [8] However, in our study residence had no significant statistical association with patient or total interval.

There was no significant association between parents' level of education and patient interval, this finding is contrary to the results of other studies, [15] where longer patient delays were

found in patients whose parents have a lower level of education, [16] these results could be influenced by the small number of parents that had high school level (12% of the fathers and 11% of the mothers). However, father's high educational level was associated with shorter physician interval.

The mean age at onset was 3.2 years old, while i previous studies the mean age at disease onset was higher 7.7 years old. [4, 16, 17, 18]

In this study we used age at onset instead of age at diagnosis in order to evaluate the influence of the age at the start of the symptoms on patient interval. Patients aged between 5 and 10 years had shorter patient lag time, however, it was expected to find shorter delays in younger patients (< 5 years) as in many studies [8, 17, 19] as younger children usually receive more care and attention so that a body asymmetry or increase in volume might be observed earlier and more easily. [20]

Gender had no significant relationship with any of time intervals in our study; this is in agreement with the finding of most previous studies. [8, 10, 21]

In this study, tumors were divided into two groups, hematological malignancies and solid tumors; among hematological malignancies lymphatic leukemia was the most common subtype; there was no significant relationship between these two groups and diagnosis or total interval, contrarily to many studies in which latency to diagnosis differs among tumor types. [4, 16, 17] A larger sample is, however, required to better assess the influence of each subtype on diagnosis interval.

Our study has some limitations, the sample small size may have influenced statistical analysis and the reporting biases may have affected the interviews used to collect data, to overcome these biases we reviewed the initial referral letters and contacted the referring doctors when possible.

Research on latency to diagnosis in childhood cancer is still in its early stages. More studies are required to evaluate factors that influence delays in order to form effective policies and programs aimed at eliminating obstacles in the cancer-care pathway for children with cancer. [4]

CONFLICTS OF INTEREST

Authors have declared no conflict of interest

CONCLUSION

Our findings were comparable with those described in developing countries, the length of physician interval and the rate of misdiagnosis shows that the index of suspicion for childhood cancers remains low in our country. Moreover patient interval was mainly influenced by mothers' educational level, thus, an increase in public awareness by educational tools such as general population campaigns and continued medical education for general practitioner and pediatricians would reduce delays in cancer diagnosis in children.

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TABLES & FIGURES

Table 1: Description of the main health insurance programs in Morocco (reference x)

Types of health insurance programs	Description	Advantages	Disadvantages
The mandatory health insurance coverage (AMO): managed by two institutions (CNOPS and CNSS)	**CNOPS** (National Social Welfare Organisations): workers and retired employees (and their legal successors) from the public sector **CNSS** (National Social Security Fund): employees and retired workers (and their legal successors) from the private sector.	- AMO covers a broad range of health services -Individuals are free to choose the doctor and the health center (either private or public sector)	- CNOPS has a chronic deficit that prevents it from honoring its commitments of reimbursing in rather short time-frames.
The medical care coverage (RAMED)	Protects the most vulnerable populations from health-related out-of-pocket expenses.	Eligible people are exonerated from any payment for a large set of medical services available in the public hospitals, the public healthcare institutions and the governmental	- the administrative complexity of the documentation that has to be submitted in order to be eligible for RAMED undoubtedly excludes the more vulnerable populations such as the illiterate and those in more remote areas. -it covers only public services

		healthcare services	-patient can not choose doctor nor health center
Private insurance corporations	Covering the employees of thousands of private companies, within the framework of group medical insurance contracts.	Individuals can go to any doctor in any clinic.	- They reimburse 70 to 80% of minor risks on the basis of the stated charge and provide little or no coverage for major risks under the practice of applying annual ceilings per beneficiary and per disease, and due to risk selection based on age and initial state of health.

Table 2: Distribution of tumor types in our study

Hematologic malignancies		**Solid tumors**	
Type of tumor	N	Type of tumor	N
Acute lymphatic leukemia (ALL)	17	Neuroblastoma	5
Lymphomas	10	Rhabdomyosarcoma	5
Acute myeloid leukemia (AML)	3	Cavum carcinoma	5
		Brain tumors	4
		Nephroblastoma	4
		Retinoblastoma	3
		Bone tumors	3
		Germinal tumors	3
		Others	3
Total	30	Total	35

