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Pseudomigraine With Prolonged Aphasia in a Child With Cranial Irradiation for Medulloblastoma

ABSTRACT

We report a 12-year-old child with episodes of migraine-like headaches with visual and motor auras a year after the surgical resection and radiation therapy for medulloblastoma. The patient presented with an episode of headache, prolonged aphasia, right hemiparesis, status epilepticus, and salt wasting. There was no evidence of a structural lesion. The neurologic deficits resolved over a period of 6 weeks. Because of the progressive deterioration in neurologic deficits, the patient underwent an extensive battery of laboratory tests and multiple neuroimages, all of which were normal. The unusually prolonged neurologic deficit in this patient without demonstrable structural lesions and his eventual complete recovery were most likely caused by ischemia in the left hemisphere secondary to vasospasm. This presentation mimics migraine headache. Evidence suggesting that this represents a long-term complication of treatment of children with central nervous system neoplasia is presented. (*J Child Neurol* 2002;17:134–138).

Cranial irradiation for brain tumors is associated with significant neurologic effects.^{1,2} The radiation effect may be divided into three stages: an acute effect generally related to brain edema; a subacute effect occurring up to 3 months after radiation causing demyelination, which typically causes a somnolence syndrome; and a late effect, which appears months to years after radiation, resulting in vascular injury and tissue necrosis. Acute and subacute effects are generally self-limiting; however, the late effect of vascular injury may progressively get worse or remain stable and may produce focal neurologic deficits, seizures, neurocognitive and developmental disorders, and endocrinologic deficiencies.

Headache may be a late sequel of radiation injury and may resemble migraine with or without an aura. We report here a child with surgical resection of medulloblastoma and radiotherapy presenting with migraine-like headaches with sensory and visual aura. He suffered a prolonged right hemiparesis with global aphasia with eventual complete resolution of the deficits in 6 weeks. During his course, he had an episode of status epilepticus and associated cerebral salt wasting.

Case History

A 12-year-old white boy was admitted to the Children's Hospital of Buffalo with a history of left-sided headache, confusion, inability to speak, and inability to adequately comprehend spoken and written words since a few hours prior to admission.

He had a near-drowning accident 2½ years ago, when an incidental cranial computed tomography (CT) scan revealed a medulloblastoma. The medulloblastoma was completely resected. Recovery was complicated by pseudomonas ventriculitis and hydrocephalus, for which he received prolonged intravenous antibiotics and a ventriculoperitoneal shunt. He had complete recovery, with no motor or intellectual deficits. He subsequently received craniospinal radiation with a boost to the posterior fossae. A total radiation dose of 3600 cGy in 180-cGy fractions was given. An additional boost of 1800 cGy resulted in the posterior fossae receiving a total of 5400 cGy. He had no acute adverse effects from radiation therapy. Follow-up magnetic resonance imaging (MRI) scans of his head and spine had not shown

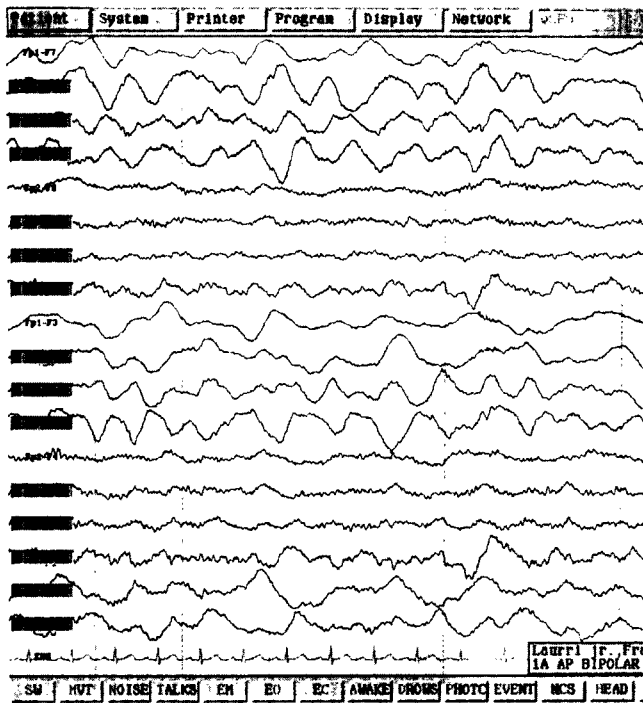


Figure 1. Electroencephalogram shows marked slowing in the left hemisphere.

