Brainstem dysgenesis: beyond Moebius syndrome

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Summary. Brainstem dysgenesis designates all those patients with congenital dysfunction of cranial nerves and muscle tone due to prenatal lesions or malformations of the brainstem. This generic term has the advantage over the eponyms Moebius 'expanded' or 'unrestricted', Robin, Cogan or Carey-Fineman-Ziter syndromes in that it has a less restrictive view and provides a frame work that enables a systematic approach to diagnosis and research of most developmental disorders involving the brainstem. The review of the literature and our experience shows that infants with a predominant rombencephalic involvement are due to brainstem prenatal disruptive vascular accidents, while cases with midbrain and cerebellar involvement and widespread malformative syndromes have most likely an underlying genetic cause. Due to phenotypic heterogeneity associated with brainstem dysgenesis, it is crucial to evaluate each case individually and to establish a specific therapeutic plan. Intervention programs should start soon after diagnosis and directed to improve functions needed for daily life activities. Even though the prognosis of patients with brainstem dysgenesis due to prenatal destructive lesions depends on the magnitude of the vascular territory involved, in most patients with brainstem dysgenesis, the prognosis is better than the initial clinical manifestations would indicate.

Key words. Brainstem malformations. Carey-Fineman-Ziter syndrome. Cogan syndrome. Congenital facial palsy. Moebius syndrome. Oculomotor apraxia. Robin syndrome. Temporo-mandibular ankylosis.

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Introduction

Congenital dysfunction of the motor cranial nerves (CN) with nuclei of origin located in the mesencephalon, bulb, or medulla is infrequent. It is well known that lesions at the bulbar or medullary level may be produced by infantile spinal muscular atrophy, congenital tumors, vascular malformations, severe perinatal trauma or hypoxic-ischemic events, and prenatal vascular accidents [1-5]. These conditions manifest, among other clinical signs, with multiple CN involvement, muscle hypotonia, feeding, and respiratory problems. Once the previously described causes of congenital bulbar palsy have been excluded, the etiology of multiple congenital CN paralysis is difficult to establish. Motor nuclei agenesis, absence of the peripheral nerves, or hypoplasia of the muscles innervated by the motor CN have been implicated along with other motor-neuron diseases [5].

Disordered brainstem (BS) development results in diverse and complex clinical conditions. Several of these combinations of CN involvement have long-standing eponyms while others carry more descriptive names. Because this group of congenital disorders does not lend itself to a brief and accurate descriptive term, the combination of abducens and facial nerve paralysis in infancy reported by Moebius in 1892 [6] gained eponymous recognition to the extent that many authors, even nowadays, use the expressions 'unrestricted', 'expanded' or Moebius plus syndrome (MS) to identify all patients in whom the involvement of these two CN is present, irrespective of how many additional clinical findings they exhibit [7,8].

Various pathogenic theories have been put forward concerning either genetically determined processes or acquired disorders of the BS during the gestation period to elucidate the origin of the 'expanded' MS. However, no single theory explains either the variability of clinical signs or the inconsistency of the neuropathological findings. The available post-mortem pathologic studies of the majority of patients with MS, or 'unrestricted' MS who died in early infancy revealed old necrotic lesions located in the paramedial zones of the tegmentum extending from the mesencephalon to the superior portion of the medulla [9-11]. According to Leong and Ashwell [12], the midline and paramedial zones of the developing BS tegmentum are poorly vascularized relative to the more lateral regions of the same structure and are therefore prone to ischemia. H. Sarnat [9] proposed that BS watershed infarcts during the embryo or fetal period were the cause of most congenital syndromes presenting with multiple CN involvement. Miller, in 1991, described the existing relationship between ocular motility and

other CN dysfunction and the ingestion of Thalidomide during embryonic development [13]. Misoprostol has also been related with MS. Clinical reports from Brazil, suggest a causal relationship between the use of this drug in an attempt to interrupt gestation and MS [14,15]. Moreover, the exposition to cocaine during gestation has been associated with developmental malformations including BSD. It has been postulated that this drug induces vascular lesions owing to its vasospasm effect on vessels of small caliber [16,17].

