Brainstem dysgenesis: report of five patients with congenital hypotonia, multiple cranial nerve involvement, and ocular motor apraxia

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This paper reports three females and two males with a distinctive congenital syndrome characterized by severe congenital hypotonia, facial diplegia, jaw ankylosis, velo-pharyngeal incoordination, pyramidal tract signs, and ocular motor apraxia. Patients were followed up at ages ranging from 20 months to 16 years. All cases of this syndrome are sporadic, without dysmorphological features, chromosomal, or MRI brain abnormalities. Electrophysiological studies indicate the brainstem as the site of the neurological dysfunction. Post-mortem CNS study of one of the patients demonstrated neuronal depletion of the IV, VII, VIII, and IX cranial nerve nuclei and intact morphology of the cerebral hemispheres. A vascular accident, early in foetal life, is the most likely cause of the clinical picture. The extent of brainstem involvement and its related clinical findings distinguishes these patients from those with Moebius, Pierre Robin, or Cogan syndromes. Outcome is better than what could be anticipated during the first few months of life given the severity of symptoms. Intelligence or developmental quotients are within the normal range for their age. Facial hypomimia, feeding, and speech articulatory performance difficulties are the main disabilities observed in these patients at follow-up.

A significant number of individuals experience facial diplegia, sucking and swallowing difficulties from birth and, later on in life, drooling and articulatory speech problems (Reilly et al. 1996). Often, these symptoms are part of a dysmorphological syndrome in which facial and limb bony structures are also involved (Illingworth 1969, Miller et al. 1989, Gorlin 1990, Abadie et al. 1996, Robin et al. 1996). Infants with predominant facial diplegia and ocular motor paresis with or without limb malformations are reported under the name of Moebius syndrome and infants with swallowing difficulties, respiratory dysfunction, and retro-micrognathia under the name of Pierre Robin or 'dysfonctionnement néonatal isolé du tronc cerebral' (Abadie et al. 1996).

There are several groups of infants with congenital facial diplegia as well as sucking and swallowing difficulties without visible malformations in which the anatomical location and the cause of their nervous system lesion have been established. First, patients belonging to the Worster-Drought syndrome, Foix-Chavany-Marie syndrome, biopercular or perisylvian syndromes have dysgenesic anomalies located in the cerebral hemispheres which interfere with normal coordination of facial, lingual, and swallowing movements in addition to motor impairment, learning disability*, and seizures (Worster-Drought 1974, Becker et al. 1989, Kuzniecky et al. 1993, Christen et al. 2000, Clark et al. 2000). Second, patients born with diseases involving any one of the components of the motor unit may present with facial diplegia, and feeding difficulties, in addition to hypotonia, respiratory distress, and arthrogryposis (Illingworth 1969, Dubowitz 1985). Third, there are numerous descriptions of individuals with congenital anomalies circumscribed to the brainstem, presenting with different patterns of cranial nerve involvement (Baraitser 1977, Campistol et al. 1983, Bouwes-Bavinck and Weaver 1986, Rappaport et al. 1987, PeBenito and Cracco 1988, Govaert et al. 1989, Abadie et al. 1996). The precise aetiology and the mechanisms of production of the lesions in this last group of infants are still unresolved and, according to the published reports, their clinical course may vary notably. Some of these patients presumably have a 'dysmaturative' process and improve spontaneously (Leroy-Malherbe et al. 1994, Franck and Gatewood 1996). Others, in which a congenital malformation of the brainstem is suspected, are left with a permanent neurological dysfunction (Kumar 1990, Abadie et al. 1996). The mechanisms of production of anomalies in this latter group may be similar to those giving rise to the oromandibular limb hypogenesis syndromes. However, until this hypothesis is proven, in our opinion they should be described separately.

We wish to report five patients with a previously undescribed syndrome characterized by: severe congenital hypotonia, facial diplegia, temporomandibular ankylosis, velo-pharyngeal incoordination, mild pyramidal track signs, and ocular motor apraxia. Electrophysiological studies indicate the brainstem as the site of the neurological dysfunction and the neuropathological study of one of the patients demonstrated neuronal depletion of most motor cranial nerve nuclei and intact gross and microscopic morphology of the cerebral hemispheres. Patients presented in this report cannot be included in any of the aforementioned well-defined syndromes owing to the concomitant occurrence of jaw ankylosis, ocular motor apraxia, velo-pharyngeal incoordination, and pyramidal tract signs

*US usage: mental retardation.

and the absence of VI cranial nerve involvement. These individuals probably have the widest possible brainstem dysgenesic lesion compatible with survival during intrauterine and extrauterine life.

