Stage 4S neuroblastoma, a disseminated tumor with excellent outcome

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ABSTRACT

Objective: To review the clinical features and outcome of all cases of stage 4S neuroblastoma treated at our center.

Methods: We retrospectively reviewed the files of all patients (n=75) with neuroblastoma treated at King Abdul-Aziz Medical City, Jeddah, Kingdom of Saudi Arabia between 1986 and 2005. We studied the clinical features and outcome of patients with stage 4S neuroblastoma.

Results: Six patients (8%) were confirmed to have stage 4S neuroblastoma. Three were boys with a median age at diagnosis of 4.5 months (range 28 days – 11 months). Four patients required no intervention. The remaining 2 patients were treated with chemotherapy due to progressive hepatomegaly and respiratory distress. No patient required radiotherapy or surgical intervention. With a median follow up of 4 years (range 9 months - 15.5 years), all patients are alive and well. Two patients continue to have a residual abdominal mass, while complete resolution occurred in the others.

Conclusions: Stage 4S neuroblastoma is a special tumor that carries excellent prognosis. Spontaneous regression may occur and intervention is only required in symptomatic patients.

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Neuroblastoma is the most common extracranial tumor in children. It arises from neural crest tissue and is metastatic in two thirds of patients at diagnosis. Stage 4S neuroblastoma is a special tumor that occurs in infants and is characterized by a localized primary (stage 1 or 2) associated with dissemination to the liver, skin or bone marrow (less than 10%).[1,2] The tumor may undergo spontaneous regression without any treatment and is usually associated with excellent outcome.[3,4] In young infants and neonates, large tumors may cause respiratory difficulty and renal obstruction. Hepatic involvement can cause massive hepatomegaly, respiratory distress and coagulopathy.[5,6] Asymptomatic patients can be safely followed up without any intervention.[7] In this study, we reviewed the clinical features and outcome of all cases of stage 4S neuroblastoma treated at our center.

Methods. We retrospectively reviewed the charts of 75 patients with neuroblastoma diagnosed and treated at King Abdul-Aziz Medical City, Jeddah, Kingdom of Saudi Arabia between 1986 and 2005 to identify patients with stage 4S disease and assess their outcome. The staging criteria of the International Neuroblastoma Staging System was used.[1] Stage 4S was defined as tumors with a localized primary tumor

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(stage 1, 2A or 2B), with dissemination limited to liver, skin or bone marrow (<10% involvement).[2] Children not fulfilling the criteria were excluded in the study.

Staging investigations included abdominal ultrasound and CT scan, skeletal survey, bone scan or metaiodobenzylguanidine scan and bilateral bone marrow aspirations and trephines. Patients were followed up clinically and by repeated ultrasounds or CT scan as clinically indicated. There are no facilities to do N-myc or other biological studies on tumor tissue in our center.

Results. Out of 75 files retrospectively reviewed, 7 were diagnosed to have stage 4S neuroblastoma. One patient was excluded as upon reviewing the staging investigations, he was found to have stage 3 disease. Six patients (8%), 3 boys were confirmed to have stage 4S and were included in the study. The median age at diagnosis was 4.5 months (range 23 days -11 months).

All patients had primary suprarenal tumor and liver involvement and 3 had skin metastases. No patient was diagnosed to have bone marrow involvement. The diagnosis was confirmed by biopsy from the suprarenal primary tumor (n=2) or skin lesion in 3 patients. The remaining patient presented with progressive hepatomegaly and severe respiratory distress and needed urgent intervention. No biopsy was carried out and the diagnosis was based on the clinical and radiological findings. Patients' characteristics and details are shown in **Table 1**.

Four patients required no medical or surgical intervention. All are well and alive, 2 with no residual mass on imaging. Two patients were treated with chemotherapy. One of the 2 patients (patient 1) presented with hepatomegaly and compression of the right kidney and inferior vena cava. He responded very well to 9 cycles of weekly vincristine and 3 weekly cyclophosphamide (CO) with complete resolution of symptoms. The CT scan post-chemotherapy showed no residual mass. The second patient (patient 2) presented at the age of 23 days with a huge hepatomegaly and increasing respiratory distress. He received 4 alternating courses of carboplatin/etoposide (CE) and cyclophosphamide/doxorubicin/vincristine (CADO) with very good response. After chemotherapy, no residual suprarenal mass could be demonstrated. No patient had surgical resection at presentation or to remove a residual mass. With a median follow-up of 4 years (range 9 months-15.5 years), all patients remain alive and well with only 2 patients still having residual mass on imaging.