From a clinical point of view, the study performed by Verzijl and coworkers in the Netherlands [18], in a series of 37 subjects with 'unrestricted MS', demonstrated that the clinical manifestations of these patients were more extensive than what Moebius initially described and could only by explained if this syndrome was the consequence of 'rhombencephalic maldevelopment'. Studies carried out by Abadie and co-workers [19] in a group of 66 patients diagnosed with the Robin sequence (RS) indicated that the clinical manifestations of these patients could not be understood on the basis of bone anatomical anomalies. They proposed that the symptoms of these infants had a neuro-embryological origin that gave rise to a dysfunction of BS structures during fetal development. There is recent literature recognizing an amalgam between destructive and developmental effects in the injured fetus because a destructive process that occurs in a rapidly developing tissue may cause both a derangement of subsequent development and injury to an already-developed structure; the less vigorous reactive cellular response to tissue destruction during early development makes it difficult to distinguish developmental (genetically determined) lesions from destructive lesions [20]. Several reports based upon studies of cases in humans or experimental animals (mice) indicated that defects in one or more genes belonging to gene families that participated in neural tube differentiation could induce dysgenesis of BS structures in a manner resembling MS or PRS [21]. The pioneer work of Engle and coworkers on congenital cranial dysinnervation disorders has led to the discovery of mutations in genes governing specifically axon guidance in in the developing hindbrain and spinal cord [22-26] (Table). Congenital central hypoventilation syndrome (CCHS) is another life-threatening genetic disease in which the defining symptoms consist of respiratory arrest during sleep or a blunted response to hypercapnia. Recently, it was discovered that CCHS is caused by heterozygous mutations of PHOX2b, a transcription factor whose loss specifically induces a loss of PHOX2b-expressing glutamatergic neurons surrounding the VII cranial nerve nuclei [27]. All these theories as well as the unceasing search for gene defects, yet, are restrictive in their approach as they only consider one or two aspects of the problem. From a medical point of view, there is a need for a more global outlook, one that takes into consideration each aspect (clinical, anatomical, etiological, pathogenic and therapeutic) playing a role in this group of disorders characterized by congenital dysfunction of the CN.

The term BSD, was first introduced in the pediatric and developmental neurology literature in 2003 and refers to all patients with congenital dysfunction of CN and decreased muscle tone due to prenatal lesions or malformations of the BS [10]. This term has turned out a useful one since it offers a brief descriptive term for this group of BS congenital disorders and because it provides a frame work that allows a systematic approach to diagnosis and research for most congenital BS developmental disorders. The progress reached in the last 25 years on human and experimental animal embryology, molecular genetics and neuroimaging have conducted to a better understanding this group of BS developmental disorders and, based on this information, several classifications have been proposed [28]. However, they overlook those BS congenital disorders with minimal or no findings in MRI studies or those in whom the cause is not genetic. In our experience, prenatal disruptive lesions located in the rhombencephalon have minimal impact in neuroradiological studies and, in most cases, are of vascular origin. Clinical manifestations in this group of patients are quite variable and are ill defined; little is known of their clinical course, prognosis and possible contribution to the origin of attention deficit hyperactive disorders (ADHD) or autistic spectrum disorders (ASD). Here we review the literature and present the most relevant data since introduction of the term BSD.

Concept of brainstem dysgenesis

Brainstem dysgenesis (BSD) is a generic or umbrella term that we proposed in 2003 to describe all patients with congenital dysfunction of CN and decreased muscle tone due to prenatal lesions or malformations of the BS [2,3,10]. The term 'dysgenesis' derives from the combination of two Greek/Latin words: *dys* + *genesis*. It is used in multiple fields of medicine to indicate the anomalous, partial, or total genesis of one organ. There is controversy with

respect to the use of this term. Some investigators argue that the term 'dysgenesis' has a genetic hereditary connotation and should therefore only be used in this context. However, other authors withstand that the word 'genesis' was used in medicine prior to the word 'gene' and accept that 'dysgenesis' can describe an anomalous development throughout gestation. Consequently, they accept that the anomalies described using that term can be due either to genetic causes or to disruptive disorders occurring prior to birth [9,12].