Method

CLINICAL DATA

Over the last 16 years we have been able to identify and follow up five patients with a distinctive congenital clinical syndrome. The first author evaluated three patients during the neonatal period and the other two during the first 3 months of life. The follow-up of these patients ranges from 20 months to 16 years of age.

The initial main problems seen in all of them were marked generalized hypotonia, and sucking and swallowing difficulties. A negative history for abortions, premature deaths, consanguinity, neurological diseases, malformative syndromes, or chromosomal abnormalities was recorded in each patient's families. The mother of patient 2 underwent amniocentesis owing to her age. This patient was delivered by Caesarean section due to premature rupture of membranes and signs of foetal distress. Patient 4 was the third child of a 21-year-old single woman, who did not follow medical supervision during this pregnancy. Patient 5 was delivered by Caesarean section at 37 weeks' gestation owing to preeclampsia. The most relevant clinical neonatal data of all these patients are summarized in Table I. Cerebral CT studies performed during the neonatal period were found to be normal in all patients as were the studies aimed at ruling out chromosomal aberrations, skeletal anomalies, and inborn errors of metabolism presenting during this period of life. All patients had abnormal X-ray deglutition studies. Muscle biopsy was performed in patient 2 due to severe hypotonia and mildly elevated plasma creatine kinase, with normal results.

The most pertinent follow-up data are depicted in Tables II and III. Muscle hypotonia, which was quite remarkable during the neonatal period, improved progressively and between 18 months to 2 years of age, muscle tone and strength were normal in all patients. All patients were ambulatory before 3 years of age, except patient 5 who is presently 20 months old. Mild pyramidal tract signs such as increased muscle tone in lower extremities, brisk deep-tendon reflexes, and jaw jerk persisted throughout patients' follow-up evaluations.

None of the patients had paresis of the extraocular muscles

Table I: Physical findings in newborn infants

Patient	*Cognitive status*	*Muscle hypotonia*	*Facial diplegia*	*Suck reflex*	*Feeding difficulties*	*Pyramidal signs*	*Associated malformation*
1.	Alert	Severe generalized	Present	Absent	Choke episodes ↑ oral secretions	Brisk DTR palmar thumb	Retrognathia T-M ankylosis wrist contractures
2.	Poorly reactive	Severe generalized	Present	Absent	Choke episodes apnea episodes ↑ oral secretions	Brisk DTR jaw jerk	Micrognathia T-M ankylosis
3.	Poorly reactive	Severe generalized	Present	Absent	Choke episodes ↑ oral secretions	Brisk DTR	Retrognathia T-M ankylosis
4.	Not recorded	Severe generalized	Present	Absent	Choke episodes ↑ oral secretions	Brisk DTR	Micrognathia retrognathia
5.	Alert	Moderate generalized	Present	Absent	Choke episodes ↑ oral secretions	Brisk DTR jaw jerk	Micrognathia T-M ankylosis

DTR, deep tendon reflexes; T-M, temporo-mandibular.

Table II: Clinical follow-up data

Patients' present age	*Motor ocular apraxia*	*Deglutition feeding*	*Facial diplegia*	*Cough reflex*	*Pyramidal signs*	*HC growth*
1. 16y	1st recorded: 15m Disappeared: 5y	Improved progressively	Persisted less marked	Abnormal	↑ DTR ↑ jaw jerk achilles clonus	3p. no decel.
2. 10y	1st recorded: 2y Disappeared: 5y	Improved progressively	Persisted less marked T-M ankylosis	Abnormal drooling++	Assymetric L>R tetraparesis achilles clonus	25p. no decel.
3. 8y	1st recorded: 13mo Disappeared: 5y	Improved progressively	Persisted T-M ankylosis	Abnormal	Brisk DTR achilles clonus	50p. no decel.
4. Died 2y	1st recorded: 13mo	Abnormal contributed to death	Persisted T-M ankylosis	Abnormal contributed to death	Brisk DTR	nr
5. 20mo	1st recorded:11mo	Abnormal Recurrent pneumonia	Persisted less marked T-M ankylosis	Abnormal drooling++	↑ DTR ↑ jaw jerk achilles clonus	50p. no decel.

