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Original article

The natural history of Cri du Chat Syndrome. A report from the Italian Register

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Abstract

The aim of this report is to provide an update on the natural history of the Cri du Chat Syndrome by means of the Italian Register (I.R.). Two hundred twenty patients were diagnosed by standard cytogenetic methods and 112 of these were also characterised by molecular-cytogenetic investigation (FISH). FISH analysis showed interstitial deletions, short terminal deletions and other rare rearrangements not previously correctly diagnosed by standard cytogenetics. The diagnosis was made in the first month of life in 42% and within first year in 82% of cases. The remaining 18% were diagnosed at an age ranging from 13 months to 47 years. At the last follow-up, patient age ranged from 8 months to 61 years. Mortality, already low, has decreased over time as it is lower between 1984–2002 compared to 1965–1983. Mortality was higher in patients with unbalanced translocations resulting in 5p deletions. Our data confirm that the cat-like cry and peculiar timbre of voice are the most typical signs of the syndrome, not only at birth but also later and these are the only signs which might suggest the diagnosis in patients with small deletions and mild clinical picture. A cytogenetic and clinical variability must be underlined. Cardiac, cerebral, renal and gastrointestinal malformations were more frequent in the patients with unbalanced translocations resulting in 5p deletions. Sucking and feeding difficulties and respiratory infections are frequent in the first months or years of life. Intubation difficulties linked to larynx anomalies must be considered. Psychomotor development is delayed in all patients but there is a variability related to deletion size and type as well as other genetic and environmental factors. However, the results showed an

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improvement in the acquisition of the development skills and progress in social introduction which should encourage caregivers and parents to work together in carrying out the rehabilitative and educational interventions.

Keywords: Cri du Chat syndrome; Cri du Chat syndrome natural history; 5p deletion; FISH; Mental retardation

1. Introduction

The Cri du Chat Syndrome (CdCS), first described by Lejeune et al. [30] in 1963, is a chromosomal disorder resulting from the deletion of the short arm of chromosome 5. The size of the deletion ranges from the entire short arm to the region 5p15.3 (5–40 Mb) [39,47]. Hallmark clinical features include a high-pitched cat-like cry, microcephaly, a distinct facial phenotype and severe psychomotor and mental retardation. The incidence is low, ranging from 1:15,000 [27] to 1:50,000 [37] live-born infants, but it is probably the most common autosomal deletion syndrome in humans [46]. Following the description of the syndrome, several clinical and cytogenetic studies in patients were reported [6,7,20,21,35–38,51]. After these initial reports, few studies have been published, principally because of the rarity of the syndrome and most of these were on isolated cases presenting clinical or cytogenetic peculiarities.

Molecular-cytogenetic analysis by fluorescent in situ hybridisation (FISH) has renewed the interest in this syndrome and allowed a molecular and phenotypic map of 5p to be defined [12,13,25,26,39]. Two genes, Semaphorine F (SEMAF) [48] and δ-catenine (CTNND2) [34], mapped to the "critical regions", and are potentially involved in cerebral development and thus their deletion may be associated with mental retardation. Recently the telomerase reverse transcriptase (hTERT) gene has been localised in 5p15.33 and its deletion might contribute to the phenotypic changes in CdCS children [55].

A clinical and molecular characterisation of 80 Italian patients in order to perform a phenotype-genotype correlation revealed clinical and cytogenetic variability. The identification of phenotype subsets associated with specific size and type of deletion is of diagnostic and prognostic relevance and allows a more personalised evaluation of each patient [10]. Early data on psychomotor development in institutionalised patients were discouraging [3,37]. Studies on home-reared patients who underwent early educational treatments demonstrate a better prognosis [5,15,17,50]. A specific psychomotor development chart on the Italian patients [9] and growth charts by a multi-centre international study [33] have been elaborated. A review on CdCS was also published [11]. FISH analysis with BAC clones in a patient without typical CdCS features, permitted a correlation of cat-like cry and mild mental retardation with a deletion in 5p15.31 at 8.5 Mb from the short arm telomere [45]. A recent genotype-phenotype relationship study using array comparative genome hybridisation enabled a refinement of the critical regions and confirmed the increase of mental retardation with the deletion size and type [56]. Another study by quantitative PCR allowed a further narrowing of the critical region for the cat-like cry and the characterisation of three candidate genes [53].

