eISSN 2255-0569

ORIGINAL

Orbital rhabdomyosarcoma in the pediatric population: A prospective, observational study from Mid-West Nepal

Rabdomiosarcoma orbital en la población pediátrica: Un estudio prospectivo y observacional del Medio Oeste de Nepal

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Received: 15 - III - 2022
Accepted: 31 - III - 2022

doi: 10.3306/AJHS.2022.37.03.108

Abstract

Background: This study was aimed to find out the demographic characteristics, clinical characteristics and prevalence of rhabdomyosarcoma in children presenting to a tertiary level hospital of terrain Nepal, over a period of nine years. The study also aimed to explore the current understanding of rhabdomyosarcoma management.

Methods: This prospective, observational study was carried out in a tertiary hospital of Mid-Western part of Nepal from November 2011 to April 2019. Histopathologically confirmed cases of rhabdomyosarcomas were included in the study. Demographics, clinical characteristics and other relevant findings were entered in a specified proforma for the study and analyzed by Statistical Package for Social Services 24. Point estimate at 95% Confidence Interval was calculated along with frequency and percentage for binary data.

Results: Among 1180 suspected children, eight (0.68%) (0.29-1.3 at 95% CI) study subjects were diagnosed to have unilateral orbital rhabdomyosarcoma. Males six (75%) outnumbered the females. The mean age of presentation was seven, 7+-1.8 (Range: 6-8) years. Embryonal variant of rhabdomyosarcoma (6, 75%) was the commonest type followed by the alveolar type (2, 25%). Proptosis was the commonest presenting feature and was present in all (8, 100%) study subjects.

Conclusions: The prevalence of rhabdomyosarcoma was higher in the current study when compared with similar international studies. The embryonal variant of rhabdomyosarcoma was the commonest type encountered. Male predilection for rhabdomyosarcoma was high when compared to the females.

Key words: orbital rhabdomyosarcoma, children, chemotherapy, metastasis, oncologist.

Resumen

Antecedentes: El objetivo de este estudio era averiguar las características demográficas, las características clínicas y la prevalencia del rabdomiosarcoma en los niños que se presentan en un hospital de nivel terciario de Nepal, durante un período de nueve años. El estudio también pretendía explorar el conocimiento actual del tratamiento del rabdomiosarcoma.

Métodos: Este estudio prospectivo y observacional se llevó a cabo en un hospital de nivel terciario del Medio Oeste de Nepal desde noviembre de 2011 hasta abril de 2019. Se incluyeron en el estudio los casos de rabdomiosarcomas confirmados histopatológicamente. Los datos demográficos, las características clínicas y otros hallazgos relevantes se introdujeron en una proforma especificada para el estudio y se analizaron mediante Statistical Package for Social Services 24. Se calculó una estimación puntual con un intervalo de confianza del 95% junto con la frecuencia y el porcentaje para los datos binarios.

Resultados: Entre los 1180 niños sospechosos, ocho (0,68%) (0,29-1,3 con un IC del 95%) sujetos de estudio fueron diagnosticados de rabdomiosarcoma orbitario unilateral. Los varones superaron en seis (75%) a las mujeres. La edad media de presentación fue de siete, 7+-1,8 (rango: 6-8) años. La variante embrionaria del rabdomiosarcoma (6, 75%) fue el tipo más común, seguido del tipo alveolar (2, 25%). La proptosis fue la característica de presentación más común y estuvo presente en todos (8, 100%) los sujetos del estudio.

Conclusiones: La prevalencia del rabdomiosarcoma fue mayor en el presente estudio en comparación con estudios internacionales similares. La variante embrionaria del rabdomiosarcoma fue el tipo más común encontrado. La predilección masculina por el rabdomiosarcoma fue elevada en comparación con la femenina.

Palabras clave: Rabdomiosarcoma orbital, niños, quimioterapia, metástasis, oncólogo.

Introduction

Rhabdomyosarcoma (RMS) is rare yet the most common soft tissue sarcoma in children[1]. The clear histologic definition of RMS was recognized by Stout in the year 1946 however, Weber first described rhabdomyosarcoma in 1854. The name is derived from Greek literature, which suggests rod shape for rhabdo and muscle for myo[2]. With an annual incidence of 4.3 cases per million children, RMS is one of the rarer malignancies[3]. First reported by Bayer orbital Rhabdomyosarcoma (RMS) is the most common primary malignant orbital tumor of childhood. RMS is a rare tumor, with an annual incidence of 4.3 cases per million children[3]. The primary site of involvement is the orbit in 9-10% of all childhood RMS[3]. Metastasis from orbital RMS is often to the lungs, liver and bone. Lymph node metastasis is seen only in 10% of cases[3].