The origin of the BSD can be genetically determined in some patients and it may be present in isolation or be part of a more extensive polymalformative syndrome. In most cases BSD is due to prenatal destructive or disruptive lesions of vascular origin. Depending on the vessels involved and the magnitude of the lesion, clinical consequences range from intrauterine death to mild involvement of one or several cranial nerves. According to our experience and the literature review, disruptive accidents occurring early in gestation are the most common cause of BSD, and thus the recurrence risk is minimal [9-11]. Clinical findings in some BSD patients may coincide with those described in well-recognized dysmorphological syndromes (e.g., Duane, Moebius, and Robin), if this is the case, the eponym indicates the predominant location of the BS lesion. Clinical manifestations in the majority of patients with BSD do not fit into any of the aforementioned syndromes, in these circumstances the term BSD should be followed by a detailed description of each patient's clinical findings and the BS segment presumably involved see (Figure).

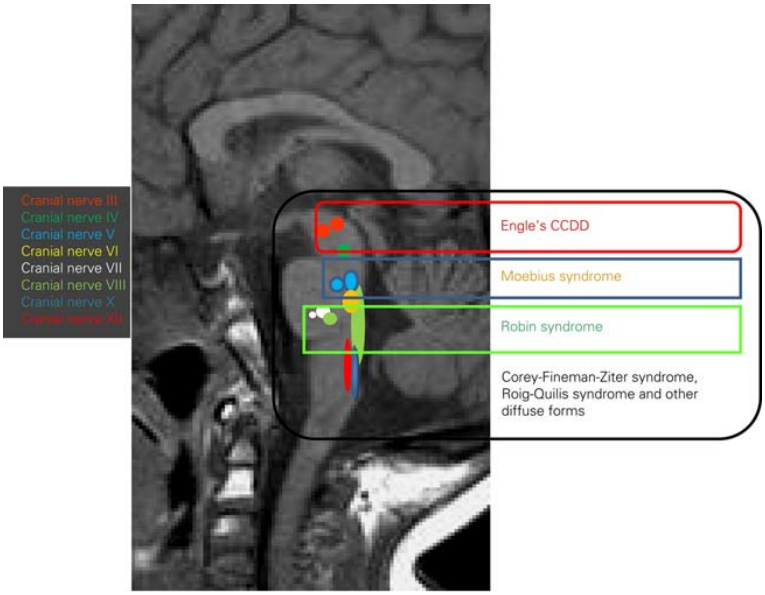
Classification

Continuous advances in developmental biology, molecular genetics, and neuroimaging have increased the interest in developmental disorders of the midbrain and hindbrain and all this amount of information has led to sophisticated developmental/genetic classifications of BS malformations [28]. Instead, we have proposed two complementary BSD classifications. A) Etiological (Table) with three main categories: a) acquired (destructive o disruptive); b) genetically determined; and c) dysmadurative [29,30]. It should be noted that disorders within each of the first two groups can present without involvement of other organs or systems or with malformations in other organs or systems (syndromic). B) Clinical**,** based on severity of the disorder (in our experience not two BSD patients present with iden-

Table. Brainstem dysgenesis: etiological classification.