Discussion. The stage of neuroblastoma and age at diagnosis are significant prognostic factors. Infants with disseminated neuroblastoma have a much better outcome than older children.[2] Stage 4s neuroblastoma is a special tumor, which accounts for 7-10% of all neuroblastoma and is associated with excellent prognosis.[8] One of its main features is that it may undergo spontaneous regression.[4,5] In young infants and neonates, the tumor may progress causing massive hepatomegaly, renal obstruction and coagulopathy that can lead to serious complications and death.[7] Symptomatic patients often need urgent intervention with chemotherapy or radiotherapy to survive as early intervention is associated with a better outcome.[5,6] Factors associated with increased

Table 1 - Patients' characteristics and details of treatment.

Patient	Age at diagnosis/ gender	LDH at diagnosis i.u/l	Histopathology	Chemotherapy	Follow up	Outcome
1	4 months / M	450	GNB	Weekly vincristine and 3 weekly cyclophosphamide x 9	15.5 years	Alive
2	6 months / F	742	GNB	None	3.5 years	Alive
3	2 months / F	2752	Undifferentiated NB	None	1.5 year	Alive
4	23 days / M	857	No biopsy	carboplatin+ etoposide alternating with CADO x 4	2 years	Alive
5*	11 months / F	NA	GNB	None	9 months	Alive
6*	3 months / M	263	Poorly differentiated NB	None	9 months	Alive

GNB - ganglioneuroblastoma, NB - neuroblastoma, M - male, F - female,
LDH - lactate dehydrogenase, reference range 100-190 i.u/l; NA - not available, CADO - cyclophosphamide/doxorubicin/vincristine
*Patients with residual mass

mortality and high risk of progression include age less than 2 months and tumors with N-myc amplification or other poor biological markers.[6,9] Assessment of organ dysfunction using an objective scoring system is proved useful in deciding whether intervention is necessary.[7] Patients with no organ dysfunction at diagnosis have better outcome. Four patients in our study, all ≥ 2 months old at diagnosis were clinically well and required no intervention. The early presentation at 23 days of age of patient 4 with progressive hepatomegaly and increasing respiratory distress meant that urgent intervention was mandatory. There is no clear documentation regarding the justification to start chemotherapy in patient. We used chemotherapy as first line modality in both patients, which proved to be effective and was well tolerated.[6] There are no clear guidelines regarding the chemotherapy regimen of choice and no firm conclusions can be withdrawn from this study. Recent data suggest that combination of carboplatin and etoposide is preferable as first line and more intensive regimen or radiotherapy should be reserved for resistant cases.[6] We used cyclophosphamide and vincristine (CO) in one patient and a more intensive chemotherapy regimen with alternating carboplatin/ etoposide/ (CE) and CADO in the other. Radiotherapy can be used in patients with gross hepatomegaly and respiratory distress, but clinical response is often partial and it may not be readily available in all centers.[6] No patient in our small series needed radiotherapy or urgent surgical intervention.

Removal of residual primary tumor was recommended in the past. Recent reports confirmed that resection of the primary tumor is not associated with better outcome.[10] We elected not to operate on the 2 patients who required chemotherapy and continued to have residual suprarenal tumor as they were clinically well and the tumor continued to regress in size with time. Further assessment showed no residual mass on imaging. Two out of 4 patients who required no intervention showed complete resolution of the primary tumor and metastases while the other 2 continue to have a residual tumor after 9 months from initial diagnosis, but remain clinically well and asymptomatic.

In conclusion, stage 4S neuroblastoma is a special tumor, which may undergo spontaneous regression. Chemotherapy is the first line treatment for symptomatic patients. Surgical resection of residual tumor is usually unnecessary.

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