Outcomes of Neonatal Bulbar Weakness

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Abbreviations:
BRs: blink responses; BW: bulbar weakness; EMG: electromyography; EMGbf: electromyography during bottle feeding; PRS: Pierre Robin sequence

What's known on this subject?
Neonatal bulbar weakness has various etiologies and a broad prognostic range. Outcomes depend on both the severity of orofacial dysfunction and the nature of neuromuscular or central nervous system underlying disorders.

What this study adds?
This is the first report of long-term outcomes in a large series of infants with neonatal bulbar weakness, showing a high risk of motor or mental disabilities, and death. Orofacial electrodiagnostic studies bring prognostic indicators regardless of underlying disorders.

Contributors' Statements:
Dr. Baudon revised patients' files and was in the process of writing the manuscript.
Dr. Renault performed electrodiagnostic studies and was in the process of writing the manuscript.
Dr Flores-Guevara performed statistical studies and was in the process of writing the manuscript.
Dr Vazquez was in charge of most patients and critically reviewed the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background/Objectives

Neonatal bulbar weakness has various etiologies and a broad prognostic range. We aimed to report outcomes in a large series of children with neonatal bulbar weakness, and to explore the association of orofacial electrodiagnostic data with outcome.

Method

We retrospectively reviewed the files of children who presented a facial, lingual, laryngeal or pharyngeal weakness at birth, and who underwent electrodiagnostic studies combining conventional needle electromyography of orofacial muscles, blink responses, and electromyography during bottle feeding. Outcome measures included the need for prolonged respiratory assistance and enteral feeding, as well as sensorimotor and cognitive impairments.

Results

Out of 175 patients, 73% had developmental disorders; 25% suffered from acquired brain damage; 2% had no apparent underlying disorders. A motor or mental impairment was observed in 71%; death occurred in 16%. Outcomes were not significantly different when comparing developmental disorders *vs* acquired brain damage, and neurogenic *vs* normal detection electromyography. Abnormal blink responses were associated with higher frequencies of respiratory assistance (p=0.03), gastrostomy (p=0.025), and death (p=0.009); moderate or severe oro-pharyngeal incoordinations were associated with higher frequencies of respiratory assistance (p=0.006), prolonged enteral feeding (p<.0001), and gastrostomy (p=0.0002).

Conclusion

Orofacial electrodiagnostic studies bring supplementary information to help the paediatrician in anticipating the management and prognosis of young infants with bulbar weakness.

Introduction

Newborn infants with bulbar weakness (BW) present with congenital facial, lingual, laryngeal, or pharyngeal dysfunction, alone or in combination; all of which have significant developmental and functional consequences. Individual course may vary from rapid discharge without any sequel to prolonged dependence on nutritional and respiratory supports, disabilities, or death. Various etiologies include neuromuscular disorders involving the motor neuron, neuromuscular transmission, or muscle, and cerebral palsies. The evaluation of a child with BW requires that major emphasis be placed on an etiological definition and a reliable prognostic assessment because outcomes depend on both the severity of orofacial dysfunction and the nature of neuromuscular or central nervous system underlying disorder.[1] Although clinical assessments have been developed,[2] predicting an outcome remains a challenging task. Available complementary investigations include videofluoroscopy,[3] fiberoptic endoscopy,[4,5] orofacial electrodiagnostic studies, and esophageal manometry.[6] By combining conventional detection of orofacial muscles, blink responses recording, and functional electromyography during bottle feeding, electrodiagnostic studies have been shown to help diagnose cranial nerves palsies and sucking/swallowing incoordination.[7,8] In this work, we report outcomes in a large series of young infants with neonatal BW of diverse causes, and explore the association of orofacial electrodiagnostic data with outcome.