Genetically determined
Without associated malformations:
KIF21A: CFEOM1. Congenital fibrosis of extraocular muscles. Bilateral ptosis and bilateral blepharoptosis and ophthalmoplegia with the eyes fixed in an infraducted position
PHOX2A: CFEOM2. Bilateral ptosis with eyes fixed in an exotropic position
TUBB2B, *TUBB3*, *KIF21A:* CFEOM3. Variable ptosis, restrained gaze movements and exotropia
MAFB, *CHN1:* Duane syndrome (also translocation involving gen *CPA6*)
PHOX2B: central hypoventilation syndrome
Associated to other malformations:
HOXA1: Atabascan BSD, Bosley-Salih-Alorainy syndrome. Horizontal ocular palsy, deafness, facial, weakness, vascular malformations, hypoventilation, developmental delay
HOXB1: facial bilateral weakness, deafness and strabismus
SALL4: Duane syndrome with radial dysplasia or Okihiro syndrome with renal anomalies
ROBO3: horizontal gaze palsy and progressive scoliosis
Ciliopaties (*AHI1*, *ARL13B*, *B9D1*, *B9D2*, *C2CD3*, *C5orf42*, *CC2D2A*, *CEP41*, *CEP104*, *CEP120*, *CEP290*, *CSPP1*, *IFT172*, *INPP5E*, *KIAA0556*, *KIAA0586*, *KIF7*, *MKS1*, *NPHP1*, *OFD1*, *PDE6D*, *POC1B*, *RPGRIP1L*, *TCTN1*, *TCTN2*, *TCTN3*, *TMEM67*, *TMEM107*, *TMEM138*, *TMEM216*, *TMEM231*, *TMEM237*, *TTC21B* and ZNF423): Joubert syndrome
CASK: brain malformations, brainstem and cerebellar hypoplasia
MYMK: Carey-Fineman-Ziter syndrome. Hypotonia, Moebius and Robin sequences, psychomotor retardation and failure to growth
DARS2: leukoencephalopathy with brainstem and medullary involvement, increased plasma lactate and lower limbs spasticity
WFS1: Wolfram syndrome. Insipid and mellitus diabetes with optic atrophy and deafness
TBX1, 22q11.2 deletion: velocardiofacial syndrome. Cleft palate, velopalatine insufficiency, cardiac defects, and learning disabilities
Acquired
Without associated malformations (in relationship with the extension of the structural lesions):
Moebius syndrome
Robin syndrome
Cogan syndrome (congenital oculo-motor apraxia)
Carey-Fineman-Ziter syndrome
Roig-Quilis syndrome
'Combination of syndromes'
Associated to other malformations:
Oro-mandibular and limb hypogenesis syndromes
Transvers terminal defects with oro-facial malformations
Moebius/Poland syndrome
Pierre Robin syndrome
Hanhart syndrome: hypoglosia, hypodactily
Glosopalatine ankylosis (Charlie M. syndrome)
Others
Dismadurative
Transient clinical manifestations

Figure. Brainstem dysgenesis: clinical forms of presentation.



tical clinical manifestations), that proposes four clinical forms:

- *Lethal form,* associated with respiratory failure and death occurring in the first few months of life [16,17,31].
- *Severe or diffuse form,* which include those patients with hypotonia and involvement of multiple cranial nerves, mild pyramidal signs, temporo-mandibular ankyloses (TMA), and feeding problems, in some of them, the CFZS could be entertained [3,7,8,11,18].
- *Moderate or intermediate form,* some of which match the descriptions of MS [6] or RS [19].
- *Mild or restricted form,* which have isolated bilateral involvement of one of the cranial nerves reflecting the disrupted segment of the BS.

For each of the last three described BSD forms there are asymmetrical or even unilateral variants for which the disruptive vascular cause is the most likely origin [2,3,32].

Clinical manifestations

Neonatal period

Bilateral VII CN involvement, muscle hypotonia and feeding difficulties are the most common presenting clinical signs of newborns (NB) with BSD. The most commonly affected CN in decreasing order of frequency are the 7th, 9th, 10th, 5th, 12th, 6th, 4th and 3rd. The decreased muscle tone in this group of patients is often associated with signs of pyramidal tract involvement (increased deep tendon reflexes, jaw jerk and Achilles clonus), probably due to concomitant corticospinal and spinocerebellar tract involvement at the BS level [33].

Feeding problems and swallowing dysfunction varies from patient to patient depending on the extent of the lesion. In NB with intermediate or restricted BSD forms in which there is mild facial involvement and intact swallowing mechanisms, tube feeding can be discontinued once muscle hypotonia improves. Some NB, particularly those presenting with lesions located in the caudal portion of the BS, may suffer from swallowing difficulties, respiratory problems, esophageal motility dysfunction and cardiac arrhythmia which, sometimes, are the cause of death. It is worth mentioning that heart rate problems are occasionally detected during the practice of conventional EEG or during sleep EEG recordings [1,32,34]. Profuse oral secretions and choking episodes are quite common in this group of NB with diffuse forms of BSD and require frequent oropharyngeal suctioning of secretions or, in some instances, it is necessary to place a continuous nasopharyngeal suction catheter. It must be taken into account that poor handling of saliva alone can cause repeated silent micro-aspiration and lead to chronic lung injury [3].