The aim of this paper is to further report on the natural history of CdCS in a large series of patients from the hospital-based Italian Register (I.R.) of the syndrome. The I.R., set up in the 80s (PCM), currently collects information on over 220 patients. Up to date clinical data in-

creases our knowledge of this syndrome and may be helpful in implementing guidelines to better assist the patients.

2. Material and methods

2.1. Patients and methods

The data of 220 patients of the CdCS I. R. up to June 2002 were analysed. The data included information provided by cytogenetic laboratories, genetic counselling services and paediatric units and the Italian Cri du Chat Children's Association. The information was collected by means of an ad hoc form that includes demographic and anthropometric data at birth and at later follow-up, clinical features of childhood and adult age, major and minor malformations and other medical problems, the institute where the diagnosis was made and cytogenetic reports. Moreover laboratory analyses, clinical documents and photos were available. Not all questionnaires provided information of all sections; therefore the total number of patients for which data were recorded is specified in each section of the results (text and tables). The patients were selected on the basis of clinical suspicion, confirmed by cytogenetic examination. They were included in the I.R. even if their personal and clinical data were incomplete because the inclusion criterion was a cytogenetic diagnosis. Of 137 patients in active follow-up, 123 were followed by the same clinician (PCM) and 14 by other doctors.

Two hundred twenty patients were diagnosed by standard cytogenetic methods and 112 of these were also characterised by FISH, 85 using phage probes [10] and 27 using YAC probes, previously mapped to 5p [32,41]. YAC DNAs were labelled by nick-translation with biotin-16 dUTP (Boehringer-Mannheim). FISH was performed as described by Lichter and Cremer [31]. Slides were counterstained with 4′,6-diamidino-2-phenylindole (DAPI) (200 ng/ml) and analysed and photographed by Power Gene 8860 (PSI, UK).

The patients with unbalanced translocations resulting in 5p deletions were studied separately from those with isolated deletions with regard to familial and neonatal data, survival, malformations, medical problems and psychomotor development in order to verify the greater severity reported in a previous study [51].

Clinical data were available for 185 patients: 159 with an isolated deletion (150 with a terminal deletion, one with a terminal deletion resulting from a paternal inversion, one with a terminal deletion with paternal mosaicism and seven with interstitial deletions), all showing typical CdCS facial features, and 26 patients with an unbalanced translocation resulting in a 5p deletion. The latter were excluded from the evaluation of the facial dysmorphism because of the possible phenotypic effect of the associated partial trisomy of another chromosome. Likewise, three patients with mosaicism that were previously reported [40] and one patient with a ring chromosome were excluded from the clinical analysis because of the misleading effect of these complex rearrangements on the phenotypes.

Evaluation of psychomotor development was performed using the Denver Developmental Screening Test II (DDTS II) [24]. The detailed method was previously reported [9]. All clinical, genetic and developmental data were collected in a database and statistical analysis was performed using the χ^2 test with Yates' correction.

Informed consent was obtained for all the individuals and their parents. Publication of the material included in this work has been authorised according to the terms of the Italian privacy law 196/03.

3. Results

3.1. Age and sex distribution

The distribution of 220 patients for age, year of birth, sex and vital status is reported in Table 1. Sex ratio M:F at diagnosis was 0.82. The sex ratio decreased from 0.89 for patients diagnosed in the period 1965–1983 (period I) to 0.75 in the period 1984–2002 (period II). The age ranged from 8 months to 61 years at the last follow-up or at death. One hundred thirty-three patients out of 137 in active follow-up were home-reared, four were institutionalised. The number of patients in our Register born in period I was 99 compared to an expected number of 274 (based on an estimated incidence of 1:50,000 live births) while in period II it was 109 (expected value = 205) ($P < 0.05$).