Methods

Participants

We carried out a retrospective study. Approval by an institutional ethics' committee was waived by our hospital's review board. We reviewed the database of our pediatric neurophysiology unit over a fifteen years period (07/01/1995 - 12/31/2010). We identified 692 patients who underwent orofacial electrodiagnostic studies before 6 months of age. We excluded 398 patients treated in other hospitals; 22 patients with unilateral facial palsy

presumed of obstetrical origin; and 14 patients with isolated cleft palate. As a result, we listed 258 patients with clinical signs of bulbar dysfunction who were treated in our hospital. We excluded 59 patients with strictly isolated Pierre Robin sequence (PRS), and 24 patients lost to follow-up before 6 months of age. Following our review, we included 175 patients and collected clinical, radiological and genetic data that contributed to their diagnoses. The data were de-identified prior to analysis. Diagnoses were established after clinical examination by a neonatologist, a maxillofacial surgeon, and a clinical geneticist. Ocular, skeletal, renal, and cardiac malformations were identified by ophthalmologic examination, X-ray, and ultrasound scans. The brain was investigated by ultrasound scan, computed tomography, or magnetic resonance imaging. Upper airways were examined using laryngoscopy. A karyotype was obtained for every patient; deletion at 22q11 was tested in 166 patients. Two etiological groups were defined: (1) developmental disorders and (2) acquired brain damage. Group 1 included patients with genetic anomalies, recognizable malformation syndromes,[9] inherited metabolic diseases, or birth defects that have not been yet classified as recognizable syndromes. Group 2 included patients with hypoxic ischemic encephalopathy, birth asphyxia, premature birth <32 weeks, or fetal exposure to toxic agents.

Orofacial electrodiagnostic studies

Electrodiagnostic examinations were all performed by one of us (FR) and were part of every patient's assessment. In case of premature birth, electrodiagnostic studies were not performed before gestational age 37 weeks. Three methods, elsewhere described in detail, were combined: conventional detection needle electromyography (EMG);[10] blink responses (BRs);[11] and EMG during bottle feeding (EMGbf).[10] In short, conventional detection EMG was used to study face, tongue, and soft palate muscles, at rest and during crying stages. Traces were analyzed manually and classified as normal; neurogenic single or reduced interference pattern; or low amplitude (full interference pattern with maximum amplitude

decreased by at least 30 %). BRs were recorded in the orbicularis oculi muscle in response to the electrical stimulation of the trigeminal supraorbital nerve; the presence of R1 and R2 components and R1 latency were analyzed, considering an asymmetry of up to 3 ms to be normal. EMGbf was used to assess the pattern of suction as well as sucking/swallowing coordination. The technique consists of a two-channel recording of the genioglossus muscle for the oral phase, as well as the thyrohyoid muscle for the pharyngeal phase, while the infant was drinking sugar-water from a bottle. Normal pattern features rhythmic spindle-shaped bursts of activity separated by a quiescent period; the two muscles alternate regularly. Abnormal patterns define oro-pharyngeal incoordination as mild, where sucking is present but the alternation between sucking and swallowing is irregular; moderate, where sucking is present but the pharyngeal phase is either synchronous or at random; or severe, where the tongue does not perform rhythmic sucking activity, and the pharyngeal phase is either inactive or tonic. Results were classified as: (1) normal oro-pharyngeal coordination or mild anomalies; and (2) moderate or severe oro-pharyngeal incoordination.

Outcome measures

We recorded the need for respiratory assistance (oxygen or non-invasive ventilation during more than 1 month, and tracheostomy) and enteral feeding (tube feeding during more than 6 months, and gastrostomy); motor and sensory disabilities, behavioural disorders, and language and educational skills. Standardized neurodevelopmental evaluation was not possible given the retrospective nature of the study and the differences in durations of the follow-up period. Patients were considered as disabled when they suffered from cerebral palsy, sensory hearing loss, poor or no language, and inability to follow a scholar course, even in an adapted school. We defined the absence of disability as normal motor development and normal or slightly delayed (≤ 2 years) school course.

Statistical methods

Numeric variables are presented as mean, median, and range; categorical variables are presented as rates. Comparison of two independent groups was performed by the Mann-Whitney U-test for numeric variables and the Fisher exact test for categorical variables. Comparison of more than two groups was performed by the One-way ANOVA test for numeric variables and the $\chi 2$ test for categorical variables. All hypotheses were constructed as 2-tailed. A P value < 0.05 was considered significant.

