

Evaluation of pathway to diagnosis of paediatric brain tumours in South India

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Abstract

Background: The incidence of brain tumours in India equate to half of those in the developed world. Delayed diagnosis is associated with a higher risk of life-threatening neurological complications at presentation and poor cognitive outcomes amongst survivors. Early detection and treatment is crucial for improving outcomes. **Aims:** The aim of this study was to analyse baseline diagnostic intervals for paediatric brain tumours in Tamil Nadu. **Methods:** Data for this retrospective study was collected via questionnaire across 8 different hospitals in Tamil Nadu. It consisted of 14 questions where doctors were asked to record data items including the date of symptom onset, first presentation to healthcare and date of diagnosis. **Results:** 114 children were diagnosed with a brain tumour between January 2018 – October 2020. The average diagnostic interval was 9.3 weeks (median 3.5 weeks), and the average patient interval is 6.1 weeks (median 0.6 weeks.). Low-grade tumours had the longest median total diagnostic interval of 6.6 weeks. The median total diagnostic interval was significantly higher in villages (7.9 weeks), as compared to patients located in District (4.8 weeks) and cities (2.3 weeks). **Conclusion:** Overall, the diagnostic interval for paediatric brain tumours were comparable to data in the UK. Moreover, all patients received an MRI within a day, indicating excellent infrastructure.. However, many low-grade and optic pathway tumours were unaccounted for. Tamil Nadu has one of the best healthcare systems in India and extending this methodology to areas with poorer healthcare provisions, is required to get representative national data.

Introduction

Brain tumours in India account for 8-12% of all childhood cancers as compared to 21% in the West ^{1,2}. Despite the rise in incidence over the past few years, reported incidence of CNS tumours in India are still just half of that in the developed world³. Many factors attribute to this presumed low incidence of brain tumours. These include incorrect diagnosis, inequality to access healthcare services and treatment abandonment. Delayed diagnosis and poor awareness are also massive barriers to the management and treatment of paediatric brain cancers. With a 5-year survival rate as low as 26.8%, early detection and treatment is key to improving outcomes for children with brain tumours⁴. Delayed diagnosis is associated with a higher risk of life-threatening and disabling neurological complications at presentation and a poor cognitive outcome amongst survivors ⁵⁻¹⁰. We have initiated a collaborative project, aiming to reduce the

diagnostic interval experienced by children diagnosed with brain tumours by enhancing the awareness of symptoms that are indicative of brain tumours in children and young people. This report focuses on the pathways and time to diagnosis of childhood CNS tumours in Tamil Nadu and compares this to existing data in developed countries using similar definitions of specific time intervals.

A patient interval (PI) is defined as the period between the first presentation of symptoms and the first notification to any health-care professional ¹¹. Longer PIs are linked to an increased risk of severe neurological complications upon presentation, as well as worse cognitive outcomes among survivors ¹². Moreover, longer PIs have adverse consequences on the child and the family’s psychological well-being, as well as upon professional relationships¹². A System interval (SI) is the period between the patients first notification to any HPC and the time they get diagnosed¹³. Total Diagnostic Interval (TDI) is defined as the period between first presentation of symptoms until diagnosis¹³. TDI is also defined as the sum of PI and SI. $TDI = PI + SI$.

Data from the UK.

At the turn of the century, the TDI in the UK ranked poorly compared to other countries. In response to that, a campaign called “HeadSmart: Be brain tumour aware” was established to raise awareness of symptoms and the importance of timely imaging. Within 7 years of implementation, the TDI dropped from 14.4 weeks to 6.7 weeks ¹⁴. The following paragraphs outline the studies conducted in the UK regarding most common symptoms and the diagnostic intervals of paediatric brain cancers.

