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Research Article

Voice Analysis in 63 Italian Cri du Chat Patients

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Abstract

Objectives: The aim of our work was to identify, specific abnormalities in vocal pattern, eventually actionable to logotherapy, in patients with Cri du Chat Syndrome (CdC) who present a peculiar, abnormal cry in newborns, possibly explained by anatomical or neurological alterations. **Study Design**: It is a descriptive study with a prospective collection of voice profile data. **Methods:** We recorded the data relative to fundamental frequency (Fo), stiff vocal attachment, intelligibility by the listener, and diplophonia. Spectrographic analysis was performed using a Computer Speech Lab recording system and the speech analysis package XYZ. **Results:** We report on voice analysis in a group of 63 Italian CdC patients: 28 infants and children (15 males) and 35 adults (20 males). No differences were observed between sexes in the mean age of onset of linguistic production, which was 2 years 4 months for males and 2 years 11 months for females. The mean and SD of Fo in infant and children CdC showed that 5/13 females, and 6/15 males were below normal limits. All adult CdC females, but one, showed Fo within normal limits; Fo is increased above the normal range in all but one adult CdC male. The percentage of stiff vocal attachment increases with age, as it is present in 30/40% of F/M infants and 66/65% of F/M adults. Intelligibility by the listener improves with age in both sexes. Forced voice was present in 46.6% of infants and 65% of adult males and 30.7% and 66.6% in infant and adult females, respectively. Diplophonia was present only in adults, in 15% and 20% of males and females, respectively. **Conclusion:** Any improvement in verbal communication, even within a picture of developmental delay, may result in favorable improvement of social relationship. We comment also on the relevance of a personalized logopedic therapy, to be started as early as possible in childhood, and to be continued also in older ages.

Keywords: Cri du Chat syndrome; Voice analysis; Speech development; High pitched voice; Larynx anomaly

Introduction

Cri du Chat Syndrome (CdC) was named after the observation of a peculiar, abnormal cry in newborns affected by 5p deletion syndrome [1]. Niebuhr reviewed data available at that time about the characteristic and possible etiologies of this symptom in a group of more than 300 patients [2].

The characteristic cat-like cry was interpreted as related to anomalies of the larynx (small, narrow, diamond-shaped) and epiglottis (flabby, small, hypotonic), as well as to neurological, structural and functional alterations [2]. For instance, malformations of the cranial base suggest associated abnormalities of the rhombencephalic brain region and of the larynx during embryonal development [3].

Indeed, brain-imaging evidence implicates a vast neural network for speech production: the supplementary motor area and the cingulate motor area are connected with the primary motor cortex; subcortical activation is in the thalamus, in the basal ganglia, in the red nucleus and in the cerebellum. Additionally, the posterior temporal gyrus was activated during speech production in both hemispheres. In the brainstem, areas such as the nucleus

hypoglossus are innervated during speech production. Cortical regions work with the basal ganglia, thalamus and cerebellum in speech control [4]. A recent paper [5] identified a small region, 5p15.2, included in the 5p- deletions as related to a high-pitched voice in CdC patients, although the data are not fully conclusive.

However, because words and voice are the final result of the work of lungs (producing adequate airflow and pressure), vocal cords (whose vibration creates audible pulses) and other parts of the vocal tract such as the tongue, palate, cheek, lips, etc.), and their physiological coordination, it is very difficult to analyze the relevance of each single component [6]. A number of papers have previously discussed some parameters of voice formation in CdC patients, but most of them were case reports, discussed a small number of cases and are not immediately comparable to our work [7-10].

We decided to study the voice and verbal communication of CdC patients in a large sample of cases, recruited through the collaboration of A.B.C. (Associazione Bambini Cri Du Chat, Italian Association of Children with Cri Du Chat), using modern technologies to obtain more objective analysis parameters. The aim of this type of analysis is to provide data that are potentially useful to develop updated methods to ameliorate patients' communication skills.

Material and Methods

During the A.B.C family meetings held from 2014 to 2018, we evaluated the voice of 63 consecutive Italian CdC patients; for all of them, the diagnosis of Cri du Chat syndrome was obtained by karyotype studies, showing a terminal deletion of the short arm of chromosome [5]. As array CGH is available only in a minority of cases, the ones with the most recent diagnoses, we did not attempt a correlation between clinical and molecular data.