Results:

Participants

The series included 175 patients (male: 84, female: 91). The most frequently presenting symptoms were the lack of sucking or swallowing and aspiration episodes. BW was frequently associated with facial malformations. On general neurologic examination, main symptoms were hypotonia, lethargy, and limb hypertonia. (Table 1) Excluding 8 patients who died prior to age 6 months, patients were followed up to age 2 years (25/167, 15%), from 2 to 5 years (48/167, 29%), or over 5 years (94/167, 56%). Genealogical data were available for 120 patients, including 18 born to consanguineous parents. A specific diagnosis was established for 134 patients, during the first trimester of life (110), or between 3 months and 7 years (24). The remaining patients had unidentified malformation patterns (36) or no apparent underlying disorder (5). (Table 2) Outcomes are shown in Table 1.

Electrodiagnostic studies

Median age at electrodiagnostic examination was 40 days (range: 2-180, mean: 54). Detection EMG distinguished 85 patients without any neurogenic EMG signs, and 90 patients with neurogenic EMG signs in muscles innervated by the facial nerve (82/90 patients), the pharyngeal plexus (56/90), and the hypoglossal nerve (31/90). Low amplitude traces were recorded in soft palate muscles in 36 patients, including 32 with cleft palate. BRs were abnormal in 45/175 patients, bilaterally absent (28) or asymmetrical (17). EMGbf observed

normal coordination or mild abnormalities in 63/145 (43%) patients; and moderate or severe oro-pharyngeal incoordination in 82/145 (57%). Regarding the 30 patients who did not undergo EMGbf, 23 showed clinical condition precluding all attempt to oral feeding, including 8 patients who died.

Statistical analyses

When comparing etiological subgroups - developmental disorders *vs* acquired brain damage -, outcomes were not significantly different. (Table 3) Patients with abnormal BRs showed higher frequencies of respiratory assistance (p=0.03), gastrostomy (p=0.016), and death (p=0.009) than those with normal BRs. Moderate or severe oro-pharyngeal incoordination on EMGbf was strikingly associated with the need for respiratory assistance (p=0.006), prolonged enteral feeding (p<0.0001), and gastrostomy (p=0.0004). (Table 4)

Discussion:

By assessing bulbar pathways and oro-pharyngeal coordination, orofacial electrodiagnostic studies gave relevant indicators for the management and prognostic evaluation of young infants with BW. Of 175 infants, their underlying disorders notwithstanding, BW frequently had poor outcome since 16% of the patients died and more than two thirds suffered from motor or mental disabilities. Comparing patients with developmental disorders versus acquired brain damage, the absence of statistically significant differences in outcomes suggests that BW by itself underlies long-term functional and developmental consequences. The small number of patients without apparent underlying disorders did not enable statistical comparisons; of the five, only one required prolonged enteral feeding and not any suffered from disability, as usually observed.[12] We acknowledge that our series do not include any case of hereditary motor neuropathy, congenital myopathy, or congenital myasthenic syndrome. In patients with cleft palate, low-amplitude myopathic EMG signs detected in soft palate muscles did not reveal a myopathic disease but indicated a localized developmental muscular

hypoplasia. When studying patients with specific diagnoses recognizable at birth, such as CHARGE association, Moebius syndrome, first arch syndromes, or congenital myasthenic syndromes, different authors found widely varying or facial dysfunctions and outcomes.[13-17] For patients with acquired brain damage, a possible association between early sucking and swallowing abilities and neurodevelopment outcome is still open to debate.[18] In a recent series of preterm infants, abnormal sucking behaviour at 46 weeks of post menstrual age was associated with neurodevelopment delay.[2] Thus, a prognostic evaluation of neonatal BW remains a challenge for the paediatrician. Video fluoroscopy and fiberoptic endoscopy are commonly used to evaluate oro-pharyngeal dysfunction but, to our knowledge, the association of their results with long-term outcome has not yet been established. In our practice, in the last twenty years, the use of videofluoroscopy prior to age 6 months has progressively declined due to the risk of aspiration and radiation exposure. Meanwhile, electrodiagnostic studies of bulbar muscles and cranial nerves became a routine diagnostic tool to look for bulbar involvement and investigate the mechanism and severity of dysphagia. These bulbar electrodiagnostic studies investigate paired cranial nerves VII, IX-X, and XII, the V to VII internuclear pathways, and the central pattern generator for swallowing involving the nucleus of the tractus solitarius and adjacent ventromedian reticular formation.[19] To that end, orofacial electrodiagnostic studies explore small sized brain stem structures and cranial nerves that are not routinely studied using magnetic resonance imaging (MRI).[20,21] Among patients suffering from congenital facial malformations, electrodiagnostic studies have revealed the neurological origin of dysphagia, even in the absence of neurological signs or abnormalities in brain images.[7] EMG of the genioglossus muscle has detected an associated hypoglossal nerve involvement in children with periventricular leukomalacia or hemorrhagic infarction.[22] In patients with PRS, the absence of neurogenic EMG signs in orofacial muscles characterized isoalated PRS, and EMGbf has contributed to assessing the severity and potential duration of