3.2. Cytogenetic and molecular-cytogenetic analyses

The results of cytogenetic and molecular-cytogenetic analyses performed in 220 patients are summarised in Table 2. All 220 patients are deleted for at least the CdCS critical region in 5p15.2 [39]. The size of deletion ranged from 5p15.2 to 5p11 (Fig. 1).

3.3. Age of the diagnosis

The precise age at diagnosis was available for 193 patients and was within the first month of life in 82 (42.5%) (including one prenatal diagnosis for advanced maternal age), before three months of age in 114 (59.1%) and between the fourth and 12th month in 44 (22.8%). In total, 158 patients (81.9%) were diagnosed in the first year of life, 35 (18.1%) at an age ranging from 13 months to 47 years. In the period 1984–2002 the percentage of diagnosis in the first month of life was higher than in the period 1965–1983 ($P < 0.05$) (Table 3).

Table 1
I.R. for CdCS. Age grouping, period of birth, sex distribution and vital status for 220 patients as at 2002

Age grouping (years)	Year of birth	Total	%	*M*	*F*	Dead	Patients in active follow-up
0–4	2002–1998	17	7.7	8	9	1	16
5–9	1997–1993	35	15.9	13	22	0	34
10–14	1992–1988	38	17.3	17	21	1	33
15–19	1987–1983	28	12.8	15	13	1	17
20–24	1982–1978	24	10.9	12	12	2	11
25–29	1977–1973	39	17.7	12	27	2	18
30–34	1972–1968	18	8.2	10	8	5	2
35–39	1967–1963	17	7.7	9	8	1	4
40–49	1962–1953	2	0.9	2	0	1	1
50–59	1952–1943	0	/	0	0	0	0
60–69	1942–1931	1	0.5	0	1	0	1
Data not available	/	1	0.5	1	0	0	0
Totals		220	100.0	99	121	14	137

Table 2
I.R. for CdCS. Cytogenetic and molecular-cytogenetic analyses for 220 patients

Chromosomal rearrangements	Total patients	%
Terminal deletions [a]	180	81.8
De novo interstitial deletions [b]	7	3.2
Familial translocations [c]	17	7.7
De novo translocations [c]	10	4.5
Terminal deletions from a paternal inversion	1	0.5
Terminal deletions from a paternal mosaicism	1	0.5
Mosaicism	3	1.4
Ring chromosome	1	0.5
Total	220	100.0

[a] For 45 patients data are not available for both parents.
[b] Seven out of 112 patients analysed by FISH.
[c] Patients with unbalanced translocations resulting in 5p deletions.

