RESEARCH ARTICLE

NEUROBLASTOMA;VARIABLE SYMPTOMS OF A NEUROGENIC TUMOR; A REPORT FROM IRAN

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Abstract

Objective

According to current data available, neuroblastoma is the most frequent extracranial solid tumor in infants and children; because of its relationship to the primitive sympathetic ganglia, it may progress or regress spontaneously to more malignant or benign forms of tumors, respectively. It is also an important cause of the Opsoclonus Myoclonus Ataxia Syndrome (OMAS), or the "dancing eyes" syndrome. The risk factor of neuroblastoma includes patient's age at diagnosis; degree of tumor spread, and selected biologic variables such as serum LDH, urinary and serum catecholamines such as VMA and HVA, ploidy and MYC-N copy numbers. So, detection of risk factors and risk directed therapy are the mainstay of patient management.

Materials & Methods

For this study the records of 43 out of 46 patients, aged less than 14 years, admitted over 8 years (1996-2004), with the confirmed diagnosis of neuroblastoma or ganglioneuroblastoma were evaluated for full course of therapy and follow up.

Results

Of the patient group, 60% were male and 40% female. The most frequent clinical stage was stage 3 (34.7%), followed with stage 4 (32.6%) and 2 (26%). Less than 2% of patients presented with pure neurologic symptoms and these responded well to treatment. Relapse was seen more frequently in stage 4 patients and less in stage 4S. The OPEC protocol, started in 81% of patients, achieved a 54% response; on the other hand, in 15%, N6 was used, with the response rate of 40%. Patient data was analyzed and interpreted using SPSS software to reveal which clinical and biologic factors improve neuroblastoma outcome.

Conclusion

Staging and patients' age at the time of diagnosis are the most important clinical factors to predict outcome, while primary tumor site and some biologic findings such as urinary VMA and serum LDH levels have a less important value

Keywords: Neuroblastoma, Malignancy, Chemotherapy, Prognosis, Adrenal, Children, Opsoclonus myoclonus

Introduction

Neuroblastoma which is the most common extracranial solid tumor of childhood and the second most frequent solid tumor in infants, aged less than 2 years, arises

from primordial neural-crest cells and may populate the adrenal gland or sympathetic ganglia, and hence has varied clinical presentations and courses)1). A distinctive feature of this tumor is its ability to regress spontaneously to ganglioneuroma or progress to more aggressive forms such as ganglioneuroblastoma or neuroblastoma(1,2). The most common site of origin of this tumor is the abdominal cavity (near the adrenal gland) but it may be found in the chest, head and neck, pelvis, central nervous system or other sites (1). This tumor has a wide range of clinical manifestations related to its site of origin, biologic products or antitumoral antibodies which may cause myoclonic/opsoclonic symptoms in these patients.

Opsoclonus Myoclonus Ataxia Syndrome (OMAS)- or "dancing eyes" syndrome-is a paraneoplastic or postinfectious movement disorder. The occurrence of opsoclonus in childhood is a remarkable clinical sign and should always prompt the search for a precipitating neural-crest tumour, particularly neuroblastoma. Although the syndrome is debilitating and typically leads to delayed motor development, it is often the cognitive and behavioural sequelae that are most important to patients and their parents. Presentation occurs typically in infancy and early childhood, most patients presenting between 6 and 36 months of age (1) Presentation with opsoclonus and myoclonus is characteristic of the syndrome and is a prerequisite for diagnosis. However, the accompanying symptoms of irritability and sleep disturbance often pose a difficult management problem. A diagnosis of OMAS results in the identification of a neural-crest tumour (commonly neuroblastoma) in about 50% of cases; patients with OMAS rarely present with neuroblastoma as the primary feature. Survival rates at 1 year in patients with OMAS and neuroblastoma are better than those for patients with neuroblastoma alone (3, 4).

Because of its malignant nature, the disease is widespread in most patients at diagnosis; hence diagnosing and treating patients early in infancy is critical and life saving (5). Over the past decade much research had been done on neuroblastoma to improve the clinician's ability to predict the risk of relapse for neuroblastoma at the time of diagnosis. Classically, the patients' age at diagnosis and its stage are the most important prognostic factors (6). However, other biologic features are also important in patients' risk, such as histologic characteristics of tumor, MYCN copy number, serum LDH and urine and serum catecholamines level (7,8,9,10).