dysphagia.[8] Among patients with congenital multiple cranial neuropathy, detection EMG could identify bulbar involvement in patients with orofacial dysfunctions attributed to a suprabulbar vascular insult at preterm or term birth.[23]

In the present series, neurogenic EMG signs were detected in half of the patients. Curiously, frequencies and durations of respiratory assistance and enteral feeding were not statistically different in patients with or without cranial nerve involvement. These results could be explained by the predominant involvement of cranial nerve VII, while airway obstruction and aspiration result from disorders of nerves IX-X and XII. Interestingly, BRs abnormalities were significantly associated with high frequencies of respiratory assistance, gastrostomy, and death. BRs explore pathways in close proximity to the respiratory and swallowing centers and running through the reticular formation. The R_1 component of BRs corresponds to an oligosynaptic reflex arc involving at least two and not more than three synapses in the pons between the main sensory nucleus of cranial nerve V and the motor nucleus of the ipsilateral cranial nerve VII. The R_2 component follows polysynaptic medullary pathways, which are more caudal and closer to the bulbar formations. Moreover, EMGbf identified patients with moderate or severe oro-pharyngeal incoordination, who showed more needs for respiratory assistance, long-lasting enteral feeding, and gastrostomy than patients with normal coordination or mild abnormalities. Finally, orofacial electrodiagnostic studies brought prognostic indicators of neonatal BW, regardless of the underlying neuromuscular or suprabulbar disorders. This study has a limitation. Indeed, despite the large number of patients we investigated, one can appreciate that 15 years is a long spell of time and that diagnostic abilities and management have improved. In fact, our investigating protocol has remained the same during that period and all patients were able to benefit from recent diagnostic genetic tools.

To conclude, early orofacial electrodiagnostic studies do provide the paediatrician with supplementary information helping anticipate the outcome of BW, given that even if identified at birth, etiology is not the only prognostic indicator.

References

1 - Roig-Quilis M. Oromotor dysfunction in neuromuscular disorders: evaluation and treatment. In: Darras BT, Jones HR, Ryan MM, and De Vivo DC (editors). *Neuromuscular disorders of infancy, childhood, and adolescence. A clinician's approach.* 2nd edition. Elsevier; 2015. pp 958-975

2 - Wolthuis-Stigter MI, Luinge MR, da Costa SP, Krijnen WP, van der Schans CP, Bos AF. The association between sucking behavior in preterm infants and neurodevelopmental outcomes at 2 years of age. *J Pediatr.* 2015;166:26-30

3 - Newman LA, Keckley C, Petersen MC, Hamner A. Swallowing function and medical diagnoses in infants suspected of dysphagia. *Pediatrics*. 2001;108:e106-e109

4 - Hartnick CJ, Hartley BE, Miller C, Willging JP. Pediatric fiberoptic endoscopic evaluation of swallowing. *Ann Otol Rhinol Laryngol*. 2000;109:996-999

5 - Da Silva AP, Lubianca Neto JF, Santoro PP. Comparison between videofluoroscopy and endoscopic evaluation of swallowing for the diagnosis of dysphagia in children. *Otolaryngol Head Neck Surg*. 2010;143:204-209