A systematic analysis released in 2007 on the presentation of childhood Central nervous system CNS tumours concluded that the most common symptoms were headache (33%), nausea and vomiting (32%) and abnormal gait or coordination (27%).¹⁵ They concluded that the factors that affect signs and symptoms are age, tumour location and neurofibromatosis status. The most common sign or symptoms in Supratentorial tumours are Unspecified symptoms raised Intracranial Pressure (47%), Seizures (38%) and Papilledema (21%). Nausea and Vomiting (75%), Headaches (67%) and Abnormal gait and coordination difficulties are the most common signs of Posterior fossa tumours. Most patients with Spinal cord tumours presented with Back pain (67%) and Abnormal gait and coordination difficulties (42%) and Spinal deformity (39%). Brainstem tumours are more commonly presented with Abnormal gait and coordination difficulties (78%), Cranial nerve palsies (52%). For central tumours, the most common signs are Headaches (49%), Abnormal eye squint (21%) and Nausea and vomiting (19%).

Another study in 2011 tracked the progression of first symptom until diagnosis of Paediatric Brain tumours ¹². It concluded that between symptom onset and diagnosis, there is an increase in symptoms and signs from a median (range) of 1 to 6, with more than half of the patients developing visual abnormalities between symptom and diagnosis. Amongst 56 children, the most common behavioural abnormality observed is lethargy. Amongst 101 children, 81 visited their General Practitioner (GP) first, followed by 79 visiting a paediatrician, 29 first visited the Emergency Department, 24 went to an ophthalmologist and 15 children visited the optician.

A population-based analysis by HeadSmart released in 2019 investigated TDI of children with brain cancers in relation to tumour type, grade, location, and age ¹⁶. It studied a cohort of ($n = 710$) children, between the ages 0- 18, with the median diagnostic age of 6.6 years. Majority of the tumours were located at the cerebellum (35.5%), followed by central (31.7%), cerebral hemisphere (22.7%) and brainstem (10.1%). More than one third of all tumours (33.5%) were Low-grade gliomas. The second most common being high – grade gliomas (9.1%) followed by Optic Pathway gliomas (5.2%). Tumours located Centrally have the longest TDI with a median of 10.5 weeks, whereas tumours located in the Cerebellum have a median of TDI of 7.4 weeks. Tumours located in the Cerebral hemisphere and Brainstem have a median TDI of 6.7 and 5.4 weeks respectively. Low grade tumours have a higher median TDI (10.4) as compared to High grade tumours (6.0.) Craniopharyngiomas have the longest median TDI of 15.1 weeks followed by Low grade gliomas 11.9 weeks and Optic pathway gliomas 10.4 weeks ¹⁶.

Data from India

Till date, there are no studies that have specifically investigated the TDI of paediatric CNS tumours across India. However, a qualitative analysis was conducted across a few states across India, which concluded that the median PI of children with childhood cancers in India is 3 days¹⁷. It also concluded that the median TDI is 36 days¹⁷. In Low Middle Income Countries (LMICs) such as India, access to timely diagnosis and treatment for paediatric cancers are often delayed by several barriers. These barriers could possibly be the used to explain the 33-day delay between PI and DI.

Barriers to Early Diagnosis in India

There are several studies highlighting the barriers to diagnosis for children with cancers across India¹⁸⁻²¹. One of the major contributors to treatment delay is lack of awareness of symptoms. This is especially complicated in the case of brain tumours, where most patients may present with non-specific symptoms such as headache, vomiting and seizures²¹. As a result, a high proportion of cases may be misdiagnosed and treated as meningo-encephalitis due to a lack of easily available neuro-imaging and neurosurgical resources, which are primarily found in tertiary care institutions²².

With 70% of the population situated in rural areas, lack of diagnostic neuroimaging facilities and establishment of referral pathways gravely delays diagnosis²³. In addition, patients faced several barriers in navigating through public hospitals as compared to private/ trusts¹⁸. Poor infrastructure and staff shortages combined with an increasing demand from the population led to longer waiting times and eventually delayed diagnosis¹⁸.

Another cause of delay in diagnosis of cancer is the lack of education and the poor perception of the severity of the disease²⁴. A cross-sectional study conducted in a tertiary centre in Odisha, India noted half of their patients had never heard of cancer before, and almost none of them were aware of the treatments available²⁵.