any evidence of tumor recurrence. The latest MRI was a month prior to the current admission. Twelve months following completion of therapy, he developed paroxysmal left-sided headaches, thought to be migrainous. He did not have significant headaches prior to surgery. The headaches were always left sided, occasionally associated with blurry vision, right hemianopia, nausea/vomiting, and sometimes with brief periods of confusion and word finding difficulties. However, he had not reported a hemiparesis, and visual deficits had not lasted more than a few minutes. He did not previously have seizures. He would have headaches an average of two times per month. He was given cyproheptadine hydrochloride as a prophylaxis for his headache, with some benefit. Two days prior to the admission, he developed another headache and was given clorazepate dipotassium in addition to acetaminophen. Prior to arrival, he was his usual self, talking fluently and functioning like any other intelligent 7th-grade honor roll student.

His family history was significant for maternal migraine of many years, with sensory aura characterized by fluctuating tingling numbness of one side of the body lasting 15 minutes to half an hour prior to the migraine. Headaches were variable, alternating from side to side, and not associated with motor, visual, or speech deficits. Two sisters, 11 years and 7 years of age, are well and did not have migraine.

Physical examination revealed a well-nourished child with a temperature of 39.5°C. Abdominal, lung, and cardiovascular system examinations were normal. He had sparse scalp hair, the consequence of radiation. Neurologic examination showed paraphasia, word finding difficulties, and anomia with isolated words numbering two to three. He was unable to name, repeat, read, and write. He understood gestures slightly better. He had a dense right homonymous hemianopia with mild right facial droop. Fundus examination was normal. Right-sided hemiparesis involved the upper extremities more than the lower extremities. He had upgoing plantars on the right. Cerebellar signs were absent. His gait was wide based, and he had difficulty with tandem walking. Because of aphasia, a sensory examination could not be done accurately.

Laboratory and Radiologic Studies on Admission

Laboratory evaluation was initially directed at excluding infective, vascular, inflammatory, and neoplastic etiologies. Complete blood count showed that white blood cells were 7700/ μ L, hemoglobin was 14.7 g/dL, platelets

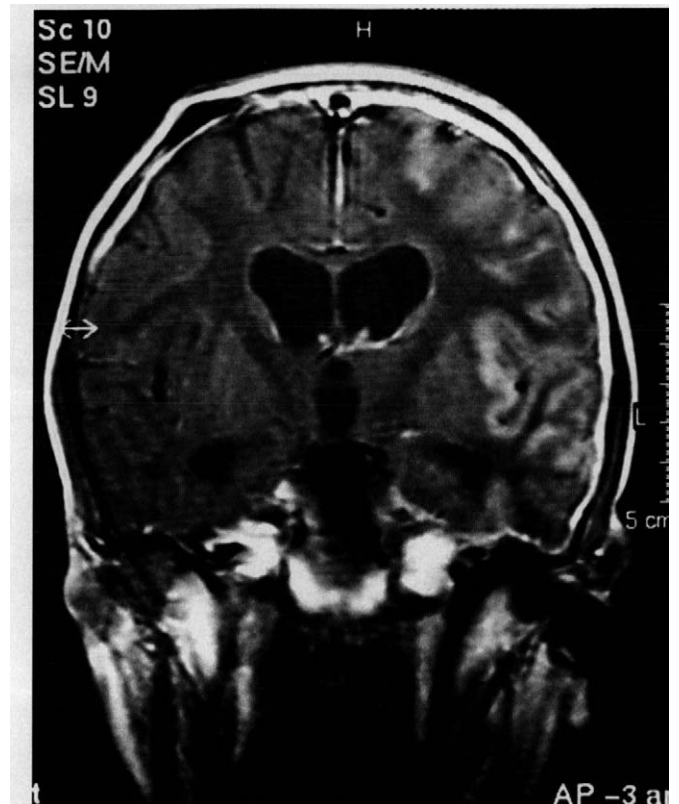


Figure 2. Magnetic resonance image showing enhancement of the cortical ribbon in the left hemisphere during the prolonged focal seizure reported in the text.