6 - Baudon JJ, Renault F, Goutet JM, Flores-Guevara R, Soupre V, Gold F, et al. Motor dysfunction of the upper digestive tract in Pierre Robin sequence as assessed by sucking-swallowing electromyography and esophageal manometry. *J Pediatr*. 2002;140:719-723

7 - Baudon JJ, Renault F, Goutet JM, Biran-Mucignat V, Morgant G, Garabedian EN, Vazquez MP. Assessment of dysphagia in infants with facial malformations. *Eur J Pediatr.* 2009;168:187-193

8 - Renault F, Baudon JJ, Galliani E, Flores-Guevara R, Marlin S, Garabedian EN, Vazquez MP. Facial, lingual, and pharyngeal electromyography in infants with Pierre Robin sequence. *Muscle Nerve* 2011;43:866-871

9 - OMIM.org: Online Mendelian Inheritance in Man (OMIM®), an online catalog of human

genes and genetic disorders. Available at: htpp://omim.org

10 - Renault F. Facial and bulbar weakness. In: Brown WF, Bolton CF, Aminoff MJ (editors). *Neuromuscular function and disease.* Philadelphia: WB Saunders; 2001. pp 1580-1600

11 - Vecchierini-Blineau MF, Guiheneuc P. Maturation of the blink reflex in infant. *Eur Neurol*. 1984;23:449-458

12 - Heuschkel RB, Fletcher K, Hill A, Buonomo C, Bousvaros A, Nurko S. Isolated neonatal swallowing dysfunction. A case series and review of the literature. *Dig Dis Sc*. 2003;48:30-35

13 - Blake KD, Hartshorne TS, Lawand C, Dailor AN, Thelin JW. Cranial nerve manifestations in CHARGE syndrome. *Am J Med Genet*. Part A 2008;146A:585-592

14 - Cooper-Brown L, Copeland S, Dailey S, Downey D, Petersen MC, Stimson C, Van Dyke DC. Feeding and swallowing dysfunction in genetic syndromes. *Dev Disab Res Rev*. 2008;14:147-157

15 - Khan A, Hussain N, Gosalakkal J. Bulbar dysfunction: an early presentation of congenital myasthenic syndrome in three infants. *J Pediatr Neuroscienc.* 2011;6:124-126

16 - Verzijl HT, van der Zwaag B, Cruysberg JR, Padberg GW. Möbius syndrome redefined. A syndrome of rhombencephalic maldevelopment. *Neurology*. 2003;61:327-333

17 - Armangue T, Macaya A, Vazquez E, Jurado MJ, Roig-Quillis M. Central hypoventilation and brainstem dysgenesis. *Pediatr Neurol*. 2012;46:257-259

18 - Slattery J, Morgan A, Douglas J. Early sucking and swallowing problems as predictors of neurodevelopmental outcome in children with neonatal brain injury: a systematic review. *Develop Med Child Neurol.* 2012;54:796-806

19 - Lang IM. Brain stem control of the phases of swallowing. *Dysphagia*. 2009;24:333-348

20 - Quattrocchi CC, Longo D, Delfino LN, et al. Dorsal brain stem syndrome: MR imaging location of brain stem tegmental lesions in neonates with oral motor dysfunction. *Am J Neuroradiol.* 2010;31:1438-1442

21 - Sugiura H, Kouwaki M, Kato T, Ogata T, Sakamoto R, 21-Ieshima A, Yokochi K. Magnetic resonance imaging in neonates with total asphyxia. *Brain Develop.* 2013;35:53-60

22 - Vijayakumar K, Rockett J, Ryan M, Harris R, Pitt M, Devile C. Experience of using electromyography of the genioglossus in the investigation of paediatric dysphagia. *Dev Med Child Neurol.* 2012;54:1127-1132

23 - Renault F, Flores-Guevara R, Baudon JJ, Vazquez MP. Congenital multiple cranial neuropathies: Relevance of orofacial electromyography in infants. *Muscle Nerve.* 2015; Mar 3. doi: 10.1002/mus.24636. [Epub ahead of print]