Associated congenital anatomical malformations found in NB with BSD such are: TMA, cleft palate, retro-micrognathia, associated or not to glossoptosis, can cause severe airway problems. Mandibular growth may be impaired or retarded, owing to trigeminal nerve involvement, [1,3,33,34] and results in varying degrees of micrognathia. TMA is a common and often over-looked clinical finding in NB or infants with BSD and often associates with retro-micrognathia and, its proposed cause is intrauterine paresis of mandibular muscles due the aforementioned 5th CN involvement. We have not found specific descriptions of TMA after reviewing different cohorts reported under the name unrestricted or expanded MS, PRS or CFZS [8,10,11,33], however, considering the clinical descriptions on those publications, TMA was present in a considerable number of the reported patients. Recently, Pasetti et al have published an infant diagnosed of CFZS with TMA [35] and Hong et al [36] have reported and infant with BSD, TMA and oculomotor apraxia. This last clinical combination (muscle hypotonia, facial

diplejía, TMA and oculomotor apraxia and mild pyramidal signs) has been found in a total of 8 patients [10,36]; we have later reported another patient [33] and consulted on another two infants with similar phenotype. It would be most interesting to know if other colleagues around the world have cared for patients with a comparable form of BSD [36].

BSD in the NB, as mentioned earlier, can be associated to malformations in other organs or systems which can divert attention from the BS as being part of the syndrome. The 'Athabascan brainstem dysgenesis syndrome' was the first report to call attention upon BS involvement as part of a polymalformative syndrome and distinguish it from MS [37]. Some years later, Athabascan syndrome was proved to be caused by a defect of the *HOXA1* gene [38] and gave us arguments to use the term BSD to designate all the patients with disordered BS development. BS involvement as part of a genetic/syndromic disorder, as a general rule, tends to be diffuse and therefore severe. Finally, a multidisciplinary team approach to manage BSD in the neonatal period has been recently reported to improve its management and prognosis [33,36].

Clinical follow-up and natural history

Muscle tone tends to improve with the passage of time and does not appear to be a significant clinical problem after 3 years of age in most instances. After the first few months of age facial diplegia, feeding difficulties, poor handling of oral secretions, dysarthria, and signs of pyramidal tract involvement, including a brisk jaw jerk are the most common clinical findings.

Adequate respiratory function is a prerequisite for successful oral food intake. Initially, feeding may be via nasogastric tube (NGT) until the airway is assessed and appropriate management is determined. TMA and an anteriorly positioned larynx can make mask ventilation and endotracheal intubation extremely difficult. Securing a patent airway may prove a very difficult task and alternative methods like laryngeal masks or even an urgent tracheostomy may be needed [39]. It is important to remember that patients with pontine involvement may develop a central hypoventilation syndrome owing to a lesion that includes the para-facial respiratory group of neurons [27,32].

Feeding problems are extremely important and can be life-threatening if not diagnosed and appropriately treated. Failure to protect the airway results in massive aspiration in some patients; in less severe cases swallowing disorders may go unnoticed or be subclinical and be misdiagnosed as reactive bronchitis and can be the cause of multiple admissions and chronic pulmonary damage. Aspiration leading to bronchial syndrome requires respiratory physiotherapy, antibiotics, and anti-inflammatory agents. Treatment of pulmonary disease must be complemented by measures such as food texture modification, dietetic review, parental counselling, and re-education aimed at preventing failure to thrive. Nasogastric tube feeding is indicated when the food volume required to meet the caloric needs is greater than the oral abilities of the infant to accommodate this volume load [39]. In some patients, gastrostomy feeding is imperative. In these circumstances it is important to establish the presence and degree of concomitant gastroesophageal reflux. Gastrostomy is necessary in cases of severe dysphagia persisting for several months and when it is associated with gastroesophageal reflux [3,33,39]. The issue of simultaneous surgical correction of gastroesophageal reflux when performing gastrostomy to avoid massive aspiration is still under debate [40].

Abnormal growth and shape of the jaw and palate, due to the inappropriate innervation of facial and intra-oral structures, are common in BSD patients and cause progressive tooth misalignment and/or malocclusion. Infants and children with facial diplegia, in addition to their initial difficulty with sucking and swallowing, will suffer from diminished or lost facial expression and difficulties with oral and mimic communicative functions along with the resulting psychological consequences. In addition to the initial difficulties in feeding, velopalatine incoordination, facial diplegia, and TMA may be the origin of the speech articulatory problems that are quite frequent in this group of patients as they grow older [3,41,42].