Since most tertiary centres located in metropolitan cities, the rural population must travel far distances to get diagnosed and treated²⁶. A study across seven care facilities in India concluded that the median travel distance was 338km, with an average travel time of 9 hours¹⁷. This increases the overall cost to families, as they would have to pay for transportation and accommodation costs. In addition, the breadwinner of the family might have to leave their job temporarily, leading to the loss of income and increased financial hardship for the family. Although National Schemes such as the Ayushman Bharat Program ensures coverage of cancer treatment for the poor, they do not address other financial burdens faced by families before they receive treatment²⁷.

Methods

The objective of this experiment it so to gather PI and TDI of Childhood CNS tumors in Tamil Nadu, South India. Care for children with brain tumours requires not only diagnostic and treatment infrastructure but also supportive infrastructure for rehabilitation and social re-integration. According to the NITI Aayog's SDG India Health Index 2020-21, which ranks the progress of achieving health outcomes, Tamil Nadu ranked as the third-best state in the country²⁸. It has also pioneered several new approaches to improve access to high-quality health services at an affordable price. Furthermore, the previous qualitative analysis did not cover cancer cases in Tamil Nadu. Based on these factors, Tamil Nadu was the ideal state to conduct this investigation and to pilot methods for early diagnosis.

Data for this retrospective study was collected via a questionnaire across eight large tertiary hospitals located in large cities in Tamil Nadu providing specialist paediatric cancer care. It consisted of 14 questions where doctors were asked to record the date of symptom onset, first presentation of healthcare, date of diagnosis, imaging and lastly the date of when a biopsy was conducted. Doctors were also asked to detail the referral pathway from the first healthcare professional seen by the patient for initial symptoms until diagnosis. Distance between the patients' home and the hospital where they were diagnosed was recorded. Other questions asked include symptoms of the patient at onset and at the time of diagnosis. Data on tumour type, location and stage was also recorded.

Results

Tumour type and location.

A total 114 cases (n= 114) of brain tumour were diagnosed between January 2018 – October 2020. Patients' age varied between 0 – 15.1 years, with the mean age of diagnosis of 6.64 years. 47% of the patients were between the ages of 5-11, 40% were aged under 5 years (40%) and 12% were over 12 years of age. Medulloblastoma (28%) and low-grade glioma (24%) were the two most common tumour types, followed by ependymoma (17%). (Figure 1.) Majority of the tumors were localised; only 8% of all cases were metastatic and about a third of all tumors were located in the cerebellum.

Route to diagnosis

The route to diagnosis is detailed in Figure 2. Upon onset of symptoms, the majority of patients (n=92) first visited a paediatrician, followed by 13 patients who visited a neurologist). 88% of all patients were treated at a private hospital. 90% of patients had 1-3 visits to HCP prior to diagnosis. There was an equal distribution of distance travelled between home and the hospital where the patient was diagnosed. Despite 64% of all patients residing in the city, only 35% of all patients travelled <20km to get diagnosed. 19% travelled <100km, 27% travelled between 100-500km and 19% travelled >500km. Almost three quarters of all patients were self- financed (73%), whereas the rest received mixed funding (11%), free treatment (9%) or were covered by insurance (7%).

Diagnostic Intervals.

The average diagnostic interval was 9.3 weeks (median 3.5 weeks), and the mean patient interval is 6.1 weeks (median 0.6 weeks.) The following results compare TDIs, PIs and SIs in relation to tumour type and location as well as age group, patient location and distance between home and hospital.

Tumour type, Low grade tumors had the longest TDI of 6.6 weeks followed by Medulloblastomas (4.6 weeks) and High-grade gliomas (3.3 weeks)(Supplemental File 1.) There is a relatively equal distribution of PI between different tumour types, with Ependymomas and High-grade gliomas having the longest PI of 0.6 weeks, Medulloblastomas with 0.5 weeks and Low-grade gliomas with the PI of 0.4 weeks. Alternatively, Low grade gliomas and Medulloblastomas had the longest SI of 0.9 weeks, followed by Ependymomas and High-grade gliomas which had the lowest SI of 0.3 weeks.