were $283 \times 10^9/L$, S was 62%, B was 12, L was 19, and erythrocyte sedimentation rate was 15 mm/h. Electrolytes, blood urea nitrogen, serum creatinine, and glucose were normal. Computed tomography of the head with contrast and shunt series showed no new abnormalities other than the previous findings. The cerebrospinal fluid from the shunt fluid showed 1 to 2 white blood cells per μ L, protein of 20 mg/dL, and sugar of 78 mg/dL. Gram stain was negative. There were no red blood cells. A lumbar puncture revealed a pressure of 8 cm H_2O , no white and red blood cells, and protein of 22 mg/dL. The cytology was negative for neoplastic cells. Polymerase chain reaction for herpes, enteroviruses, and Epstein-Barr virus was negative. Antinuclear antibodies and lupus screen were negative. Antiphospholipid antibodies, protein C, and protein S were negative. An echocardiogram was normal. Electroencephalography (EEG) revealed marked slowing in the left hemisphere without epileptiform activity (Figure 1), suggesting structural disease.

Clinical Course

He was treated with ceftriaxone and acyclovir. The hemiparesis became more pronounced over the first week of admission. The temperature fluctuated up to 39.5°C. Magnetic resonance angiography and two MRIs obtained over a 7-day period failed to show new findings. On the 7th hospital day, he developed right-sided focal seizure, which progressed to generalized status epilepticus lasting up to an hour and requiring intubation and ventilation for 2 days. He was treated with lorazepam, phospherytoin, and phenobarbital. He had hyponatremia (serum sodium, 124 mmol/L) with salt wasting (urine sodium 200 mmol/L) and profuse diuresis of up to 15 L of urine per day following the seizure requiring hypertonic saline and fluid replacement. He had developed a rash following intravenous phenytoin. His rash did not resolve despite discontinuing phenytoin. Acyclovir and phenobarbital were also discontinued.

Repeat lumbar puncture following the status epilepticus was negative. Magnetic resonance imaging showed enhancement of the cortical ribbon of the left hemisphere (Figure 2). The repeat magnetic resonance angiography showed questionable beading of the left distal middle cerebral artery,

suggesting the possibility of a vasculitis. He was started on methylprednisolone 1 g/day for 5 days for presumed vasculitis. A cerebral angiogram done the following day was normal, without evidence of vasculitis or ischemia.

Recovery began the 12th hospital day, and the salt wasting resolved after 1 week. No further seizures occurred, and the fever subsided over the next week. Aphasia resolved over the next few weeks. At 6 weeks post hospitalization, he was back to normal. He resumed 7th-grade classes, performing just below his previous level. At discharge, he was placed on cyproheptadine. However, further episodes of brief headache occurred the next 2 weeks. Cyproheptadine was discontinued, and he was started on verapamil. He has had no significant headache since.

Discussion

This case presented a diagnostic challenge. The initial impression was that of a complicated migraine with a prolonged aura. However, his complicated past medical history and the worsening deficits initiated a broad range of investigations. The diagnoses considered were encephalitis/meningitis with stroke, radiation-induced vasculitis, stenosis/dissection of the left internal carotid and middle cerebral arteries, recurrence of medulloblastoma, other central nervous system malignancies, bland and infective emboli, other vasculitides, hypercoagulable states, mitochondrial disorders such as mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) and genetic syndromes such as cerebral autosomal-dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL).

The cerebrospinal fluid examination on three occasions did not show evidence of an inflammatory, infective, or neoplastic etiology. However, the patient was covered with ceftriaxone and acyclovir because of the presence of significant fever. Initial CT scan and MRI/magnetic resonance angiography did not show a change in ventricular size or focal lesions, excluding the possibility of shunt malfunction, stroke, recurrence of the tumor, and inflammatory and demyelinating disorders. The radiation-induced vasculitis was unlikely because of the normal MRI and normal cerebral angiogram. The patient was given corticosteroid pulse dosing for 5 days because of beading seen on the distal middle cerebral artery. This was later considered artifactual as the cerebral angiogram was normal.

The enhancement of the left hemispheric cortical ribbon was most likely because of the prolonged focal seizure. This appeared following the seizure and had resolved on the subsequent MRI 2 days later. The marked slowing of the left hemisphere on the EEG is suggestive of a functional impairment of that hemisphere. The hemispheric slowing, however, can also be a feature of hemiplegic migraine.³ His EEG had normalized at the time of discharge 3 weeks later.