Like other childhood malignancies, orbital RMS can often present as a masquerading disease. There are reported incidences of RMS masquerading acute lymphocytic leukemia (ALL)[4]. The first contact clinicians like the Ophthalmologist or a pediatrician plays an important role in the management of rhabdomyosarcoma due to the aggressive nature of the disease which can threaten both life and sight in children[4].

The sudden onset of the disease, aggressive in nature with a possibility of sight loss as well as loss of life warrants an excellent core of team dealing with this disease with the Ophthalmologists and Pediatricians playing a vital role. Rhabdomyosarcoma being the commonest primary malignancy in the orbit in children needs more attention especially in developing countries and countries like Nepal due to the varied and aggressive presentation of the disease. The paucity of knowledge in the developing countries about RMS regarding early diagnosis and management protocols further elaborates the importance of the disease. When timely diagnosed and treated orbital RMS does have high five-year survival rates. This study thus was aimed at finding out the demographics, clinical characteristics, and prevalence of rhabdomyosarcoma in a tertiary care hospital of Mid-West Nepal, besides exploring the current management protocols.

Materials and methods

This was a prospective, observational hospital-based study carried out in a tertiary level hospital of Mid-Western Nepal from November 2011 –April 2019. The hospital serves as a center for patients coming across the Indo-Nepal border and also millions of people from Western–Far western Nepal. Ethical clearance was obtained from the Institutional Review Board (IRB) before the study was commenced. The study strictly adhered to the tenets of declaration of Helsinki. A convenience sampling technique was used to reach a sample size. After explaining the purpose of the study and confidentiality of data collection, informed consent was obtained from the parent /guardian.

All patients visiting the department of Ophthalmology willing to get enrolled in the study were included in the study. The patients who were not willing, who did not provide informed consent were automatically excluded.

Demographic characteristics of the study participants were entered using a specified proforma for the study. The study participants were evaluated clinically in detail in the following sequence: visual acuity measurement of each eye separately (unaided and with a pinhole), extra-ocular movement assessment, cover test, cover-uncover test, refraction using a Heine Beta 200 retinoscope, anterior segment examination with a slit lamp, and dilated fundus examination using an indirect Ophthalmoscope using +90 D Volk lens, Tropicamide eye drops were used for fundus dilatation. Evaluation of proptosis was carried out separately. Local lymph nodes were palpated to rule out local spread. Clinical photography was done in a few cases for record purposes. Radiologically, clinically and histopathologically confirmed cases needing referral were referred accordingly to higher oncology centres of Nepal and abroad.

In subjects where the initial diagnosis was not confirmed, communication with the referral hospital and the patient informant was maintained to reach the final diagnosis and also the management process. In cases where the informants expressed their willingness to go abroad, the subjects were referred abroad with proper documentation.

Protocols used in the study:

An international guideline was followed for the management of study subjects[4].

Histologically RMS was classified into the following histological subsets in the study subjects;

1. Embryonal RMS (ERMS): Most common accounts for 60-70% of all childhood RMS. Histologically ERMS is characterized by spindle-shaped cells which have a stromal-rich appearance morphologically and are similar to developing muscle cells. ERMS also has two variants and they are Botryoid ERMS and Spindle-shaped ERMS[5-7].
2. Alveolar RMS (ARMS): Aggressive variant of RMS with potential to metastasize quickly[6,7].
3. Anaplastic RMS: This subtype has the worst prognosis of all RMS5,[8-11].

Due to unclear origin and potential association with ERMS, an extremely rare variant of RMS known as sclerosing RMS was not included as a histological subtype in the current study[11].

Different parameters were taken into account for the prognosis of orbital RMS as per the literature[12]. The current Children's Oncology Group protocols for the treatment of RMS were used in staging and predicting the outcome of the treatment of orbital RMS. Risk classification was done using the tumor site[13,14].

Statistical analysis

An interobserver value of Kappa was used for the validity of diagnosis and any value more than 0.8 was considered strong agreement. Data entry and analysis were done using Statistical Package for the Social Sciences (IBM SPSS Inc, Chicago, Delaware, United States) version 24. Descriptive statistics were applied, and results were expressed as frequencies whereas continuous variables were expressed as mean±SD or median. Prevalence and Point estimate at 95% Confidence Interval (CI) was calculated.

