Dumbbell Neuroblastomas

Kum Saati (Dumbbell) Nöroblastomlar

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Abstract: Included in this study were 56 children with primary extracranial Neuroblastomas (NB) (n=44) and Ganglioneuroblastomas (GNB) (n=12) who were admitted and treated at two institutions between January 1982 and March 1997. Thirteen of the 56 patients had epidural spinal canal invasion and spinal cord compression due to extension of primary tumor (Dumbbell Neuroblastoma-DNB). Five of these cases (case no: 4, 5, 10, 11, 12) were treated at the University of İstanbul, Institute of Pediatric Oncology, Turkey. The time from diagnosis of the primary disease to diagnosis of spinal canal invasion ranged from 0 day to 40 months. Of the 13 patients with epidural spinal canal invasion, 4 had GNB and 9 had NB. Spinal cord compression was the initial clinical finding in eight of the NB patients. The neurological symptoms and signs varied from progressive spastic paraparesis to complete paraplegia with or without sphincter disturbances. In one of the patients with paraplegia, the tumor had also invaded the left lumbosacral plexus. Two of the thirteen patients had a congenital tumo, that were diagnosed soon after birth. Seven of the 13 cases had laminectomy and epidural tumor removal with or without chemotherapy and/or radiation therapy, and six cases treated by radiotherapy and/or chemotherapy. Histological assessment in two (case no:8 and 13) patients revealed that the disease had matured to GN. Four of the 13 patients died, 2 were lost during follow-up, and 7 patients went into remission and were followed for 8-84 months. At the time the results were analyzed, 4 patients were asymptomatic and 3 were experiencing neurologic sequelae. In conclusion; we diagnosed DNB in 23.2% of our NB and GNB cases. Chemotherapy should be the treatment of choice for DNB, even in the cases that recur after successful chemotherapy and associated with neurological impairment. Laminectomy and tumor removal is recommended for patients whose neurological symptoms rapidly worsen of in spite of chemotherapy.

Key Words: Chemotherapy, dumbbell tumor, ganglioneuroblastoma, neuroblastoma, laminectomy.

Özet: Ocak 1982 ve Mart 1997 tarihleri arasında University of Kentucky Medical Center ve İstanbul Üniversitesi, Tıp Fakültesi, Pediyatrik Onkoloji Enstitü'lerinde 56 pediyatrik olgu, nöroblastom (NB;n=44) ve gangliyonöroblastom (GNB;n=12) tanısı ile teşhis ve tedavi edildi. Bu vakaların 13'ünde primer tümörün epidural spinal kanal invazyonu sonucu spinal kord tutulumu söz konusu idi (Dumbbell-kum saati nöroblastom; DNB). Bu 13 vakanın 9'u NB, 4'ü GNB idi. Primer hastalığın tanısı ve spinal kanal tutulumu arasında gecen süre 0-40 ay arasında değişmekteydi. Sekiz hastada spinal kord basısı semptomları primer hastalığın ilk bulguları olarak değerlendirildi. Nörolojik semptomlar, sifinkter kusuru ile veya sifinkter kusuru olmaksızın progresif paraparezi ve total parapleji ile karakterize idi. Bir vakada parapleji ile beraber lumbosakral pleksus tutulumu da mevcuttu. İki vakada konjenital DNB söz konusu olup doğumdan hemen sonra teşhis edilmişlerdi. Tedavi olarak 4 vakaya yalnız cerrahi (laminektomi ve tümör rezeksyonu), 5 vakaya radyoterapi ve/veya kemoterapi, 4 vakaya ise cerrahi, kemoterapi ve radyoterapi (kombine tedavi) uygulandı. İki vakada histolojik olarak tümör matürasyonu görüldü. Bu iki vakada histolojik yapı tedaviler esnasında malign form olan GNB-NB'dan benign form olan gangliyonörom'a (GN) dönüşmüştü. Takipte 4 vaka kaybedildi, iki vaka takipten çıktı ve geri kalan 7 vaka 8-84 ay boyunca takip edildi. Remisyonda olan bu 7 vakanın 4'ü asemptomatikti ve 3 vakada nörolojik sekel oluşmuştu. Sonuç olarak; NB-GNB vakalarının %23.2'sinde DNB olarak bulundu. DNB tedavisinde kemoterapi ilk tercih olmalıdır. Kemoterapi sonucu remisyon elde edilip daha sonra nüks eden vakalarda da kemoterapi yine ilk tercih edilen tedavi olmalıdır. Laminektomi ve tümör rezeksyonu kemoterapiye cevap vermeyen ve kemoterapiye rağmen hızla nörolojik tabloda kötüleşme olan vakalar için tavsiye dilmektedir.