Hyponatremia caused by inappropriate antidiuretic secretion is a well-known complication of many systemic illnesses.⁴ However, hypovolemia with salt wasting in the setting of an acute intracranial disease is less common and not well understood. The renal salt wasting is thought to be mediated through atrial natriuretic factor.⁵ In our patient, salt wasting was observed after the patient had the first status epilepticus, 7 days after admission. The salt wasting resolved with the improvement in the patient's condition in about 1 week's time.

According to the International Headache Society guidelines, the migraine with prolonged aura can result in reversible deficits lasting up to 1 week.⁶ However, if the deficits last longer than 1 week,

they are called migrainous infarctions. Typically, these patients show evidence of focal brain infarctions or atrophy. In the adult population, migraine headaches are known to be associated with brain infarctions. In children, reports of migrainous infarctions are infrequent; only a handful of patients are reported in the literature. For the diagnosis of migrainous infarction, the International Headache Society stipulates that the patients should have a past history of migraine with aura. The present attack should be typical of previous attacks, and the neurologic deficits should not reverse within 7 days. Neuroimaging may demonstrate ischemic infarctions in the relevant area. Other causes of infarction must be ruled out by relevant investigations. Our patient does not fully fulfill the International Headache Society criteria for migraine as his headaches were always one sided and the prolonged deficits were not associated with a structural lesion. This classification system also mandates that the headache not be associated with specific vascular or nonvascular disorder known to cause headache.

Familial hemiplegic migraine is a distinct autosomal-dominant syndrome genetically linked in a majority of patients to chromosome 19.⁷ It is characterized by recurring episodes of hemiparesis or hemiplegia during the aura phase of the migraine attack, and the deficit can typically last up to 1 hour in most of the patients but, occasionally, may last days to weeks. The family history in our patient was not suggestive of familial hemiplegic migraine.

CADASIL is again a genetic syndrome linked to chromosome 19; which presents with migraines that frequently occur before the fourth decade followed by transient ischemic attack, lacunar strokes, and multi-infarct dementia.⁸ This is a disease of the small cerebral vessels without hypertension. Neuroimaging in these patients is usually abnormal with subcortical white-matter lesions. The normal MRI and absence of a family history in our patient is against this diagnosis.

MELAS is a maternally transmitted mitochondrial disease, which presents with poor growth, focal or generalized seizures, recurrent acute episodes that resemble strokes or prolonged transient ischemic attack, recurrent vomiting with lactic acidosis, and histologic confirmation by ragged red fibers on muscle biopsy.⁹ Some patients have migraine-like headaches initially. Neuroimaging in these patients is usually abnormal, with subcortical lesions. Our patient did not have clinical or neuroimaging features of this condition.

A syndrome of pseudomigraine with temporary neurologic deficits and lymphocytic pleocytosis has been described.¹⁰ In a series of 50 patients reported by Gomez-Aranda et al, a consistent feature was the presence of cerebrospinal fluid pleocytosis, which was not present in our patient. The neurologic deficits ranging in duration between 5 minutes and 3 days were completely reversed in these patients. None of these patients had structural lesions on neuroimaging and none had preexisting intracranial tumors or radiation therapy. Migraine-like episodes in these patients are thought to be related to an aseptic inflammation of the meninges.

Several authors have reported radiation-induced vasculopathy in children with strokes and focal neurologic deficits.^{11,12} These patients had associated vascular or parenchymatous brain lesions demonstrated on neuroimaging.

Shuper et al reported migraine-like episodes with reversible neurologic deficits following cranial irradiation and chemotherapy in 1995.¹³ Theirs was the first report of a migraine-like vasospas-

Table 1. Clinical Data in Children With Pseudomigraine

Number	Age (yr)	Tumor Type/Location	Radiation Dose (cGy)	Time Since Completion of Treatment (yr)	Symptoms and Duration
1	6.5	PNET/PF	CSRT, 2400 Local, 5500	2	Right-sided headache, visual loss, less than 15 min
2	15.5	Ependymoma/PF	CSRT, 3000 Local, 5500	2.8	Right-sided numbness, left homonymous visual loss, less than 60 min
3	10.5	PNET/pineal	CSRT, 3600 Local, 5500	1.2	Aphasia, right hand tingling, less than 60 min
4	11.5	PNET/PF	CSRT, 3600 Local, 5400	1.2	Right-sided weakness, aphasia, visual loss, less than 60 min
5*	12	Medulloblastoma/PF	CSRT, 3600 Local, 5400	2.5	Right hemiparesis, aphasia, right hemianopia, lasting less than 60 min, except current episode