Persistent drooling is common in BSD because of difficulties with swallowing and lip closure. Less-affected patients accommodate to this problem while others improve with age. In some cases, poor handling of only saliva can produce repeated silent micro-aspiration and lead to chronic lung injury [41-43]. Drooling cause distress, as it is socially isolating, interferes with school or work, and leaves chronically irritated skin that may become infected. Tooth decay is particularly common in children who are tube fed or who have reduced saliva due to medication or surgery. Surgery has been proposed to improve facial expressions and lip closure; the recommended age for this type of intervention is 5 to 6 years [44]. Development of language in children with BSD who present with facial and lower brainstem involvement is delayed and always ac-

companied by problems with speech articulation. The patterns of speech dysfunction seen in these patients range from mild to severe dysarthria associated with dyspraxic inconsistencies. The main articulatory problems relate to phonemes that require intact labial motor function such are P, B, M, or sounds that involve friction of the tongue against the palate such are R, FR, PR. The quality of speech production may be worsened by conductive hearing problems secondary to chronic serous otitis which is caused by Eustachian tube malfunction due to the secondary deformities of intra-oral structures and velo-palatine insufficiency [3,42].

It has been common to loosely refer to the defects in ocular motility in patients with multiple CN involvement as abducens paralysis or external rectus paralysis. However, in almost every case in which a detailed ophthalmological has been done later in childhood or adulthood shows that the defects in ocular motility are more complex than a simple III or VI nerve palsy [45]. As far as congenital oculo-motor apraxia is concerned the defect in ocular motility points to pathways reaching the center for horizontal saccades or the center itself as the site of the lesion [10,45]. Lack of appropriate innervation of palpebral muscles and lacrimal glands gives rise to a poor corneal humidification and increases the risk of ulcers that may require surgical replacement by amniotic membrane.

Cataplexy episodes induced by intense emotive states were observed after three years of age in one patient of our cohort [33] and in another reported at the 2014 congress of the Spanish neuropediatric society by Martínez-Salcedo et al. It has also been reported in patients with Duane syndrome [46]. Cataplexy is attributed to the inappropriate activation, during the waken state, of rhombencephalon neuronal circuits involved in the loss of muscle tone that occurs during REM sleep [47].

Cognitive development of patients with BSD is closely related to its clinical form; is seldom involved in the intermediate or restricted forms but is frequently altered in the diffuse forms of BSD. In the cohort of patients with expanded MS, reported by Fons et al [48], psychomotor retardation was recorded in 60% of the subjects during the first few years of live and, on follow-up, 27% of the surviving members of this group had moderate to severe intellectual disability. In the cohort of 22 patients with the diagnosis of MS and older than 18 years, Pérez-Aytés [49] reported that 6 of them completed university studies; 7 concluded high school studies and 9 finished elementary studies. Social and work integration was adequate and 11 of these 17 individuals, however, episodes of fear and anxiety were reported during adolescence in all of them. Chorazy [50] described the natural history of a 32 years old patient with MS who was able to complete university studies and his major disability were social interaction difficulties owing to his lack of facial expression and dysarthria. Most individuals of our cohort were in school age, half of those who could reliably perform an IQ test gave abnormal results, most of them fulfilling criteria of attention deficit disorder. Three patients of our BSD cohort have shown signs compatible with the ADS. Although most experts relate ADS to cerebral cortical dysfunction, BS involvement has been reported as another possible pathogenic mechanism of autism. Hashimoto et al [51] described a decrease in size of the BS and cerebellar vermis in a MRI study of children with autism. Courchesne [52] summarized the BS pathological findings in ADS: superior olive agenesis, facial nuclei dysgenesis, reduction of Purkinje neurons, and BS and cerebellar hypoplasia. Gillberg and Steffenburg [53] reported ten cases of ADS in a cohort of patients with 'expanded MS'; they postulated an early neuro-embryologic defect giving rise to a dysfunction of BS structures as the basis of ADS. In our opinion, the lack, of an accurate clinical selection criterion in most published cohorts does not allow a reliable correlation between BS involvement and ADS. Our experience shows that no patient with intermediate or restricted forms of BSD presented with ADS. The diffuse forms of BS involvement are at more risk to associate with the ADS. Hopefully, future research on different clinical forms of BSD will point to the disrupted areas of BS most likely to give raise to ADS.

