Spinal Canal Involvement in Neuroblastoma

Toby Trahair, BSc(Med), MBBS, PhD, FRACP[1,2], Stefania Sorrentino, MD[3], Susan J. Russell, MBBS, FRACP[1], Hugo Sampaio, MBBCH, Mphil, FRACP[4], Laurent Selek, MD, PhD[5], Dominique Plantaz, MD, PhD[6], Claire Freycon, MD[6], Thorsten Simon, MD, PhD[7], Kathelijne Kraal, MD, PhD[8], Maja Beck-Popovic, MD[9], Riccardo Haupt, MD[10], Shifra Ash, MD, BSc[11], and Bruno De Bernardi, MD[3]

Between 5% and 15% of children with neuroblastoma have spinal canal involvement (SCI) owing to tumor extension through the intervertebral foramina into the spinal canal. Patients with SCI are frequently less than 2 years of age, have biologically favorable disease, and usually experience excellent survival. Up to 65% of patients with SCI have symptoms and signs, including back pain, kyphoscoliosis, and neurologic signs (eg, paraparesis and/or paralysis, loss of motor skills, weakness, change in gait, and bladder or bowel dysfunction). Symptomatic SCI may be underrecognized, especially in infants. Although many patients experience symptom improvement, recently retrospective studies have shown unacceptably high rates (60%-75%) of long-term disability. Long-term functional outcomes might be improved by the earlier recognition of individuals with symptomatic SCI, and the development of better, evidence-based treatment guidelines through a prospective, international registry for neuroblastoma with SCI. The neuroblastoma registry, coordinated by the European Neuroblastoma Research Network, has been designed to identify clinical and treatment related risk factors for poor long-term functional outcomes. We present 2 clinical cases and a focused review of neuroblastoma with SCI.

Case Presentations

Case 1

A previously well 5-month-old boy presented to his general practitioner after his parents noted a lump developing in the left paraspinal region over the previous 2 weeks. The parents first detected the lump while massaging his back. The boy had been well and developing normally with no parental concerns. Although antenatal ultrasound imaging showed him to be small for gestational age, he was born at $38^{4/7}$ weeks with a birthweight of 2.6 kg. His general practitioner obtained an ultrasound study that demonstrated a large, bilobed, soft tissue mass extending from the paraspinal region into the retroperitoneum. Additional history revealed a change in bowel habit with a reduction in stool frequency over the preceding 2-3 weeks.

Clinical examination demonstrated a well-appearing infant with a 5×3-cm mass in the left thoracic paraspinal region. Neurologic examination was notable for subtle frog leg positioning, normal power in the upper limbs, a suggestion of reduced power in both lower limbs, normal upper limb reflexes, difficulty eliciting the left knee jerk, and otherwise absent lower limb reflexes. Sensation and the anal wink reflex were preserved. The overall clinical impression was of an infant with a paraspinal thoracic mass, change in bowel habit, and subtle lower limb neurologic signs suggestive of evolving spinal cord compression. An urgent magnetic resonance imaging scan demonstrated a large, left, paraspinal mass extending from T12 to L4 with intraspinal extension over multiple levels (L1/2, L2/3, L3/4, and L4/5). The intraspinal tumor displaced the conus at the L1, with compression of the cauda equina between L2 and L4 and effacement of the cerebrospinal fluid space (**Figure**, A). The opinion of multidisciplinary review was that neuroblastoma was the most likely diagnosis. Although there was clinical evidence of spinal cord compression, it was felt that neurosurgical decompression was unlikely to benefit the patient without a significant risk of additional damage owing to the location of intraspinal tumor at the cauda equina. The patient was started on dexamethasone and proceeded to biopsy of the paraspinal mass. Frozen section tumor histopathology confirmed a small round blue cell tumor consistent with neuroblastoma. Postoperatively, the patient was commenced on chemotherapy (etoposide, carboplatin, and vincristine) 25 hours after initial presentation. A diagnosis of favorable histology neuroblastoma without MYCN amplification was confirmed. The patient received 4 cycles of intermediate risk chemotherapy with an excellent tumor response. At last clinical review, 13 months after presentation, he is clinically well with normal developmental milestones, normal bladder and bowel function, and an unremarkable neurologic examination.

Case 2

A 9-month-old girl presented to her local hospital with a cough and respiratory distress after choking on formula in the context of a viral respiratory tract infection with increased work of breathing. Additional history included delayed motor

SCI Spinal canal involvement

From the [1]Kids Cancer Center, Sydney Children's Hospital; [2]School of Women's & Children's Health, University of New South Wales Medicine, Randwick, Australia; [3]Unit of Pediatric Oncology, Giannina Gaslini Children's Hospital, Genova, Italy; [4]Department of Neurology, Sydney Children's Hospital, Randwick, Australia; [5]Neurosurgery Department; [6]Pediatric Department, University Hospital Centre of Grenoble, Grenoble, France; [7]Pediatric Oncology and Hematology, University of Cologne, Cologne, Germany; [8]Department Pediatric Oncology, Princess Máxima Center, Utrecht, the Netherlands; [9]Department of Pediatrics, Hematology-Oncology Unit, University Hospital, Lausanne, Switzerland; [10]Epidemiology and Biostatistics Unit, Giannina Gaslini Children's Hospital, Genova, Italy; and [11]The Rina Zaizov Hematology-Oncology Division, Schneider Children's Medical Center of Israel, Petach-Tikva, Israel