HC, Head circumference; DTR, deep tendon reflexes; T-M, temporo-mandibular; no decel., no deceleration.

or strabismus. All of them, however, were noted as infants to develop head thrust when required to direct their gaze to a target opposite to their visual field. Feeding difficulties and velo-pharyngeal incoordination varied significantly in each individual; patients 4 and 5 were particularly affected and management became even more difficult due to the associated, severe, gastro-oesophageal reflux. These two patients experienced frequent bouts of aspiration pneumonia that required gastrostomy and anti-oesophageal reflux therapy. Coughing or sneezing reflexes in the three older patients were substituted by bizarre oropharyngeolingual movements, which were partially functional.

MRI studies were performed during the follow-up period in four patients. Abnormalities at the perisylvian region, brainstem calcifications, or findings described in Moebius syndrome (Pedraza et al. 2000) or Cogan syndrome (Sargent et al. 1997), were absent. Funduscopic examination of the eyes was normal in all cases. Cognitive status of the surviving patients was found within the normal range for the age when the test was performed. IQ in older patients was obtained using the WISC-R scale. Patient 2's IQ was found to be borderline, which was attributed to her abnormal perinatal history and the related periventricular leukomalacia found on the MRI study performed at 3 years of age. Abnormal voluntary and involuntary facial gestures or grimaces, and feeding and speech articulatory performance difficulties were the main disabilities observed in these patients at follow-up. Physiotherapy specifically aimed to ameliorate their jaw ankylosis improved their feeding and language functions.

ELECTROPHYSIOLOGICAL STUDIES

Motor nerve conduction of the facial nerve, blink reflex, and electromyography of the orbicularis oculi, masseter, and lingual muscles were performed at different ages on the surviving patients. Facial nerve conduction velocities were obtained by stimulating the facial nerve using a bipolar stimulator at the mastoid process. The active recording electrode was placed on the edge of the mouth on the orbicularis oris muscle, and a reference electrode was placed on the same point on the opposite side. Amplitudes and latencies of the direct responses obtained after supramaximal stimulation were recorded and evaluated. For blink reflex studies, the recording electrodes were kept on the centre of the inferior orbicularis oculi muscle, while the reference electrode was placed on the edge of the eye. The supraorbital nerve was stimulated percutaneously using a bipolar stimulator. At least four responses were obtained from the right and left orbicularis oculi muscles simultaneously. The shortest latencies to the initial deflection of the ipsilateral R1 and bilateral R2 were recorded. EMG studies were performed using concentric needle electrodes; both the activity at rest and at the maximal contraction were evaluated (Jaradeh et al. 1996). All studied patients showed abnormal results. Patient 1 was examined at age 15 years and showed a neurogenic pattern in muscles innervated by V (masseter), VII (orbicularis oris), and XII (lingual) cranial nerves. Blink reflex showed absence of R1 with preservation of the R2 and Rc components at the normal latency range. Patient 2 had absent R1, R2, and Rc blink reflex responses without evidence of motor neuron loss at the nucleus of the cranial nerves (normal motor evoked potential of the facial nerve and normal EMG pattern of the specific muscles). Patient 3 showed a neurogenic pattern in the masseter muscle and absent R1 and Rc bilateral responses. Patient 5 had both a neurogenic pattern in all examined muscles and abnormal blink reflex responses with a delayed R1 component and absence of Rc and R2.

PATHOLOGICAL STUDIES

Patient 4 died at the age of 2 years owing to massive aspiration pneumonia. Parents allowed post-mortem studies restricted to the brain. No gross abnormalities were seen on naked eye examination, except for mild atrophy of the brainstem. Formalin-fixed paraffin-embedded sections were obtained from the following areas of the cerebral cortex: frontal (area 8), orbitary, anterior cingulate, anterior insular, primary motor, primary somatosensorial, upper, middle, and inferior temporal, primary visual, visual associative, parahippocampal; hippocampus, and dentate gyrus; amygdala; anterior caudate and putamen; middle striatum and pallidus; thalamus, including anterior, dorsomedial and posterior regions; subthalamus; hypothalamus; cerebellar vermis, cerebellar hemispheres and deep cerebellar nuclei; as well as consecutive sections of the midbrain, pons, and medulla oblongata. Sections were stained with haematoxylin and eosin, luxol fast blue-Klüver Barrera and cresyl violet (Nissl stain), or