Anahtar Sözcükler: Kemoterapi, dumbbell tümör, gangliyonöroblastom, nöroblastom, laminektomi.

INTRODUCTION

NB is the most common intraabdominal malignancy in children, but accounts for less than 10% of all childhood cancer (6). This form of neoplasia arises from, and may occur in, any organ of neural crest origin (6). NBs are sensitive to chemotherapy and radiotherapy, and sometimes undergo spontaneous regression or maturation (1). Clinical presentation depends on the primary site affected, the presence or absence of metastases, and the production of active metabolites. Ninety percent of NBs produce catecholamines and 25% of affected children are hypertensive (1).

NB arising from a paravertebral ganglion has an unusual tendency to grow through the intervertebral foramen, forming a dumbbell-shaped or hourglass-shaped, mass (1). The intraspinal component may cause neurologic symptoms of spinal cord compression with paralysis, and/or incontinence. The majority of patients with DNB have a good chance for survival (1,14). The incidence of spinal epidural extension of NB ranges from 6% to 25% in various series, and may occur by direct extension from a paraspinal primary tumor or from vertebral bone metastases. DNB is the most common malignant cause of spinal cord or nerve root compression in children (11,13). Although chemotherapy is safe and effective (3), the treatment strategy remains controversial. Previous reports suggested that more than 30% of patients with preoperative neurologic deficit remain unchanged or impaired after completion of therapy (4,7,11,12).

In this study, we retrospectively reviewed the records of 13 DNB cases in total of 56 NBs and ganglioneuroblastomas (GNBs), and discuss optimal treatment, particularly for symptomatic and relapse DNB cases.

PATIENTS AND METHODS

Between January 1982 and March 1997, we reviewed the medical records of 56 cases with NB or GNB. Thirteen (23.2%) of these cases had DNBs. The diagnoses were made based on tissue examination/bone marrow biopsy, detection of tumor markers in the blood and urine and radiological studies including abdominal and pelvic ultrasound, axial computed tomography (CT) scans and magnetic resonance imaging (MRI). Epidural spinal canal invasion were determined by axial CT scan, MRI and/or myelography. The clinical, radiological, histologic data and outcome for the 13 DNB cases are outlined in Table I.

The applied the most widely used staging system for NB, that of Evans et al (2), as described below:

Stage I: Tumor confined to the organ or structure of origin.

Stage II: Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved.

Stage III: Tumor extending in continuity beyond the midline regional lymph nodes may be involved bilaterally.

Stage IV: Remote disease involving skeleton, organs, soft tissues, or distant lymph node groups.

Stage IV-S: Otherwise classified as having stage I or II but with remote disease confined to one or more of the following sites; skin, liver, or bone marrow (without radiographic evidence of bone metastases). Most patients with this stage are under one year of age.

For tumors arising in midline structures, penetration beyond the capsule and involvement of the lymph nodes on the same side is considered stage II. Bilateral extension of any sort is considered stage III.

RESULTS

Thirteen patients had epidural spinal canal invasion and spinal cord compression due to extension of their primary tumor. The histologic types were NB in 9 cases, and GNB in 4 cases. The time from diagnosis of the primary disease to diagnosis of spinal canal invasion ranged from 0 days to 40 months. Two of these cases had congenital DNB. Spinal cord compression was the first clinical finding associated with the tumor in eight patients. Radiological diagnoses were made by the MRI, axial CT scan and/or myelography. The clinical findings ranged from progressive spastic paraparesis to complete paraplegia with sphincter disturbances. In one of the patients with paraplegia the tumor had also invaded the left lumbosacral plexus. Seven of the 13 cases had laminectomy and epidural tumor removal with or without chemotherapy and/or

Table 1.Clinical, radiological, histological data and outcome of the 13 DNB cases.