Different treatment protocols may be used based on the wide range of biologic and clinical findings in neuroblastoma. However, in spite of technological advances in modern medicine, the tools to detect some of these important prognostic factors are unavailable in developing countries, and treatment is carried out based on the previously mentioned risk factors. Risk directed therapy is hence implemented according to patient's age at diagnosis, degree of tumor spread, and selected biologic variables such as serum ferritin and LDH, urine catecholamines level, tumoral calcification and if available MYC-N copy numbers and TRKA expression(11,12). These markers accompanied with histopathologic findings of the tumor (Schwanian stroma, ganglionic differentiation, and mitotic activity) have the most practical prognostic significance in treatment strategy planning (8).

In addition to distal short arm of the chromosome number 2 amplification (MYC-N amplification) and TRKA expression, deletion of 1p, 11q or unbalanced gain of 17q are also very important to predicting factors in prognosis. Other biologic markers such as serum LDH and Ferritin levels, urinary catecholamine excretion and presence of calcification in the tumor have less important values (13). On the other hand, presence of myoclonus/ opsoclonus symptom is a good predicting factor.

Patients and Methods

This study enrolled all children, aged less than 14 years old with diagnosis of neuroblastoma, ganglioneuroblastoma and ganglioneuroma managed in Mofid's children hospital in Tehran, between 1996 and 2004. Patient diagnosis had been confirmed with an unequivocal pathology report or presence of neuroblasts in bone marrow aspiration or biopsy, in addition to increased urinary catecholamines. Evaluated clinical and biologic markers in this study were age, sex, primary site of the tumor, serum LDH and urinary catecholamine levels, intratumoral calcification, clinical stage of the tumor, the chemotherapeutic protocols used in these patients and their outcome. MYC-N amplification status was not

assessed because of the unavailability of FISH method during this study. Patients were mostly treated with two standard protocols, the OPEC and N6; for a minority, we used a combination of these. Response to therapy was documented as favorable (complete remission without significant complication) and unfavorable response (relapse or death during or after completion of treatment plan).

Results

Forty-six patients with full criteria of neuroblastoma, managed at the Mofid Children's hospital, over a period of 8 years, entered in our study; of these were excluded because they disagreed with the treatment strategy. Initial age of our patients were 3 months to 12 years old with the mean age of 30.1 months (SD = 27.7 mo.). They comprised of 28 boys and 18 girls in all age groups (Male/ Female = 1.6 / 1) with the peak of male predominance in the first year of life (M/F = 3:1). The most frequent stage of disease observed at diagnosis was stage 3, diagnosed in 16 patients (34.7%), followed by stage 4 in 15 (32.6%); on the other hand stage 1 was not diagnosed in any. As shown in table 1, the advanced stage of disease is more frequent in patients over 2 years old. One patient presented with opsoclonus and myoclonus symptoms without any abnormalities in brain CT scan. His presenting stage at diagnosis was 3, and he responded well to therapy.

Primary tumor site observed most commonly in adrenal gland, followed by bone marrow and retroperitonium (table 2); tumor site and relation to stage of disease are summarized in table 3.

High urinary catecholamines (Vanyl Mandelic Acid and Homo Vanilic Acid) were seen in 65%, and were not related to the patients' stage or response to therapy; on the contrary, normal serum LDH level, seen in 30% of patients, was accompanied with a good response to therapy in 85.7%.

Histopathologically, favorable histology was detected in 17%, while in the remaining 83% this was unfavorable. Neuroblastoma and ganglioneuroblastoma were detected in 89% and 11% of patients respectively, but no ganglioneuroma was found.

In those with histology of ganglioneuroblastoma, the response rate was good in 60% and poor in the remaining 40%. However, a good response was seen in 46% with neuroblastoma pathology.