For each patient we collected anamnestic data, including sex, age, and the mean age at which the patients were able to achieve holophrasic language, and performed phoniatric evaluation.

We performed voice recording (for each patient, separately, in a quiet room without background noise and in the presence of parents) and spectrographic analysis using a Computer Speech Lab recording system (CSL 4500- Kay Elemetrics Corp [2]. Bridgewater Lane, Lincoln Park, NJ 07035, USA), using the Speech analysis package XYZ.

We recruited patients on a voluntary basis, among those participating in ABC family meetings, without any selection for sex, age or karyotype. Data from available patients were grouped according to sex and age (Table 1), and normal values were obtained from the literature [11].

In voice analysis, we recorded the data relative to fundamental frequency (Fo) (normal values: 175-245 Hz as in Mathieson [12]), number of harmonics, background noise, stiff vocal attachment and forced voice, intelligibility by the listener, melodic monotony, oral disorders, deficient mastication, hypernasality, untimbred voice, and diplophonia.

The study was proposed by the Scientific Committee and approved by the Ethical Review Board (ERB) of the Associazione Bambini Cri du Chat. Parents of each patient provided written informed consent after receiving a detailed description of the study's methods and aims.

Details about the results of phoniatric analysis of each patient are available as anonymized data.

Results

In Table 1, we report the demographic data of the patients studied, and a summary of voice analysis for the whole group of cases.

	Infant and Children	**Infant and Children**	**Adults**	**Adults**
	males	**females**	**males**	**females**
Number	15	13	20	15
Age (years)	(1-13)	(6-11)	(14-38)	(18-48)
Reduced number of harmonics	9	11	7	7
Background noise in sound spectrograms	9	7	7	8
Stiff vocal attachment, forced voice/glottal stop	7	4	13	10
Intelligibility (in relation to the recording of words and phrases –see table 2)	1	1	4	5
Melodic monotony	1	1	4	5
Oral disorders, deficient mastication/swallowing	5	5	6	6
Hypernasality	1	2	5	4

Untimbred voice	0	1	3	1
Diplophonia	0	0	3	3

Table 1: Age, sex and results of voice analysis of 63 Italian CdC patients.

In Table 2, we enter the results of Fo, which is the frequency at which the vocal cords are opening and closing; it was recorded for the four groups of cases, in relation to their ability to form sentences, single words or single syllables or vowels.

	Infant and Children	**Infant and Children**	**Adults**	**Adults**
	males	**females**	**males**	**females**
Number of patients	15	13	20	15
Type of verbal communication				
Sentences: N of patients (fundamental frequency, Hz: mean ±SD; range)	2 (208,0±14,1; 198-218)	2 (216,0±33,2; 193-240)	7 (217,2 ± 9,23; 194-227)	6 (201,0±21,8; 173-240)
Single words: N of patients (fundamental frequency, Hz: mean ±SD; range)	6 (214,5±13,6; 202-234)	3 (213,3±20,2; 195-235)	10 (200,5± 21,2; 178-235)	7 (192,5±18,9; 166-220)
Vowel emission/syllables: N of patients (fundamental frequency, Hz: mean ±SD; range)	7 (213,8±14,5; 193-236)	8 (214,9±15,9; 201-251)	3 (157,7±47,1; 112-206)	2 (196±15,5; 185-207)
Normal values, range			105-160	175-245

Table 2: Results of fundamental frequency (Fo) analysis of 63 Italian CdC patients. Normal values from L. Mathieson. [12].

No differences were observed between sexes in the mean age of onset of linguistic production: the mean age of acquisition of holophrasic language (calculated on the total number of cases able to achieve it), was 2 years and 4 months for males (n 18, range 1-6 years) and 2 years and 11 months for females (n 12, range 1-6 years). Similarly, at ages above 2 years, 81.8% (27/33) of males were able to produce single words or sentences, compared to 87.4% (21/24) of females.

Six patients (two males and four females) were not evaluated because their ages were less than 2 years. For infants and children, Table 2 shows the mean and SD of Fo, separately for males and females, for each type of verbal communication. Comparison with age-specific controls, showed that in females 8/13 fell within normal limits (175-245 Hz), while 5/13 were below. Similarly, in males 9/15 were within normal limits and 6/15 were below.

All adult CdC females showed Fo within normal limits (175-245 Hz) for sentences and vowels or syllables, with only one case slightly below the normal range for single words; Fo is increased above the normal range (105-160 Hz) in all but one adult CdC male, for all groups of voice emission (sentences, single words, vowels or syllables).