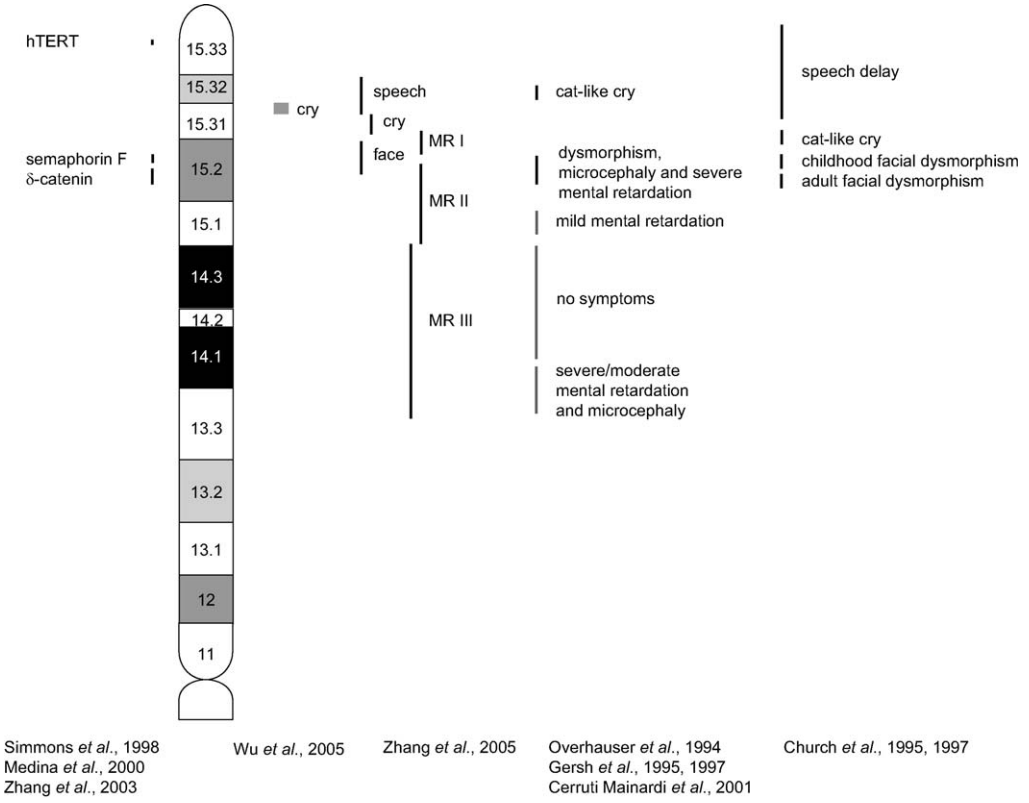

Fig. 1. Phenotypic map of 5p for the critical regions for the cry and for other signs of CdCS. MR, mental retardation, increasing in severity from MR I to MR III. Vertical grey lines in p15.1, p14 and p13 refer to clinical symptoms reported in individual families with interstitial deletion. Chromosome bands are reported according to ISCN (1995) [28].

Table 3
I.R. for CdCS. Age of diagnosis for 193 patients [a] in the period 1965–2002

Age of diagnosis	Number of patients	%	Periods of diagnosis			
			1965–1983	%	1984–2002	%
In the first month	82	42.5	28	32.9	54	50.0[b]
2–12 months	76	39.4	36	42.4	40	37.0
13 months-5 years	26	13.5	17	20.0	9	8.3[b]
Over 6 years	9	4.7	4	4.7	5	4.6
Total	193	100.0	85	100.0	108	100.0

[a] Patients with precise diagnosis age available (156 with terminal deletions, seven with interstitial deletions, 26 with unbalanced translocations resulting in 5p deletions, three with mosaicism and one with ring chromosome).
[b] $P < 0.05$.

3.4. Family and neonatal data

In the period 1965–1983 the mean maternal and paternal age at birth, available for 46 patients with isolated deletions, was respectively 27 years and 7/12 (standard deviation (S.D.) = ± 5 years and 2/12) and 32 years and 6/12 (S.D. = ± 5 years and 10/12). In the period 1984–2002 the age for the 74 patients with isolated deletions was respectively 29 years and 7/12 (S.D. = ± 5 years and 2/12) and 33 years and 11/12 (S.D. = ± 7 years and 2/12). The mean gestational age for 126 patients with isolated deletions was 38 weeks and 5 days (S.D. = ± 2 weeks and 1 day). The mean birth weight, for 151 patients with isolated deletions was 2614 g (S.D. = ± 483 g), the mean length was 46.9 cm (S.D. = ± 3.5 cm) in 92 patients with isolated deletions and the mean head circumference at birth was 31.8 cm (S.D. = ± 2.1 cm) in 86 patients with deletions. There were no significant differences for the 27 patients with unbalanced translocations resulting in 5p deletions.

3.5. Survival

The death of 14 patients out of 220 has been reported (6.4%, seven males and seven females) (Table 4). Nine patients had a terminal deletion and five had an unbalanced translocation resulting in a 5p deletion (three familial, two de novo). Mortality was higher in patients with unbalanced translocations resulting in 5p deletions (5/27 = 18.5%) than in those with terminal deletions (9/189 = 4.8%) ($P < 0.05$). Eleven out of 106 patients (10.4%) diagnosed in the period 1965–1983 died compared to only three out of the 114 (2.6%) diagnosed in the period 1984–2002 ($P < 0.05$).

3.6. Clinical features I and II

Table 5 reports the facial dysmorphism and other typical features observed at diagnosis in 159 patients with isolated deletions, for which the data were available. Included are follow-up data in 49 out of 159 patients. Changes in clinical features with age are reported in Table 6.