Tumour Location

Hemispheric/ overlapping lesion had the longest TDI of 4.7 weeks, followed by tumors in the Posterior fossa/cerebellum and Ventricles which had a TDI of 4.1 weeks each (Supplementary File 2). Brainstem and tumors located on the Midline had TDIs of 2.7 and 2.1 weeks respectively. Similarly, Hemispheric/overlapping lesions had a significantly longer PI of 1.6 weeks compared to tumors situated at the Ventricle with a PI median of 0.4 weeks. Alternatively, tumors with the longest SI were in the Ventricle, with a median SI of 1.2 weeks, this was closely followed by Brainstem tumors with a median SI of 1.1 weeks. Tumors situated at the Midline had the lowest median SI of 0.1 week.

Age Group

Children aged 12 and above had the longest TDIs as compared to children between the ages of 5-11 who had the shortest median TDI (Supplemental File 3). The median PIs decreased with increase in age, patients under 5 had the longest PI of 1.6 weeks as compared to a median PI 0.4 weeks for patients aged 12 and above. Additionally, older patients exhibited with a significantly longer SI of 2.2 weeks, compared to children under 5, who had a much shorter SI of 0.6 weeks.

Patient Location from first HCP

TDI was significantly higher in patients living in villages (7.9 weeks) compared to patients located in districts (4.8 weeks) and cities (2.3 weeks.) (Figure 3A) There is no significant difference between the PI of patients from village (2.0 weeks) with those from districts (1.8 weeks.) Additionally, there is a vast difference between

the SI of patients living in villages (3.0 weeks) as compared to patients living in the district (0.8 weeks) and city (0.3 weeks).

Distance between home and diagnostic hospital

Figure 4A details TDI Diagnostic intervals by distance between home and hospital. There is a weak correlation between distance and TDI. Patients who were less than 20 kilometres (km) away from the hospital had a significantly shorter TDI of 3.0 weeks as compared to patients who were 100-500 km away from the hospital with a TDI of 4.5 weeks. Patients who were 20-100km away from the hospital were diagnosed had the shortest median PI of 0.3 weeks as compared to patients who were <20kms who had the longest median PI of 1.0 week. The median SI was longest in distances 100 – 500km (2.0 weeks), followed by 20-100 and 500+km which had a median SI of 0.9 weeks each. Patients less than 20km away had the shortest SI of 0.1 weeks.

Signs and Symptoms at initial onset and at diagnosis

The average number of symptoms is 1.7 at onset and 1.9 at diagnosis (Table 1). Vomiting and headache were the most common symptom at onset and diagnosis, with 62% of all patients showed signs of vomiting. 44% of patients exhibited with motor problems, with the most common symptom being abnormal gait (35%) and focal motor weakness (15%). Visual problems were seen in 26% of all patients at diagnosis, with the most common symptom being reduced acuity (14%) and abnormal eye movements (7%). Only 2% of all patients exhibited weight loss. The most common behavioural problems were lethargy, reported in 5% of patients.

Discussion

Data on the spectrum of CNS tumors remains to be consistent with studies in India and in the West. Medulloblastoma, low- grade glioma and ependymoma are the most common CNS tumors. However, very few optic pathway tumors were diagnosed, as compared to the UK, where optic pathway tumors make up 5.2% of all tumors. A possible explanation for this could be that these tumors are diagnosed and treated elsewhere, for example by ophthalmologists, reflecting the fragmented nature of care in India. Furthermore, this study detected a greater proportion of high grade/ metastatic tumors compared to low grade tumors. Tumors that did not need any form of treatment or chemotherapy were not reported in this study.

Low-grade tumors have significantly higher TDI than high grade tumors. This is consistent with past research, which concluded that aggressive tumors had relatively shorter TDIs²⁹. This is due to the rapid onset of symptoms, leading to a quicker diagnosis. On the other hand, slow growing tumors take longer to be diagnosed and hence are identified at an advanced stage. Low-grade gliomas were seen to have one of the highest TDIs in the UK and South India, where the SI was twice as long as the PI. This could possibly be due to lack of proper referral pathways or the failure to detect signs and symptoms as being related to a brain tumour by the initial HCPs.

Tumours located on the midline had the lowest TDI of 2.1 weeks, which is strikingly different to the UK data which concluded that anatomically midline tumors were associated with longer TDIs (Table 2). Inversely, cerebellar tumors had one of the longest TDI of a median of 4.1 weeks, whereas cerebellar tumors were seen to have one of the shortest TDIs of 7.4 weeks. Whilst we cannot ascertain the reason behind this discrepancy, we will review this in future surveys. Table 2 shows the differences between TDIs and PIs the HeadSmart data in the UK and this study findings based on tumour type.