Table 1: Clinical features and outcome in 175 patients with neonatal bulbar weakness

	Number of patients (%)
Orofacial presenting symptoms	
Orofacial malformations	127/175 (73)
Aspiration, choking/gaging episodes	121/175 (69)
No swallowing	115/175 (66)
No sucking	88/175 (50)
Glossoptosis	40/175 (23)
Amimia, hypomimia	25/175 (14)
Ophtalmoplegia	17/175 (10)
General neurological signs	
Hypotonia	47/175 (27)
Lethargy	27/175 (15)
Limb hypertonia	14/175 (8)
Outcome	
Respiratory assistance required during more than one month*	37/173 (21)
Enteral feeding during more than 6 months**	105/167 (63)
Gastrostomy**	65/167 (39)
Motor or mental disabilities**	118/167 (71)
Death	28/175 (16)

* 2 patients died prior to 1 month of age

** 8 patients died prior to 6 months of age

Table 2: Detection electromyography and etiology in 175 patients with neonatal bulbar dysfunction

	With neurogenic EMG signs	No neurogenic EMG signs
	90	**85**
Developmental disorders	***64***	***63***
- Chromosomal aberrations	**7**	**8**
- Recognizable malformation syndromes	**36**	**36**
Moebius	**10**	**0**
First arch	**3**	**7**
CHARGE*	**7**	**2**
Stickler	**1**	**4**
22q11 deletion	**2**	**3**
Kabuki	**0**	**3**
Noonan	**1**	**2**
Fryns	**1**	**1**
Orofaciodigital	**0**	**2**
Prader Willi	**0**	**2**
Single cases of other syndromes	**11**	**10**
- Unidentified malformation patterns **	**16**	**20**
- Inherited metabolic diseases***	**3**	**1**
Acquired brain damage	***24***	***19***
- Preterm (25-32 weeks)	**7**	**5**
- Localized brainstem ischemia	**6**	**2**
- Birth asphyxia at full term	**7**	**2**
- Fetal exposure to toxic agents	**4**	**10**
No apparent underlying disorder	***2***	***3***

* CHARGE association: colobomata, heart disease, atresia of the choanae, retarded growth and development, genital hypoplasia, and ear anomalies or deafness

** Patients showing combined malformations that are not yet classified as recognizable syndromes.

*** Including 2 patients with pyruvate dehydrogenase deficiency, 1 with abetalipoproteinemia, and 1 with dysmyelination (ADCY6 mutation)

Table 3: Outcome of neonatal bulbar weakness according to etiology*

Outcome measures (170)*	**Developmental disorders (127)**	**Acquired brain damage (43)**	***p***
Respiratory assistance > 1 month**	26	11	0.52
Enteral feeding > 6 months***	80	24	0.47
Gastrostomy***	48	17	0.86
Motor or mental disabilities***	88	30	1.00
Death	20	8	0.64

* Excluding 5 patients without an identified underlying disorder;

** Except patients who died prior to age 1 month;

*** Except patients who died prior to age 6 months;

p: Fisher's exact test

Table 4: Association of orofacial electrodiagnostic data and outcomes in 175 infants with neonatal bulbar weakness

	Detection EMG (175)			**Blink Responses (175)**			**EMG during bottle feeding (145)**		
Outcome measures	Neurogenic	Normal	*p*	Abnormal	Normal	*p*	Abnormal	Normal	*p*
	(90)	(85)		(45)	(130)		(82)	(63)	
Respiratory assistance > 1month*	23/89	14/84	ns	15/44	22/129	**0.03**	20/82	4/62	**0.006**
Enteral feeding > 6 months**	57/84	48/83	ns	28/40	77/127	ns	59/79	23/60	**<0.0001**
Gastrostomy**	36/84	28/83	ns	22/40	42/127	**0.016**	34/79	9/60	**0.0004**
Motor or mental disabilities**	59/84	59/83	ns	29/40	89/127	ns	53/79	41/60	ns
Death	19	9	ns	13	15	**0.009**	14	6	ns

*Except patients who died prior to age 1 month; **except patients died prior to age 6 months; *p*: Chi-squared test