A reduced number of harmonics causes a more monotonous and less intelligible voice: it is present in 60% of male infants and 84% of female infants, while a similar reduction is present in 35% of male adults and 46% of adult females.

Background noise is more common in male infants than in females (60% vs. 53%), and improves with age, but only in males (adult males 35%) while it remains stable in females (adult females 53 %).

The percentage of stiff vocal attachment increases with age, as it is present in 30/40% of F/M infants and 66/65% of F/M adults. Intelligibility by the listener (in relation to the recording of words and phrases, see Table 2) improves with age in both sexes, ranging from 12.5% to 23.5% in males, and from 20% to 38.4% in females (see Tables 1 and 2).

Melodic monotony also changes with age, with similar figures. Forced voice was present in 46.6% of infants, 65% of adult males, 30.7%, and 66.6% in infant and adult females, respectively. Hyper nasality was present in 6.6% and 25% of infant and adult males, respectively, and in 15.3% and 26.6% of infant and adult females, respectively. Untimbred voice was present in a very limited number of cases (Table 1). Diplophonia was present only in adults, in 15% and 20% of males and females, respectively. Oral disorders, deficient mastication and swallowing are present in approximately 30% of cases, without any differences with age.

Discussion

Acoustic digital analysis of verbal signals provides information on features such as frequency, intensity, harmonic structure and formantic. The non-invasive modality of this kind of analysis makes it feasible for pediatric patients as well as in

patients affected by developmental delay. Furthermore, it can be performed in a short period of time, thus overcoming the problems of reduced attention and/or concentration.

It is possible to record what the child can say, and even the emission of a prolonged vowel. Spectrographic analysis considers the coordinated functioning of the respiratory tract, larynx and vocal cords, mouth and tongue muscles, pharynx, oral cavity, nasal and paranasal sinuses.

Finally, voice analysis can be used to follow changes during logopedic treatment, so that it can be used to evaluate its efficacy and success. It appears that in children the voice is often low pitched in comparison to controls, and modifies with age, with females reaching the normal range, while adult males still have high pitched voice.

With respect to the reduced number of harmonics, there is an improvement with age, but for both sexes, an impairment is still present in consistent percentage of cases. The likelihood of improving this parameter is limited because the presence of cognitive impairment hampers conscious communication. Background noise (Table 1) is the expression of dysfunction in voice production and emission, and as it may be caused by different problems, in this set of patients might be related mainly to postural problems. In fact, many patients usually keep their head slightly bent forward; thus, postural improvement may be of helpful.

The changes in stiff vocal attachment with age are related to pneumofonic incoordination, and seem to worsen with age. Intelligibility by the listener as well as melodic monotony is always slightly better for females than males at any age, and might be improved by asking the patient to repeat the nursery rhyme.

The increase in the percentage of CdC patients showing forced voice/glottal stop with age might be related to the development of kyphosis/scoliosis in many of them. Additionally, hypotonia is common in patients with CdC, although it is more frequent in younger patients, [13] and hypotonia of oral and tongue muscles has been frequently observed in our group of cases.

Oral dyspraxia is related to dyspraxia of muscles in the mouth and tongue, and in turn is related to difficulties in expressing phonemes, and generally does not change with age. Hypernasality increases with age, so we suggest that this modification might be related to the concurrent changes in facial morphology; in fact, in all patients, the round face observed in childhood consistently changes finally resulting in an elongated face after puberty [14]. The relevance of laryngeal abnormalities as the cause of neonatal high-pitched voice has been attributed to morphological laryngeal alterations in the first published cases [15]. Subsequently, a number of different laryngeal abnormalities [13,16], or no abnormalities were reported in a number of cases; [2] therefore, a central origin was taken into consideration. Kjaer and Niebuhr [3] discussed the possibility of the involvement of a cranial developmental field from which neurons migrate to the larynx.

Untimbred voice and diplophonia are seldom observed and are likely related to general neurological disturbances. It is well accepted that the human vocal tract makes use of pre-existing mechanisms of control of the breath, and of the activity of mouth, tongue, glottis and larynx inherited from ancestral species. The quality of vocal sounds results from vibratory resonance with movable tissues and air pockets throughout the head and torso.

In terms of spoken language, speech and language input (speech perception and comprehension) is processed by both brain hemispheres, whereas language output (the planning and control of speech) is weighted toward the left hemisphere in more than 90% of the population [4].