Table III: Follow-up laboratory findings

Patients' present age	*Cranial MRI recording*	*X-Ray deglutition studies*	*BAEPs*	*Sleep EEG*	*Cognitive status*
1. 16y	Normal (11y)	Velopalatine incoordination	Normal	Not done	IQ100 dysarthria
2. 10y	Periventricular leukomalacia thalamic lesions (3y)	Velopalatine incoordination CT: T-M ankylosis	Abnormal ↑latency III-V ↑amplitude	Normal EEG, abnormal respiratory pattern	IQ<78 dysarthria
3. 8y	Normal (5y)	Velopalatine incoordination CT: T-M ankylosis	Normal	Normal	IQ 100 dysarthria
4. Died 2y	Normal (18mo)	Velopalatine incoordination	Normal	Normal	Normal social-adaptive development
5. 20mo	Normal	Velopalatine incoordination CT: T-M ankylosis	Abnormal ↑latency III-V	Normal respiratory pattern cardiac arrhythmia	Normal social-adaptive development

T-M, temporo-mandibular;

processed for immunohistochemistry to glial fibrillary acidic protein (GFAP, Dako, 1:600) and lectin histochemistry to microglia (*Lycopersicum esculentum*, Sigma, L-0651, 1:100). Visualization was carried out with the avidin-biotin-peroxidase method (ABC kit, Vector, Vectastain) or with a modified labelled streptavidine technique (Dako LSAB®2 System Peroxidase). Selected sections of the brainstem were processed with the method of in situ end-labelling of nuclear DNA fragmentation (Oncor) following the instructions of the supplier.

No abnormalities were found in the cerebral cortex, amygdala, caudate, putamen, pallidus, thalamus, hypothalamus, cerebellar cortex, and deep cerebellar nuclei. The substantia nigra, colliculi, red nucleus, locus ceruleus, and pontine nuclei were also normal, as well as the inferior olives and the nucleus ambiguus. However, neuronal loss and mild gliosis was encountered in the nuclei of the cranial nerves IV, VII, VIII, and IX. Reactive microglia was rare, and no increase in nuclear DNA vulnerability was seen with the method of in situ end-labelling of nuclear fragmentation. Mild gliosis was also observed in the medial reticular formation of the medulla oblongata. Myelin stains disclosed slight myelin pallor in the cerebral hemispheres and brainstem with no accompanying pathology. Inflammatory infiltrates were absent.

Discussion

The children described in this report belong to the group of patients with congenital malformations circumscribed to the brainstem. We have been able to find several reports, most of them published as cases of Moebius syndrome, that are similar to the ones described here (Henderson 1939, Thakkar et al. 1977, Towfighi et al. 1979, Sudarshan and Goldie 1985, Govaert et al. 1989, Voirin et al. 1991, Igarashi et al. 1997, Lammens et al. 1998). All these patients, like the ones we report, were sporadic cases and showed muscle hypotonia, facial diplegia, and swallowing difficulties. In addition, some had various combinations of oculomotor paresis, trismus, central respiratory dysfunction, and gastro-oesophageal reflux. Most of them died during the first few months of life and, in those patients in whom post-mortem studies were available, there were signs of old para-medial tegmental necrosis extending down to the upper medulla. No mention of ocular motor apraxia was found in any of these reports. The explanation could be either because it did not occur in these patients or because they died before this sign could be detected.

The nosological classification of patients with congenital multiple cranial nerve involvement is still unresolved. Infants with predominant facial diplegia and ocular motor paresis are reported under the name of Moebius syndrome or Moebius sequence. Infants with swallowing difficulties, respiratory dysfunction and retromicrognathia under the name of Pierre Robin sequence or 'dysfonctionnement néonatale isolé du tronc cerebral' (Abadie et al. 1996). This approach, although it is a practical one, does not allow adequate classification of patients with extensive cranial nerve involvement. Therefore, it is not surprising that terms such as Moebius sequence or Moebius spectrum disorders have been coined to embody patients with a clinical presentation exceeding that pointed out initially by Moebius (1888). Several authors (MacDermot et al. 1990, Norman et al. 1995) have recommended restriction of the term Moebius syndrome to individuals with congenital VI and VII nerve paralysis, as they have assumed that the mechanisms by which the damage occurs and the genetic implications of this syndrome may differ from other brainstem dysgenesis syndromes. The patients presented in this report probably have the widest possible brainstem lesion compatible with survival during intrauterine or extrauterine life. Their signs and symptoms encompass those of Moebius, Cogan, and Pierre Robin syndromes. It is worthwhile noting, from a prognostic point of view, that motor tone began to improve in our patients after the first few months of life, and that the ones who survived their cardio-pulmonary complications showed a remarkable functional amelioration of their symptoms.