Results

Among 1180 suspected children during the study period, eight (8, 0.68%) (0.29-1.3 at 95% CI) study subjects were diagnosed to have unilateral orbital rhabdomyosarcoma. Male study subject (6, 75%) dominated the females (2, 25%). Two (2, 25%) of the study subjects were across the border while the remaining six (6, 75%) were from Nepal. The mean age of presentation of the study subjects was 7+-1.8 years (Range 6-8). All study subjects (8, 100%) of RMS were sudden in onset. There was no difference in the laterality of the orbit involved (4) 50% right and 4 (50%) left orbit. The demographic characteristics, clinical characteristics, management protocols and outcomes of the participants are summarized in the table (**Table I**).

Discussion

In the current study, eight participants were diagnosed to have rhabdomyosarcoma, all were unilateral, with male predilection, this finding in the study was comparable with studies done elsewhere for RMS[12,15,16]. However, for orbital RMS female predilection is more which differed from the findings of this study. The current study had two non-Nepali citizens as study subjects and six participants from Nepal, a total of just eight cases over nine years all from the Asian continent. This finding of the study again was comparable with the current literature about the disease which says there's slightly a lower prevalence of orbital RMS in Asian children in comparison to others (**Table I**)[15,16].

Table I: Showing epidemiological, and clinical characteristics of the study participants.

Detail Findings of Rhabdomyosarcoma Study Subjects † (N = 8)			
Total Number of Rhabdomyosarcoma Diagnosed ‡ (n = 8)			
Symptoms/Signs/Cases features	**Present/Yes**	**Absent/No**	**Percentage (%)**
Gender: Male (M), Female (F)	6 (75.0% M), 2 (25.0%, F)		100
Any known predisposing risk factors		8(100%)	100
Sudden onset	8 (100%	0	100
Mean age of presentation (Years)		**7 (6-8+-1.8)**	
Pain	6 (75.0%)	2 (25.0%)	100
Swelling	6 (75.0%)	2 (25.0%)	100
Weight loss	2 (25.0%)	6 (75.0%)	100
Fever	4 (50.0%)	4(50.0%)	100
Severe conjunctival chemosis	8 (100%)	0	100
Local spread	2 (25.0%)	6 (75.0%)	100
Bilateral involvement		6 (100%)	100
Laterality of rhabdomyosarcoma: right (R), Left (L) ‡	4 (50.0%, R) 4 (50.0%, L)		100
Non axial proptosis	8 (100%)	0	100
Metastasis	2 (25.0%)	6 (75.0%)	100
Rapid progression	6 (75.0%)	2 (25.0%)	100
Cervical lymph node involvement	2 (25.0%%)	6 (75.0%%)	100
Diminished vision	8 (100%)	0	100
Incisional biopsy done	8 (100%)	0	100
Homogenous soft tissue mass eroding nearby bony structure in CT scan	8 (100%)	0	100
Histological type of rhabdomyosarcoma: Embryonal (E), Alveolar (A) ‡	**6 (75.0%, E) 2 (25.0%, A)**		100
IRS treatment protocol followed	8 (100%)	0	100
Excision of the tumor (Complete: C, Incomplete: IC)	6 (75.0% IC), 2 (25.0% C)		100
Chemotherapy (VAC*, IVA)**	6 (75.0%, VAC), 2 (25.0% IVA)		100
Radiotherapy	6 (75.0%)	2 (25.0%)	100
Sight saved in last follow up	0	8(100%)	100
Lives saved in last follow up	6 (75.0%)	2 (25.0%)	100

*Vincristine, actinomycin D, Cyclophosphamide.
**Ifosfamide, vincristine, actinomycin D
† Total number of study subjects diagnosed with rhabdomyosarcoma.
‡ Total number of rhabdomyosarcomas, not applicable for ticking the box for positive or negative findings.

There have been no established predisposing risk factors in the current study (**Table I**), this correlated fine with the updated literature of rhabdomyosarcoma with regards to pathophysiology and risk factors as it is believed that the reason behind rhabdomyosarcoma is unknown[16].

Genetic level studies weren't carried out in the current study with any subjects thanks to the study limitations. The alveolar variant of RMS is believed to be related to chromosomal translocations and fewer common translocations involving the PAX genes[17,18]. Loss of heterozygosity is seen within the embryonal subtype[19]. There was no history of parental use of cocaine and marijuana among the parents of the study subjects in the current study. The finding of our study did not compare well with a study done elsewhere20, which reported a correlation of parental use of cocaine and marijuana in RMS children.