Case no, Age, Gender	Primary tumor & Stage	Location	Symp& Duration	Neurol. Symp& Duration	Neurol. Exam	Imaging Studies	Other Neurol Compl	Other Syst. Compl	RX	Relapse Recurrence	Relapse or recurrence RX	Last FU Out-Come	Sequelae
1; 4, F US	NB, IV	Thorax lymphad-enopathy	lymphad-enopathy	Asymp	N	CT Scan	Skull mets	Multiple bone mets	XRT+CT	25 mos after remission	-	Lost to FU	
2; 2, M US	GNB, II	Thorax lymphad-enopathy	Resp. Dyst	Asymp	N	MRI	-	-	Surgery	-	-	15 mos alive asymp	
3; 2, F US	GNB, III	Thorax	NS	BLEW 4 weeks	BLEW3/5, BDTR- R babinsky+	CT Scan	-	-	Surgery+ CT	-	-	23mos alive asymp	
4; 25d, M TR	NB, IVS	Abdomen	Con-genital	BLEW Con-genital	Paraplegia	CT Scan	-	-	Surgery	-	-	73 mos alive	Parap-legia, BBI
5; 1.5, F TR	NB, III	Abdomen	NS	BLEW	Paraplegia	CT Scan	-	DIC	CT	-	-	Died of DIC	
6; 11, F US	NB, III	Abdomen	NS	BLEW, 2 months	Paraplegia	Myelo-graphy	Plexus & skull mets	Multiple mets	Surgery+ CT+XRT no response	-	-	Died, 7 mos after RX	-
7; 1, F US	NB, IV	Abdomen	NS	PBLEW, BBI, 16 months	Paraplegia Urinary Retention	CT Scan	Skull mets CNS inf,	-	XRT+CT	-	-	48 mos alive	Neuro-genic bladder
8; 1, F US	NB, III	Thorax	NS	RLEW 2 weeks	Spastic Para-paresis	CT Scan	-	-	Surgery+ CT	2 yrs	Check below		
8; 3, F US	GN, II	Thorax	NS	widening gait, 4 weeks	Spastic Para-paresis	MRI	_	-	Surgery+ XRT	-	-	12 mos alive asymp	
9; 13, F US	NB, III	Thorax	NS	Back & L leg pain	Normal	CT Scan	-	Multiple mets	CT+XRT	-	-	Died 8 mos after DX	
10; 11, F TR	NB, IV	Abdomen	NS	BLEW	Paraplegia BBI	CT Scan	-	Multiple mets+ Renal failure	CT+XRT improve d except BBI	6 mos after Para-plegia	XRT+CT improve d except BBI	15 mos alive	Chronic renal failure+ BBI
11; 4, F TR	GNB, I	Thorax	NS	Asymp.	Normal	CT Scan	-	-	Surgery	-	-	Lost to FU after 8 mos RX	
12; 4, F TR	NB, IV	Thorax	NS	Unable to walk 6 mos	Paraplegia	CT Scan	Skull mets	Multiple mets	CT improve d	21 mos later	CT improve d	Died 5 mos after relapse	
13; 0, F US	NB, III/ GN	Thorax	Con-genital	Difficulty walking L p.spinal mass	Spastic para-paresis	CT Scan	-	PDA+ Pre-mature birth	Surgery	_	_	84 mos alive asymp	

Abbreviations: Symp; symptom(s), Neurol; neurological, Syst; systemic, Compl: complication(s), mets; metastases, RX; treatment, XRT; radiation therapy, CT; chemotherapy, BLEW; bilateral lower extremity weakness, PBLEW; progressive bilateral lower extremity weakness, BBI; bowel bladder incontinence, p.spinal; paraspinal, PDA; patent ductus arteriosus, mos; months, DX; diagnosis, FU; follow-up, US; cases treated and followed in the United States (UKMC), TR; cases treated and followed in Turkey (İst. Univ. Inst. Ped. Oncol.)

radiation therapy, and six cases treated by radiotherapy and/or chemotherapy.

Histopathologic evaluation of two cases (case 8 and case 13) during the second and third operations respectively revealed that the tumor had matured to ganglioneuroma (GN), the mature form of GNB. In case 13, the tumor was congenital, was located in posterior mediastinum and had invaded the spinal canal at T5-6 level, but had not associated with

neurologic symptoms. Initially the patient received chemotherapy only. Three years later, she developed progressive bilateral lower extremity weakness. Axial CT scan of chest showed a thoracic tumor extending into the spinal canal. Following T3-T7 total laminectomy and total removal of the extradural tumor, the patient's neurologic exam returned to normal. The histopathologic diagnosis at that time was ganglioneuroma (GN). A left-sided thoracotomy and partial tumor resection were done 3 months after the laminectomy. The histopathologic diagnosis of the mediastinal tumor was also GN.

Case 8 had stage III NB, that recurred 40 months after the chemotherapy, and laminectomy with gross tumor removal. At 20 months after the laminectomy, the patient had undergone two consecutive thoracotomies for debulking the mediastinal tumor. The new histopathologic diagnosis at that time was GN. Forty months after the laminectomy the patient developed progressive bilateral lower extremity weakness. MRI of the thoracic spine revealed a mass located in the posterior mediastinum, which extended into the spinal canal. Following T3-T10 total laminectomy and gross tumor removal, the patient's neurological condition improved. The histopathologic diagnosis of the dumbbell tumor was GN.