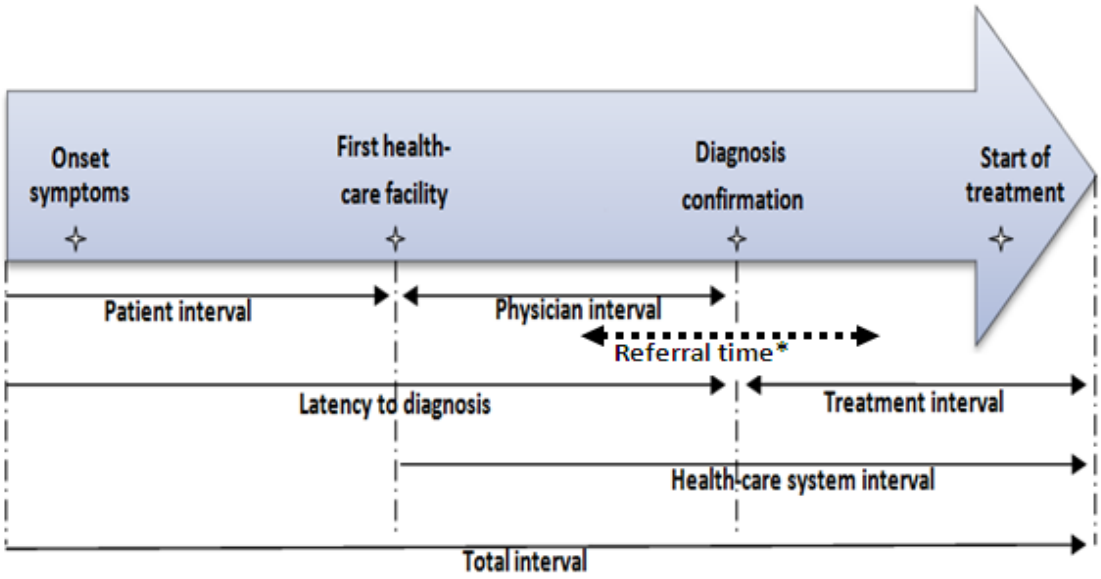
Table 3: Latency to diagnosis and treatment (days)	**Median**	**Mean**	**Min - Max**
Patient interval	5	18	0 - 270
Physician interval	24	59	1 - 360
Latency to diagnosis	37	200	4 - 367
Referral time	1	1.7	0 - 30
Treatment interval	2	6.7	0 – 105
Healthcare system interval	33	70	4 - 405

Total interval	42	86.8	6 - 494

Table 4: Factors of latency to diagnosis and treatment

Variables	N (%)	Patient interval (days) Median	Min-Max	p	Physician delay (days) Median	Min-Max	p	Total interval (days) Median	Min-Max	p
Gender Female	34 (53)	7	0- 240		28	2 - 360		51	6 – 376	
Male	31 (47)	5	0- 270	0.652	21	1 - 360	0.507	41	10-494	0.341
Age at onset(years)										
< 5	30 (46)	6	0- 270		20	1-360		43	7-494	
5–10	23 (35)	4	0- 21	**0.018**	28	2-360	0.388	41	6- 391	0.758
>10-16	12 (19)	7	5-150		30	4 -120		56	7- 184	
Family size										
Small (3-4)	35 (54)	7	0 – 270		24	1-360		44	9-412	
Medium (5-6)	17 (26)	7	0- 240	0.808	23	2-360	0.847	42	11-494	0.314
Large (>7)	13 (20)	5	1-90		28	1-211		32	6-216	
Residence Urban	44 (67)	5			27			41		
Rural	21 (33)	7	0-240	0.191	22	2-279	0.774	42	6-494	0.556
			0-270			1-360			7-412	
Father's level of education										
None	18 (28)	7	0-90		58	1-360		89.5	7-370	
Elementary/Secondary	39 (60)	7	0-270	0.245	20	1-360	**0.019**	41	9-494	0.357
High school	8 (12)	1.5	1-15		39	2-105		42.5	6-112	
Mother's level of education										
None	24 (37)	6	0-150		31	1-360		76.5	7-494	
Elementary/Secondary	34 (52)	7	0-270	**0.048**	20	2-360	0.062	40.5	6-412	0.171
High school	7 (11)	1	0-150		36	17-120		41	19-127	
Father's age										
20 – 30 years	9 (14)	7	1-30		20	3-360		32	9- 412	0.272
31 – 40 years	25 (38)	7	0-30	0.643	28	5-360	0.448	41	10-391	
41 – 50 years	23 (36)	5	0-270		26	1-360		59	7-494	

➢ 50 years	8 (12)	7	1-90		21	2-97		26	6-129	
Mother's age										
20 – 30 years	24 (37)	7	0-30		20.5	3-360		41	9-412	
31 – 40 years	27 (41)	5	0-270	0.404	24	1-360	0.517	42	10-494	0.790
> 40 years	14 (22)	7	0-90		25	1-360		42.5	6-370	
Parent's Employment										
None of them	5 (7)	7	3-150		28	1-60		34	7-184	
One of them	54 (83)	7	0-270	**0.008**	235	1-360	0.653	41.5	6-494	0.481
Both	6 (10)	1	0-5		43.5	7-105		50	32-112	
Health insurance										
RAMED	43 (66)	7	0-270		23	1-360		42	7-412	
AMO	14 (22)	3.5	1-15	0.141	23.5	2-279	0.806	33	6-293	0.247
Private	8 (12)	3	0-30		34.5	2-120		57.5	15-127	
First doctor										
Pediatrician	15 (23)	2	0-10		36	2-360		44	6-391	
Surgeon	38 (59)	7	0-90	**0.011**	21.5	2-360	0.632	37.5	7-412	0.292
General practitioner	12 (18)	7	0-270		27	1-120		50	7-494	
Type of the first health facility										
Public	39 (60)	7	1-360	0.453	22	1-360	0.90	37	7-376	0.122
Liberal	26 (40)	4.5	1-360		49.5	1-360		56	4-494	
Type of tumor										
Solid tumors	35 (54)	7	0- 270		22	1-360	0.640	44	7-494	0.107
Hemopathy	30 (46)	4	1- 30	0.140	25	2-278		38	6-293	



*: Some patients were referred to our department prior to confirmation of cancer diagnosis, the referrel time was included in the diagnosis time, for other patients it was included in the treatment interval since they were referred after confirmation of diagnosis

Figure 1: Definition of the types of diagnosis and treatment intervals