All patients received a Magnetic Resonance Imaging (MRI) scan the same day they arrived at the hospital, which indicates good imaging infrastructure in the specialist centres. The age-specific differences in TDI are interesting. Children <5 years of age were noted to have relatively short TDI, but longer PI. This could be explained by the inability of young children to clearly express how they are feeling and can often lead to a substantial delay. Older children aged 12 and above were seen to have the highest TDI, with a significantly longer SI. Adolescent patients are present distinct psychological and physiological challenges that can lead to certain signs and symptoms going undetected and this is in keeping with previous studies

Patients who lived in the city had a significantly shorter TDI, PI and SI as compared to patients who lived in villages. However, the correlation between distance from home and hospital where the first diagnosis was made is a bit unclear. The risk of visiting more HCPs prior to diagnosis increases with distance as patients living more than 20km away from the hospital are 8.6 times more likely to have visited more HCP prior to diagnosis.

Signs and symptoms are consistent with UK data. Special consideration must be given to recognizing motor and visual signs. Earlier studies indicate the difficulty of assessing these signs in children. Furthermore, behavioural signs such as lethargy are also hard to assess, but must also be given importance as they are the most common behavioural sign of tumour¹². A further study on the most common signs and symptoms presented by specific tumors in India could help raise awareness to HCPs and could aid in reducing SI for some tumors.

Since most of the data was collected from retrospective notes from the doctors, there is likely to be some recall bias. Since most hospitals in this experiment were privately owned or run by Non- Governmental Organizations (NGOs), it does not account for cases diagnosed at public institutions. There were also social factors where the patients may not have wanted their doctor to know that they visited more doctors thereby under-reporting HCPs seen.

A prospective study or data collection from cancer registry would be the ideal way obtaining this type of data. However, there is no national registry data that contains this information and this survey provides key baseline data upon which further awareness programmes to promote early diagnosis can be evaluated.

The strategies needed to overcome identified barriers should involve proper education and training of health-care workers and involve establishing clear referral pathways. It is crucial for all paediatricians and primary healthcare providers to be sensitized to signs of cancer in children. There have been initiatives in India to aid this. A National Training Project under the Indian Association of Paediatrics IAP PHO Chapter has played an important role in promoting early detection and referral for paediatric cancer cases³⁰. HCPs not only should be trained but should also have guidelines that can aid them in diagnosing brain cancers earlier. HeadSmart is a campaign established in the UK, which assists HCPs in the assessment of children who may have brain tumours¹⁴. This guideline has drastically helped reduce diagnostic intervals of paediatric brain cancers in the UK. A similar guideline tailored to the Indian system can greatly benefit HCPs in India.

Another strategy to combat delay in diagnosis is to establish a clear referral network through government health care policies. Current protocols such as MCP-841 has improved overall survival of Acute Lymphocytic Leukaemia (ALL)³¹. Establishment of a proper referral pathway for paediatric brain cancers can significantly benefit patients by reducing patient and diagnostic intervals, which can lead to quicker treatment.

Additionally, more resources should be invested to incorporate holistic care for all patients. A study in TATA Memorial Hospital concluded that holistic patient support, which involved Accommodation, Nutritional and Educational support, made a measurable impact on children with haematological malignancies³². This can aid in reducing the financial burden and help prevent treatment abandonment.

Overall, the diagnostic intervals for paediatric brain tumors were comparable to data in the UK. Moreover, all patients received an MRI within a day, indicating that infrastructure was not a barrier in this study. However, many low-grade and optic pathway tumour were unaccounted for. A possible explanation could be that optic pathway tumour could have been treated at an ophthalmologist setting. Tamil Nadu has one of the best healthcare systems in India, meaning that the data presented cannot be extrapolated to other states or to the whole country. Extending this methodology to other areas with poorer healthcare provisions, could provide a better understanding of diagnostic intervals at a national level.

Conflict of Interest

The author declares that there are no conflict of interests.

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