Congenital ocular motor apraxia has been reported as isolated neurological disturbance, associated with a variety of CNS anomalies or neurodegenerative diseases (PeBenito and Cracco 1988). The ophthalmological findings and the clinical course of our patients coincide with what has been reported in the literature as congenital ocular motor apraxia. It should be noted that more than half of the patients with Cogan syndrome have associated oral motor dysfunction, hypotonia, and developmental delay, as do the patients that we are reporting (Rappaport et al. 1987). The cause and anatomical location of congenital ocular motor apraxia is not known. Frontal lobes, cerebellum, and upper brainstem have been proposed as possible locations. Cogan himself postulated that the syndrome was due to a developmental arrest or to delayed myelination of the pathways for conjugate gaze (Cogan 1952). Physical examination and results of the electrophysiological studies of our patients, together with the neuropathological findings of patient 4 lend support to this hypothesis and point to the pathways reaching the centre for horizontal saccades or the centre itself, as the site of the lesion in congenital ocular motor apraxia. Furthermore, a common pathogenic mechanism could underlie the speech articulatory problems observed in our patients and in those with Cogan syndrome.

Proper diagnosis of patients who are similar to the ones we are reporting may be difficult to achieve unless it is made during the first few months of life. Once hypotonia and ocular motor apraxia subside, facial diplegia, feeding difficulties, poor handling of oral secretions, articulatory speech problems, and signs of pyramidal tract involvement, including a brisk jaw jerk, are the predominant clinical signs. Therefore, it is conceivable that patients identical to the ones reported here have been included into the Worster-Drought syndrome. Neuropathological findings of patient 4 largely matched neurological deficits but, unfortunately, they did not allow the cause of the abnormality to be determined. No inflammatory infiltrates were observed and signs of acute or progressing damage (i.e. DNA nuclear fragmentation) were lacking. The involved brainstem structures of our patients, based on the clinical and pathological findings, probably extend from the vicinity of the IV cranial nerve nucleus at the midline and paramedian zones of the pontine tegmentum down to the upper medullary centres which control oesophageal motility and heart rate. The nature of the lesion is destructive rather than systemic for there is evidence of clinical involvement of descending cortical tracts (pyramidal signs, ocular motor apraxia) and 'scattered' gliosis in neuropathological studies. The cause of the different brainstem dysgenesis syndromes is beginning to emerge. According to Leong and Ashwell (1997) the midline and paramedian zones of the developing brainstem tegmentum are poorly vascularized relative to the more lateral regions of the same structure. It is conceivable that a vascularly mediated lesion (thrombosis, ischemia, haemorrhage)

occurring during early foetal life, depending on the vascular territory involved, could give rise to different destructive lesions and, therefore, to different clinical syndromes. The mechanisms of production of anomalies in this last group may be similar to those giving rise to the oromandibular limb hypogenesis syndromes. However, it is difficult to understand why in some patients extensive facial or limb bony abnormalities should occur and not in others (Bouwes-Bavinck and Weaver 1986, Webster et al. 1988, St Charles et al. 1993)

Several reports both in humans and experimental animals indicate that defects in one or various genes belonging to gene families which participate in the program of neural tube differentiation, can induce dysgenesis of brainstem structures. These malformations also give rise to clinical manifestations resembling Moebius or Pierre Robin syndromes (Lufkin et al. 1991, Chisaka et al. 1992, Barrow and Capecchi 1996). Finally, defects on some of these developmental genes which continue to be expressed in adult life in order to preserve viability of specific cellular types (Sarnat 1992) could explain genetically determined brainstem dysgenesis syndromes with selective neuronal drop out.

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