Following completion of chemotherapy (OPEC or N6 protocols), the duration of which was between 18 months and 7 years (mean 3.8 years), we found a survival rate of 14% in stage 4 and 100% in stage 4s. Stage 2 and 3 had survival rates of 75% and 53% respectively (table 4).

Table 1: Stage of disease in patients in different age ranges

Stage / Age	1	2	3	4	4s
< 12 m	0	4 (25%)	7 (43%)	2 (12.5%)	3 (18.7%)
13-24 m	0	5 (62.5%)	1 (12.5%)	2 (25%)	0
25-36 m	0	0	3 (42%)	4 (58%)	0
37-48 m	0	2 (25%)	2 (25%)	4 (50%)	0
>48 m	0	1 (16%)	3 (42%)	3 (42%)	0
sum	0	12 (26%)	16 (34.7%)	15 (32.6%)	3 (6.5%)

Table 2: Primary tumor site in relation to patients' age

Site / Age	Adrenal	retroperitoneal	Bone	Head & neck	Posterior mediastinal	Liver	Bone marrow	Brain	skin
<12 m	9 (56%)	3 (18.7%)	1 (6.2%)	2 (12.5%)	3 (18.7%)	2 (12.5%)	2 (12.5%)	2 (12.5%)	1 (6.2%)
13- 24 m	3 (37.5%)	2 (25%)	0	2 (25%)	2 (25%)	0	1 (12.5%)	0	0
25- 36 m	6 (85%)	1 (14%)	0	0	0	1 (14%)	4 (57%)	1 (91.4%)	0
37- 48 m	4 (50%)	1 (12.5%)	2 (25%)	0	3 (37.5%)	0	2 (25%)	2 (25%)	0
48 m>	3 (42.8%)	3 (42.8%)	2 (28%)	1 (14.5%)	0	0	4 (57%)	0	0
Sum	25 (54%)	10 (21.7%)	5 (10.8%)	5 (10.8%)	8 (17.3%)	3 (6.5%)	13 (28%)	5 (10.8%)	1 (2.1%)

Table 3: Stage of the patients in relation to their primary tumor site

Site / Stage	1	2	3	4	4s	Sum
Adrenal	0	5 (41.5%)	9 (56.2%)	9(60%)	2 (66.6%)	25 (54%)
Bone marrow	0	1 (8.3%)	0	11(73.3%)	1 (33.3%)	13 (28%)
bone	0	1 (8.3%)	0	4 (26.6%)	0	5 (10.8%)
liver	0	0	0	3 (20%)	0	3 (6.5%)
brain	0	0	1 (6.2%)	4 (26.6%)	0	5 (10.8%)
Head & neck	0	2 (16.5%)	0	2 (13.3%)	1 (33.3%)	5 (10.8%)
Posterior Mediastinal	0	3(25%)	2 (12.5%)	3 (20%)	0	8 (17.3%)
Retroperitoneal	0	2 (16.5%)	5 (31.2%)	2 (13.3%)	1 (33.3%)	10 (21.7%)
Skin	0	0	0	0	1 (33.3%)	1 (2.1%)

Table 4: Response rate according to patient stage of disease

Response rate / Stage	Good response	Poor response	Sum
1	0	0	0
2	9 (75%)	3 (25%)	12 (100%)
3	8 (53%)	6 (47%)	14 (100%)
4	2 (14%)	12 (86%)	14 (100%)
4s	3 (100%)	0	3 (100%)
sum	22 (51.2%)	21 (48.8%)	43 (100%)

Discussion

Neuroblastoma is a malignant primordial neural-crest tumor, found almost always in children and infants. According to the children cancer group (CCG) report by Golden et.al, this tumor has a mean age of 22 months at presentation which is earlier than the (5,6) more recent report of 30.1 months(6). In the case of delayed diagnosis, disease stages become more advanced and the patients are older, so their prognoses are more guarded (1,2). SEER and NCI reports revealed that early screening programs may reasonable because the advanced stage of disease is more prevalent in unscreened cases, but final prognoses did not change with screening(5,14,15,16 ,17). In our study, 32% of all patients presented with stage 4 which is lower than the SEER and NCI reports, 42% and 45% respectively, but in patients over 12 months, our findings (43%) are comparable. Interestingly our observation revealed that later diagnosis was not accompanied with more stages 4 of the disease. Overall in patients aged over 2 years, 86% of patients had stage 3 and 4 of the disease.