Finally, social psychologists comment that the perception of an individual by others is heavily influenced by first appearance [54]. The interaction with someone who has diffuse or intermediate forms of BD is therefore compromised before spoken communication even begins. In addition to facial inexpressiveness and speech involvement, more intimate issues such as drooling result in the social exclusion of disabled individuals from school or society. To improve the prognosis in this group of patients, it is imperative to anticipate these issues and consider interventions that will help children to develop and maintain relationships as they grow into adulthood and avoid the risk of social exclusion [55].

Diagnosis in infancy and childhood

Diagnosis of BSD relies heavily on the appropriate

interpretation of clinical findings during the neonatal period and it is difficult to achieve unless is suspected as early as possible. Once hypotonia subsides and the other presenting symptoms improve, facial diplegia, feeding difficulties, poor handling of oral secretions, dysarthria, and signs of pyramidal tract involvement, including a brisk jaw jerk are the remaining symptoms. Therefore, it is conceivable that patients in whom the diagnosis of BSD was missed in early infancy will be diagnosed as atypical forms of cerebral palsy or Worster-Drought syndrome when evaluated during childhood [56,57].

All of the available electrophysiological studies (NCV, EMG, blink reflex, BAEPs, sleep EEG with polysomnographic recording) are difficult to perform and evaluate in neonates or infants; nonetheless, they are crucial for identifying the brainstem origin of this disorder [1,33,34]. Moreover, EMG/NCV studies performed soon after birth are essential for excluding other muscular or PNS involvement. Myotonic dystrophy, spinal muscular atrophy, or other congenital myopathies that may present with a clinical picture similar to BSD can additionally be excluded by the appropriate molecular genetic studies [23]. In one patient of our NB cohort with BSD [33], we changed his diagnosis on follow-up when we found that he had a congenital myopathy due to mutations in the gen *RYR1* [41]. Recently, the groups of Engle and Jabs have identified a compound heterozygous or homozygous *MYMK* missense mutations in affected members of four siblings pairs and one simplex case of a form of CFZS [58]. Neurophysiological studies performed in most of our cohort of patients throughout their follow-up period showed abnormalities in more than one test depending on the extent of the brainstem involvement. The blink reflex test was the most sensitive for detection of brain stem dysfunction and was abnormal in most patients in whom it was performed. BAEPs also have the power to localize the lesion at the brain stem but have lower sensitivity. There was no correlation between the severity of the neurological impairment and the number of abnormal tests. Until neuroradiological studies designed to detect brain stem malformations in neonates or infants are routinely available, the combined use of different electrophysiological techniques provides the greatest diagnostic information during this period of life in BSD patients [3,59]. Conventional radiology can be of great help in cases where bone malformations, TMA, velopalatine incoordination, or gastroesophageal reflux are identified. Despite its poor diagnostic efficiency, standard MRI examination of suspected BSD patients is mandatory because it is crucial for detection of other pathologic conditions and allows the identification of patients with congenital oromotor disorders associated with CNS malformations, especially those with symmetrical perisylvian polymicrogyria [56,57,60]. Verzijl et al [61] reviewed neuroradiological studies reported in 57 patients carrying the diagnosis of Moebius syndrome. Findings in 42 patients were considered unremarkable. Hypoplasia of the brain stem was demonstrated in 5 patients by CT studies and in 13 patients by MRI studies; a hypoplastic cerebellum was seen in 4 CT and 7 MRI studies. The use of modern MR imaging sequences, particularly current steady-state free precession (SSFP) sequences are particularly informative to delineate the morphology of the posterior part of the pons and medulla and for the reliable identification of the cranial nerves in their cisternae course, owing to greater spatial resolution for assessment [3]. In our cohort, using the aforementioned sequences, more than 70% of cases depicted tegmental hypoplasia of varying degrees that mainly involved the dorsal aspects of the pons and medulla and, in three of them, the neuroradiological findings were asymmetric. It should be noted that in all subjects of our cohort the studies were done during childhood in contrast with the studies of Pedraza [62] and Verzjil et al [61] that were performed during adulthood.