*Patient presented in this report; all other patients from the Shuper et al report.⁷

PNET = primitive neuroectodermal tumor; PF = posterior fossa; CSRT = craniospinal radiation therapy; Local = total local radiotherapy.

tic condition produced by radiation and chemotherapy without demonstrable structural lesion. They reported four children who, following cranial irradiation and chemotherapy, had an onset of paroxysmal events characterized by severe headache associated with nausea, vomiting, and transient neurologic impairment lasting from a few minutes to 1 hour. Structural deficits were not noted in these patients. These patients were worked up extensively for recurrence of tumor, radiation necrosis, and vascular disease; none were found.

Our patient presented with many features suggesting migraine headache. His aura consisted of right visual hemianopia followed by left-sided headache and aphasia. The headache and neurologic symptoms had been paroxysmal over a period of several months. At the time of the last admission, however, neurologic symptoms lasted over 4 weeks and appeared to be associated with structural damage. Despite many MRIs, magnetic resonance angiograms, and cerebral angiography, structural disease was not identified. Electroencephalography suggested physiologic abnormalities in the left hemisphere. The neurologic signs, the onset of status epilepticus, and an MRI suggesting a major metabolic event affecting the blood-brain barrier corroborated this. All of these, however, resolved with time without residual deficits. The lack of structural findings on MRI tended to rule out radiation necrosis, frank infarcts, and other forms of radiation damage.

As in the Shuper et al report,¹³ we concluded that this patient presented with transient migraine-like episodes without demonstrable structural deficits. This case further documents the role of radiation and adds to the original report of Shuper et al of the potential development of a vasospastic-like phenomenon occurring many months after radiation. The pathophysiology of its causation and the role of radiation are yet to be elucidated. Yet we are left with the inference that radiation, perhaps because of injury to the vascular endothelium, lends itself to recurring vasospastic events. The total dose of radiation to the whole head was 3600 cGy. However, the boost to the posterior fossae includes the posterior two-thirds of the temporal lobes. Hence, the temporal lobe received more radiation than that given to the craniospinal axis. This may account for the predominantly temporal lobe symptoms. Why this mainly involves the dominant hemisphere remains conjectural. Curiously, all of the four patients reported by Shuper et al had posterior fossa tumors, received a radiation boost to the posterior fossae, and presented with dominant hemispheric symptoms. Except for the cur-

rent episode in our patient, in whom the deficit lasted several weeks, all of the other episodes were similar to the ones reported by Shuper et al (Table 1).

This report is but another of the increasing list of treatment-related complications associated with the care of children with central nervous system neoplasia. Recognition of this complication and chronicling of its natural history are important to further document treatment-related problems and to help alleviate the fears in patients and health care providers that paroxysmal events with a focal signature do not necessarily imply recurrent or metastatic disease.

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Open-Label Study of Botulinum Toxin for Upper Limb Spasticity in Cerebral Palsy

ABSTRACT

The objective of this study was to assess the efficacy of botulinum toxin for upper limb spasticity in cerebral palsy. An open-label study was conducted in 11 children with cerebral palsy. Post-botulinum toxin assessment was conducted in weeks 1, 4, and 16, with averaged scores being analyzed. The Clinical Global Impression Scale of the mothers showed marked, moderate, and mild improvement in five, four, and two cases, respectively. The Modified Ashworth Spasticity Scale score showed a statistically significant decrease in the mean spasticity score ($P < .003$). Other tests were performed depending on the cognition of the child. Increase in joint motion occurred in all five children assessed using web space ($P = .043$). For the Jenson Hand Function Test, improvement occurred in all five cases assessed ($P < .03$). Four of five (80%) children could perform tasks that they failed before they were given botulinum toxin. Botulinum toxin is useful in decreasing spasticity and improving the upper limb function of young children with cerebral palsy with normal cognition. Motivated families should be selected with a specific target of using botulinum toxin as an adjunct in a habilitation program. (*J Child Neurol* 2002;17:138-142).