Anti tumor antibodies which react against the patient's cerebellum, may cause opsoclonus/ myoclonus symptoms. Only one of our patients with this problem developed involuntary, rapid eye movement in all directional gaze (opsoclonus) and irregular jerking of muscles of the limbs and trunk (myoclonic jerking). Although the patient's tumor was cured, his neurologic symptoms persisted throughout the 12 months of follow up. Data report this to be a good prognostic factor that improves patients survival because of its good biologic factors and presence of antitumor antibodies (1). Usually several months are need for improvement of neurological symptoms, but sometimes, they may remain for life.

The disease presented more frequently in male patients than in female (M/F=3/2), and was more pronounced during the first year of life (M/F=3/1).

Children with neuroblastoma and opsoclonus-myoclonus syndrome have adverse long-term neurologic sequelae compared with those without opsoclonus-myoclonus syndrome. In a review of 23 cases of neuroblastoma and myoclonic encephalopathy, Senelick et al. observed a residual neurologic deficit in 82% and persistent mental retardation in 36%. Only 13% had no long-term central nervous system (CNS) abnormalities (19). Koh et al, monitored 10 such children. All had a favorable stage of neuroblastoma and all were disease free at the time of the report; however, all but one had significantly delayed development (20) Telander et al. in a study of 10 children with neuroblastoma and opsoclonus-myoclonus syndrome demonstrated adverse neurologic sequelae in most of the patients. Eight had hyperactivity and irritability, three had psychomotor retardation, and one had seizures and chorea (18,19,20).

The most prevalent site of involvement at time of presentation (54%) was the adrenal; we observed 78% entire abdominal involvement. Overall bone marrow was the second most common site of primary tumor involvement, observed in 28% of cases, but in patients over 1 and 2 years old this increased to 37% and 45% respectively. Brodeur in his report noted to the

40% adrenal involvement in patients over than 12 months old (13). According to the POG and CCG reports, intrathoracic and head and neck tumors are more frequent in infants less than 24 months old (5,6).

Urinary catecholamine excretion showed no difference in those patients who responded to treatment and in non-responders. But low serum LDH levels correlated strongly with lower stages of disease.

Three patients were not evaluated continuously and excluded from our observation. Of the remainder, 51% had good response with minimal treatment complications and no recurrences in the 18 months to 7 years of follow up. In a thorough evaluation, 74% finished their full doses of chemotherapeutic regimens, but 31% had recurrences of disease between 4 to 18 months completion of therapy. In spite of alternative chemotherapeutic regimens, all patients with recurrent disease expired; 25% of total deceased patients, died during their initial treatment protocols (19.7% due to disease progression and 5.3% of treatment complications).

Our initial treatment regimens consisted of OPEC in 81%, and N6 in 15%; the remainder received a combination of regimens. Of patients, in 26% who received OPEC protocol, recurred after completion of therapy and 20% expired during therapy (disease progression or treatment complication); good response was observed in 54% on the OPEC regimen. In the N6 protocol group, however, good response rates were seen in 40%, treatment related death in 20% and recurrence in 40%.

Radiotherapy was not a routine treatment strategy in neuroblastoma but was used as a palliative modality in only 2 patients without any change in their life span. Nor was stem cell transplantation performed in any patient.

Because of the limitations of genetic study and FISH method, MYCN copy number and TRKA gene were not investigated.

One of the most important problems in patients' management was the lack of responsibility in some patients to follow current regimens especially in recurrent or advanced stages of disease; no responses were seen in recurrent cases and all of them deceased because of their disease progression. In spite of chemotherapy, stem cell transplantation which is an alternative modality in the newest treatment strategies was not performed in our patients. In addition, MYC-N copy number studies should be checked routinely to manage patients as a risk related strategy (21,22,23).

As a major problem, MYC-N amplification and copy number was not applicable so treatment was only stage based; in addition, bone marrow transplantation which is one the most important treatment modality was not performed in any patients.

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