Furthermore, two different language systems (lexical/semantic and grammatical) are correlated with the activity of two distinct brain areas of the left hemisphere (temporal and frontal, comprising inferior frontal regions: Broca's area and more anterior parts, and superior and middle temporal regions: Wernicke's area) and are mediated by different learning processes (explicit and implicit memory) [17]. With regard to the cerebellum, this structure determines verbal fluency, expressive and receptive grammar processing, the ability to identify and correct language mistakes and writing skills, via neuroanatomical connectivity with frontal and prefrontal regions [18].

The only anatomical and functional available observation in patients with CdC was provided by Cistaro, et al. using (^{18}) F-fluorodexyglucose PET, who observed in six cases that the main hypometabolic region detected was the left inferior temporal and homolateral temporal pole cortex (Broadman area 20, 34 36, 38) [19]. These regions are involved in verbal production and comprehension, working memory and selective attention to speech. Furthermore, the left Broadman area 20 is involved in the process of language associations and perceptual skills. In addition, hypometabolism was also detected in the right frontal subcallosal gyrus (BA 34) and the caudate body and in the cerebellar tonsils.

Currently the pathogenesis of voice abnormalities in Cri du Chat patients is associated not only with anatomical alterations in the epiglottis and larynx but also with structural and/or functional neurological alterations [20]. The frequent observation of postural abnormalities and stiffness of thoracic and abdominal muscles may also play a relevant role. Based on our set of data obtained by spectrographic analysis of voice, anamnestic records, and phoniatric evaluation, we fully support this hypothesis.

In fact, laryngoscopic examination, showed mostly transient hypotonia in the cases studied with normalization at follow-up. Laryngoscopic examination was not performed within this study, but data available for Italian patients undergoing anesthesia, confirms that it is nor a major problem [21].

In our opinion, voice abnormalities are more likely related to hypotonia of the upper aerial and digestive tracts in addition to oral dyspraxia and to the swallowing difficulties present in a high percentage of cases13 and often persists in adulthood. Altogether, these factors modify the resonance in the upper part of the larynx.

A higher Fo with wide ranges, impairment of vocal function, increased background noise, and alterations of harmonics are all expressions of a dynamic system more likely to be dysfunctional, and thus with a central origin of the problem.

After grouping patients as a function of age (Table 1 and 2), we speculate that CdC cases in whom verbal skills are present, show mainly severe problems in coordination of all the systems needed for voice production.

Certainly, genetic factors play a relevant role and a recent paper by Chehimi, et al. attempted to recognize a region of minimal overlapping of the deletion associated to the cat cry [5]. Previous studies have suggested the possible involvement of genes such as MARCH6, FLJ25076, ADAMTS16, and ICE1 located in different regions (5p15.2), (5p15.31) and (5p15.32), respectively, but the relevance of the effect of each single gene is far from being defined.

In our experience, about 2/3 of CdC patients are able to pronounce at least one single word, but many of them reach only very limited verbal communication, despite logopedic therapies [22]. In the cases we studied, who are representative of the average available Italian medical assistance for the CdC population, logopedic care has been always late, short-timed and not intended to modify specific voice abnormalities.

In conclusion, it is likely that a different approach, based on the early initiation of logopedic treatment, associated with voice analysis and finalized, in a personalized way, to improve, modify or correct specific abnormalities, might give much better results in the future. Of course, logopedic treatment should be continued in adolescent and adult ages, also establishing synergic work between professionals, parents, teachers and other supporting personnel.

In general, the knowledge of specific voice emission problems related to each patient is likely to be helpful in improving verbal communication in the future. We expect the efficacy of logopedic treatment to be maximal if coordinated with all other support therapies, including correction of postural abnormalities and other physiatric alterations (Table 3). Even if the results seem to be limited, logopedic treatment should be started early, and better coordinated, if possible, with additional specific voice emission treatments. The global evaluation of patient's development will indicate if and how much nonverbal communication will be of help in everyday life.

Abnormal posture
Stiffness of thoracic and abdominal muscles
Pneumophonic incoordination
Oral breathing
Deficient mastication and swallowing
Buccolingual dispraxia

Table 3: Physiatric alterations observed in 63 Italian CdC patients and interacting with vocal and verbal production.

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Conflict of Interest

The authors have declared that no competing interests exist.

Authors Contributions

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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