The mean age of presentation in the current study was 7 years (6-8+-1.8) in the study subjects in our study, this finding from the present study was comparable to the prevailing knowledge that in orbital RMS the mean age of presentation of the children is 5-9 years[21]. In the current study, the demographic characteristics and clinical characteristics of the study findings as summarized in table one was highly comparable to studies done elsewhere (**Table I**)[3,4]. Intergroup Rhabdomyosarcoma Study (IRS) management protocol was followed in the current study,[4] also keeping in mind the present Children's Oncology Group (COG) treatment and management protocols for RMS[13,14]. Chemotherapeutic agents utilized in the study were Vincristine, Actinomycin D, and Cyclophosphamide (VAC) in most subjects whereas, in two study subjects Ifosfamide, Vincristine and Cyclophosphamide were given as that they had local lymph node metastasis and extensive tumor mass, but none of the study subjects received doxorubicin and cisplatin which are believed to extend the survival rate when given along with VAC regimen[22]. On a median within the study subjects, 10 cycles of chemotherapy were given. Local resection of the tumor with a 2 cm tumor-free margin could not be done in two cases owing to the extensive involvement of the orbit and therefore the ocular tissue. Whereas in six cases (75%) resection of the tumor was done with a good excision up to 2 cm from the tumor margin. Radiotherapy was given to all the cases who survived initial chemotherapy and resection of the first tumor. Sight loss was irreversible because the study subjects needed exenteration surgery. During the study, one study subject of the alveolar variety of RMS with metastasis passed away, the other study subject with alveolar type recurred after treatment and subsequently passed away (**Table I**). The management protocol of the current study was comparable to studies done elsewhere[10,16]. Overall, 5-year survival rates have improved to over 80% in RMS subjects with localized disease, consistent with the recent literature on RMS[22]. However, in metastatic disease, the five-year survival rate is reported to be extremely low at just about 30%, the explanation why two of the study subjects with metastatic disease (**Table I**) in the current study passed away during the treatment phase[23]. Even though combined use of high-dose myeloablative therapy and autologous stem-cell rescue has not improved outcomes for these patients with metastatic disease[24]. In an analysis of knowledge collected by the Surveillance, Epidemiology, and End Results (SEER) program, mortality was highly associated with age, size, and histology[25]. The findings from SEER stated that the 5-year survival rate was highest in children aged 1-4 years (77%) and was worst in infants and adolescents (47% and 48%, respectively). Orbital and GU sites were the foremost favorable (86% and 80%, respectively). Unfavorable sites included tumors of the extremities (50%), retroperitoneum (52%), and trunk (52%). The prognosis for the Embryonal variant of RMS was best (67%) when compared with alveolar histology (49%)[25] . Even if the recurrence occurs after initial therapy has been completed most patients with local recurrence are curable with salvage therapy[25]. In the current study explanation for mortality is probably attributed to incomplete resection of the tumor especially within the alveolar RMS subtype, age of the study subjects (adolescents), and presence of metastasis which is comparable with the existing knowledge regarding RMS and its prognosis as per SEER[25].

Recent update on chemotherapy of rhabdomyosarcoma

In a phase II trial of 87 patients with rhabdomyosarcoma who had experienced a primary relapse or disease progression and whose prognosis was unfavorable, temsirolimus (Torisel) proved superior to bevacizumab (Avastin) as add-on therapy. At 6 months, event-free survival in these patients, whose prognosis was unfavorable, was 65% with temsirolimus versus 50% with bevacizumab, when these agents were added to a chemotherapy regimen of vinorelbine and cyclophosphamide[26,27]. At 6 months, the response rate also favored temsirolimus (47.4% vs 27.5%) as did the number of complete responses (5 vs 4) and also the number of partial responses (13 vs 7), the speed of progressive disease was also better with temsirolimus (28% vs 10%)[26,27]. In a second study of 461 children with intermediate-risk rhabdomyosarcoma, adding irinotecan to combination treatment with vincristine, dactinomycin, and cyclophosphamide (VAC) didn't improve overall or event-free survival. However, the regimen containing irinotecan resulted in an exceedingly lower rate of hematologic toxicity and cumulative dose of cyclophosphamide[26,28].

Rhabdomyosarcoma is a very rare malignancy and is difficult to diagnose, a similar study from Nepal or similar settings with a large sample size focusing on orbital rhabdomyosarcoma would be useful. This article provides a baseline for treatment/management of rhabdomyosarcoma along with establishing the diagnosis.

Conclusions

The prevalence of orbital rhabdomyosarcoma in the current study was higher when compared with other studies. Male predilection is more than the female in rhabdomyosarcoma. Embryonal variant of rhabdomyosarcoma is the commonest subtype. Metastatic disease, alveolar variant both are life and sight threatening.

Acknowledgements

We would like to acknowledge the study subjects and their informants for their cooperation and regular follow up. We would like to pass our debt to the hospitals where the cases were diagnosed and managed.

Source of Support: None
Interests conflict: The researchers declare that they have no conflict of interest

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