Various methods have been used in children with cerebral palsy to improve spasticity. This includes oral medication (benzodiazepines, baclofen, dantrolene)¹ and surgical release of tendon contractures.² Oral antispastic medication induced a central sedative action. More recent techniques used for treating spasticity of the lower limbs include continuous intrathecal baclofen infusion.³

Botulinum toxin type A is a reversible neuromuscular blocking agent that has been used extensively in treating patients with dystonia such as blepharospasm, hemifacial spasm, cervical dystonia, or strabismus.^{4,5} Its use in spasticity was first tried in multiple sclerosis in 1990.⁶ The use of botulinum toxin was also documented in spastic mouse models in increasing the muscle length as compared to controls.⁷ The use of botulinum toxin in children with cerebral palsy was first reported in 1994.⁸ Subsequently, a few studies on children with the spastic or athetoid type of cerebral palsy documented its value as a short-term adjunctive ther-

apy.⁹⁻¹³ Reports on the use of botulinum toxin in upper limb spasticity cerebral palsy have been scarce.¹⁴⁻²⁰ The objective of this study was to determine the efficacy and tolerability of botulinum toxin in children with cerebral palsy in reducing spasticity and improving upper limb function.

Subjects and Methods

Children with cerebral palsy currently followed up in the Children's Habilitation Institute of Duchess of Kent Children's Hospital were recruited into the study. Static function of the upper limb must have been present for 3 months before being recruited. The inclusion criteria included moderate spasticity of the upper limb with a Modified Ashworth Spasticity Scale score of at least 2, dynamic deformity, no fixed joint deformity, and no previous surgery. Children with fixed joint contractures were excluded. The cohort consisted of 11 children (7 boys, 4 girls). The mean age was 6 years, 2 months (range = 2 years to 15 years, 6 months). The type of cerebral palsy was hemiplegia ($n = 9$; 4 left, 5 right), spastic diplegia ($n = 1$), and spastic triplegia ($n = 1$). All children were ambulatory. The children were evaluated prior to the observation period for 3 months, postinjection (weeks 1, 4, and 16), with the same parameters.

Baseline evaluation prior to botulinum toxin injection consisted of objective measurement of upper limb function with standardized tests by the physiotherapist and occupational therapist. One or more of the following parameters were analyzed for each child depending on the cooperativeness, cognitive level, and functional ability. The average value in the three assessments was analyzed:

1. Spasticity (evaluated for all cases: biceps, pronator teres/pronator quadratus, adductor pollicis brevis). The degree of spasticity was assessed using the Modified Ashworth Spasticity Scale.²¹ The score was as follows: 0 = normal (no increase or decrease in tone); (1) = mild (slight increase in muscle tone, "catch" in limb movement or minimal resistance of movement through less than half of the range); (2) = moderate (marked increase in muscle tone through most of the range of motion, but the passive movement of the affected part is easily performed); (3) = severe (prominent increase in muscle tone with difficulty in passive movement); and (4) = extreme (affected part is rigid in flexion and extension). The mean Modified Ashworth Spasticity Scale score of the muscle assessed was compared pre-botulinum toxin and post-botulinum toxin injection.
2. Measurement of range of joint motion by goniometer ($n = 3$) (cases 3, 7, and 8) and hand map (web space) (cases 1, 3, 5, 7, and 11). The degree of active joint movement was measured after the injection (elbow extension, hand supination, and thumb abduction). The maximum space between the thumb and first finger was measured with a simple imprinting technique on a hand map (ie, web space).
3. Muscle power of the hand including palmar strength (using the Jamar hand dynamometer) and pinch strength, measured in five children. (cases 3, 5, 7, 8, and 11).
4. Jenson Hand Function Test ($n = 5$) (cases 2, 5, 6, 8, and 9). The mean time taken to achieve seven items of hand function (after three trials) was scored. The seven items included writing, card turning, picking up small objects, stacking up checkers, stimulated feeding, lifting up of light objects, and lifting up of heavy objects. The averaged time score achieved after injection was compared to the averaged time taken for each task before the injection. The time score taken for the normal hand was also assessed to take away the learning effect.
5. Clinical photograph of hand maps and video recordings of the actual assessment procedures, taken to document any changes.

Evaluation for the mother included the following:

1. Report of onset, peak effect of action, and any side effect.
2. Clinical Global Impression Scale—a Likert scale of 7 with 4 = no change, 1 = very much improved (>75%), 2 = much improved (50-75%), 3 = minimally improved (25-50%), 7 = very much worse (>75%), 6 = much worse (50-75%), and 5 = minimally worse (25-50%).