Two patients (cases 10 and 12) were admitted with paraplegia. Both individuals improved after chemotherapy and were able to ambulate without assistance. However, both relapsed with neurological deterioration and became paraplegic 8 and 21 months, respectively, after having completed their course of chemotherapy. Three weeks after relapse and the start of a second course of chemotherapy, both cases had improved and were once again able to ambulate independently.

Of the 13 patients, four died due to progression of the primary disease or relapse while on chemotherapy or in follow-up period, and two patients were lost during follow-up. The other 7 patients were followed for 8-84 months (mean, 43.5 months) . Three patients developed neurologic sequelae of bowel and bladder incontinence, and one patient (case 4) also developed total paraplegia.

DISCUSSION

In this report, we present and discuss the different treatments used in 13 cases of DNB. Most previous publications have been retrospective reports that had covered a variety of treatment approaches (3,4,7,10,12,14). After retrospectively reviewing the results of our study we have adopted a much more conservative strategy for treating DNB. We now recommend chemotherapy as the treatment of choice, even for recurrent DNB that is associated with progressive neurologic impairment.

In our patient group, the incidence of DNB was 23.2%. This figure has been reported as 6% to 25% in different series (4,7,11,12,14). In our study, 3 of 13 DNB cases were asymptomatic, and the primary tumor was located in thoracic cavity in 7 cases. In infants and children with demonstrated paraspinal tumors, there is often asymptomatic extension of tumor into the neural canal. In approximately 40-55% of the cases, the intraspinal component may not be clinically apparent (6,10). Therefore, any child in whom a paraspinal mass of unknown origin is discovered, should undergo CT scan and/or MR imaging of the spinal canal in the involved area. With regard to treatment, early reports suggested laminectomy and gross tumor removal (4,7,10). According to Massad et al (7) regardless of the biological behavior of the tumor, the treatment of choice in the early stage should be complete excision of both the primary tumor and its intraspinal extension, and this procedure should be followed by chemotherapy and radiotherapy.

Our patient group includes two cases (cases 10 and 12) that presented with paraplegia, and both improved following chemotherapy, to the point of being able to ambulate without assistance. These two patients relapsed with neurological deterioration and became paraplegic at 8 and 21 months, respectively, after having completed their course of chemotherapy. Most significant to this study is that, although 3 weeks passed between the noted neurological deterioration and the start of their second course of chemotherapy, both cases had improved and were able to ambulate, again at 3 weeks into the second round of chemotherapy. Even when there was DNB recurrence following the first chemotherapy regimen both patients achieved neurologic improvement with a second course of chemotherapy. Hayes et al (3) also suggested chemotherapy as an alternative to laminectomy and radiation therapy even for paraplegic patients.

Seven of the 13 patients we studied underwent laminectomy and gross tumor resection. When removal of a DNB is indicated, it is generally recommended that the intraspinal portion should be removed first, and that a marker (a silver clip, for

example) be left at the most lateral limit of the dissection site. This prevents traction on the tumor tissue and neural structures which can produce epidural bleeding, if dissection is first made in the paraspinal area (10).

The incidence of spinal column deformity after laminectomy for DNB have been reported as 56% in patients who survived more than five years (60 months) (9). Spinal deformity is reported to occur in 70-75% of children after spinal irradiation for NB, even in those who do not undergo spinal surgery (10). In addition, radiation therapy may not improve the survival in localized disease (8). According to Mayfield et al (9), the factors associated with the development of spinal column deformity in patients treated for NB include multilevel laminectomy for tumor removal and decompression, orthovoltage radiation therapy exceeding 3000 rads, and asymmetrical radiation of the spine. Fortunately in our study we encountered no problems with spinal deformity, in either the surgically treated or those who received radiotherapy. However, our mean follow-up period (43.5 months) may not have been long enough to witness this orthopedic complication.

In conclusion; chemotherapy alone is an excellent alternative to radiotherapy and laminectomy in the management of DNB, even for patients with tumor recurrence associated with progressive neurologic impairment. Neurosurgical decompression should be reserved for patients in whom chemotherapy fails to resolve neurological impairment, or for those who experience rapid progressive neurological deterioration in first 24 to 72 hours, in spite of chemotherapy. A high proportion of DNB patients who undergo chemotherapy have better prognosis, excellent survival time, and are, in fact, cured by this treatment. It is important that we manage with conservative treatment whenever possible, in order to leave these children with minimal long term effects of therapy.

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