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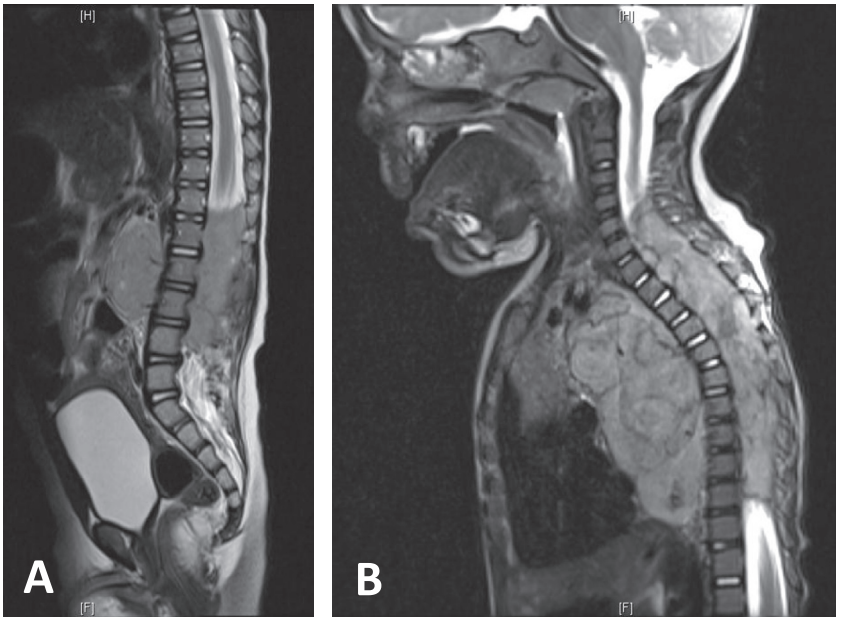

Figure. **A,** Case 1, T2-weighted sagittal magnetic resonance imaging demonstrating multilevel infiltration into the spinal canal from L1/2-L4/5 with intraspinal extension to the T11/12 level. **B,** Case 2, T2-weighted sagittal magnetic resonance imaging demonstrating multilevel thoracic intraspinal extension.

development and a presumed torticollis treated at age 6 months by a chiropractor. The child was not able to roll over or sit without assistance. She had had a paucity of spontaneous lower limb movements since birth, although the child had been noted to have some antigravity, lower limb movement. Bladder and bowel function were thought to be normal. Clinical examination noted moderate respiratory distress with subcostal retractions, but a clear chest on auscultation. She was noted to be lying in a frog leg position with no spontaneous lower limb movements, increased lower limb tone, hyperreflexia, and clonus. A chest radiograph demonstrated a large mediastinal mass. Magnetic resonance imaging revealed a $6.1 \times 5 \times 8.2$-cm mass in the left hemithorax with mediastinal displacement. Intraspinal tumor extension was demonstrated at multiple levels from C5 to T9 (**Figure**, B). The clinical impression was chronic paraparesis secondary to spinal cord compression from a thoracic intraspinal tumor, most likely neuroblastoma. The opinion of multidisciplinary review was that neurosurgical decompression was unlikely to benefit owing to the longstanding paraparesis with established clinical signs of chronic neurologic impairment. An ultrasound-guided needle biopsy was performed and a presumptive diagnosis of neuroblastoma was made based on the demonstration of small round blue cells on frozen section. The child was commenced on chemotherapy (etoposide, carboplatin, and vincristine) 61 hours after first presentation to the emergency department. Formal pathology confirmed a diagnosis of favorable histology neuroblastoma without MYCN amplification. The patient was treated with 8 cycles of intermediate risk chemotherapy and resection of the extraspinal, intrathoracic tumor. Persistent severe neurologic impairment (lower limb paraparesis, inability to bear weight, and abnormal lower limb reflexes) remained 13 months after the initial presentation demonstrated in the accompanying **Video** (available at www.jpeds.com). There has been minimal improvement in lower limb motor function with perineal sensation and some antigravity movement (hips, knees, and ankles), but an inability to bear weight.

Discussion

These cases highlight the clinical challenge of identifying and managing spinal cord compression in neuroblastoma, which can result in devastating, disabling, lifelong consequences in patients who otherwise have an excellent chance of cure. Neuroblastoma is a cancer of younger children with 90% of patients diagnosed before 5 years of age.[1] Neuroblastoma arises along the sympathoadrenal axis with abdominal primaries being most common followed by thoracic and pelvic tumors. Tumor spreads by direct extension, as well as lymphatic and hematogenous dissemination. Incremental progress in neuroblastoma biology and genomics, the introduction of refined clinical stratification systems, clinical trials, and the identification of new therapies have led to improved survival.[2-7] Known neuroblastoma risk factors are summarized in the **Table**. Although the majority of neuroblastomas are sporadic, familial susceptibility loci (6p22 locus and *BARD1*) and predisposition genes (*ALK1* and *Phox2b*) have been identified.[8-12] Neuroblastoma treatment formulation synthesizes clinical, pathologic, biologic, and genetic factors that predict clinical behavior, risk of relapse, and chance of cure and stratifies patients into different risk groups (low, intermediate, and high risk).[2,3] Non–high-risk neuroblastoma has the potential for spontaneous regression and/or tumor maturation and can be managed with risk-based observation or low intensity chemotherapy, with surgical