Prognosis

The prognosis of BSD depends on the cause and extent of the disruptive lesion or the impact of the abnormal developmental process involving the BS. In most non-genetic cases, the outcome is better than the initial clinical manifestations would indicate [3,33] As mentioned previously, some neonates can present with a dysmaturative, reversible BS disorder described as 'transient pharyngeal incoordination in the newborn' or 'syndrome de retard de maturation de la succion-déglutition', for which the prognosis is excellent [29,30]. Once the diagnosis of BSD is made, a multidisciplinary team approach that covers developmental, neurological, behavioral, speech and language, and cognitive areas is essential [33,36,39,42,43]. The sequelae and prognosis for the survival of BSD patients is determined by the severity of respiratory insufficiency and heart rate disturbances, the extent of the deglutition disorder, and the degree of gastroesophageal reflux. It is crucial to evaluate each patient individually in order to stablish a specific plan of treatment. Inter-

vention programs must start soon after diagnosis is made and address the following goals [3,42,63]:

– Respiratory.
– Safe and efficient oral feeding, in case of severe dysphagia determine the most appropriate moment to practice gastrostomy.
– Prevent joint ankyloses or deformities and, when indicated, use orthoses.
– Provide maximal limb motor independence.
– Improve, as much as possible, the level of verbal communication and provide alternative /augmentative methods of communication for those patients unable speak.
– Psychological and educational support.

Conclusions

The concept behind the term BSD has turned out a useful one:

– It provides a frame work that enables a systematic approach to diagnosis and research of most congenital disorders involving the brainstem.
– This generic term has the advantage over the eponyms MS, 'expanded' or 'unrestricted' MS, PRS, CFZS in that it provides a less restrictive view for this uncommon group of patients, allowing the inclusion of patients that present with concomitant alteration of high and low CN or in whom either the 6th or 7th CN are spared or when oculo-motor apraxia is part of the clinical picture.
– Places the emphasis on the natural history of this group of disorders which is of outmost importance for anticipating health problems and facilitate a better care.

The challenge is to be able to predict the natural history of each of the forms of BSD and consequently offer the parents an accurate genetic counselling and the best possible therapies for the BSD form of their child. Finally, children with congenital lesions involving selectively the brainstem are an extraordinary model through which to learn about, among other things, the relationship between initial feeding difficulties and speech motor disorders as well as the role of the brain stem in higher cortical functions.

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Disgenesia troncoencefálica: más allá del síndrome de Moebius

Resumen. El termino 'disgenesia troncoencefálica' se aplica a los pacientes que presentan afectación congénita de múltiples pares craneales, hipotonía muscular y signos leves de afectación de la vía piramidal. Este término es ventajoso respecto al uso de epónimos tales como Moebius, Robin, Cogan y Carey-Fineman-Ziter, ya que es menos restrictivo y ofrece un nuevo enfoque para comprender las causas y su patogenia, así como para mejorar el tratamiento de este grupo de alteraciones del desarrollo que afectan exclusiva o predominantemente al tronco del encéfalo. La revisión de la bibliografía y nuestra experiencia muestran que la mayoría de los casos con afectación selectiva del rombencéfalo se deben a lesio-

nes disruptivas prenatales, mientras que en los casos con afectación del mesencéfalo y el cerebelo, así como en los síndromes polimalformativos con afectación destacada del troncoencéfalo, la topografía de las lesiones es más difusa y menos específica, y la causa hereditaria, más probable. Debido a la amplia heterogeneidad fenotípica asociada a la disgenesia troncoencefálica, es esencial realizar una evaluación individualizada y establecer un plan de tratamiento específico. Los programas de rehabilitación deben comenzar poco después del diagnóstico y centrarse en mejorar las habilidades motoras, dotando al paciente de las herramientas necesarias para afrontar las necesidades diarias en función de la morbilidad asociada. Aunque el pronóstico de la disgenesia troncoencefálica secundaria a lesiones disruptivas depende de la localización y la extensión del territorio vascular afectado, en general, el pronóstico de los pacientes con disgenesia troncoencefálica es mejor de lo que las manifestaciones clínicas iniciales harían suponer.

Palabras clave. Anquilosis temporomandibular. Apraxia oculomotora. Malformaciones del tronco del encéfalo. Parálisis facial congénita. Síndrome de Carey-Fineman-Ziter. Síndrome de Cogan. Síndrome de Moebius. Síndrome de Robin.