Table 4
I.R. for CdCS. Causes of death of 14 patients

ID number	Age at death	Causes of death	Karyotype
38	1 day (1975)	Respiratory insufficiency	46,XX,del(5p→pter)
86	2 months (1986)		46,XX,del(5)(p13→pter)
45	1 day (1968)	Congenital cardiopathy	46,XXdel(5)(p12→pter)
47	1 year (1975)		46,XX,–5,+der(5)t(1;5p) fam
49	4 days (1979)		46,XY,–5,+der(5)t(5p;X) de novo
87	4 days (1982)		46,XX,–5,+der(5)t(5;8)(p11;p11) mat
91	1 day (1991)		46,XX,–5,+der(5)t(5;16)(p15.1;q24) pat
4	14 months (1965)	Respiratory infection	45,XY,–5,+der(5)t(5p;15) de novo
12	5 months (1970)		46,XY,del(5p→pter)
63	16 years (1984)	Intestinal occlusion	46,XY,del(5p→pter)
27	29 years (1983)	Hepatitis	46,XY,del(5)(p13→pter)
64	14 years (1984)	Convulsions, tachycardia, cardiopathy	46,XY,del(5p→pter)
185	3 months (1999)	Sudden death	46,XY,del(5)(p14→pter)
15	6 years (1976)	Unknown	46,XX,del(5p→pter)

ID: identification.

Table 5
I.R. for CdCS. Clinical features (I)

	159 patients [a] at diagnosis	%	49 patients [b] at diagnosis	%	49 patients [b] > 15 years	%
Facial features						
Round face	96/115	83.5	29/31	93.5	1/48	2.1
Prominent metopic bossing	58/82	70.7	16/21	76.2	12/41	29.3
Broad nasal bridge	102/117	87.2	31/35	88.6	28/43	65.1
Lateral downward slanting palpebral fissures	70/123	56.9	21/38	55.3	14/47	29.8
Hypertelorism	105/129	81.4	34/41	82.9	29/46	63.0
Epicanthal folds	119/132	90.2	39/43	90.7	27/48	56.2
Strabismus divergent/ convergent	48/101	47.5	18/34	52.9	21/47	44.7
Short philtrum	52/86	60.5	15/23	65.2	43/49	87.8
Down turned corners of the mouth	81/100	81.0	31/32	96.9	27/42	64.3
Low-set ears	81/116	69.8	21/30	70.0	15/46	32.6
Microretrognathia	119/123	96.7	37/38	97.4	33/46	71.7
Other clinical features						
Typical cry/acute voice	141/147	95.9	46/48	95.8	30/45	66.7
High arched palate	62/74	83.8	13/14	92.9	23/40	57.5
Short neck	41/73	56.2	7/15	46.7	10/39	25.6
Transverse flexion creases	103/112	92.0	38/40	95.0	38/40	95.0
Hypoplasia thenar eminence	42/57	73.7	10/14	71.4	26.35	74.3
Small pelvis	31/42	73.8	4/7	57.1	13/24	54.2
Diastasis recti	43/56	76.8	5/8	62.5	20/27	74.1
Hypotonia	78/108	72.2	34/35	97.1	1/40	2.5

[a] 159 patients with isolated deletions (152 with terminal deletions and seven with interstitial deletions) for which the data were available.

[b] Longitudinal study on 49 out of 159 patients (47 with terminal deletions and two with interstitial deletions) for which it has been possible to evaluate the persistence of the clinical features in time.

Table 6
I.R. for CdCS. Clinical features (II)

	50 patients[a] > 15 years	%
Facial features		
Thin/long face	34/48	70.8
Asymmetric face	16/45	35.6
Supra-orbital arch prominent	13.42	31.0
Long/coarse nose	18/39	46.2
Full lower lip	19/42	45.2
Dental malocclusion	36.48	75.0
Other clinical features		
Miopia	5/34	14.7
Short metacarpals	38/46	82.6
Short metatarsals	30/40	75.0
Scoliosis	20/47	42.6
Muscle hypotrophia	6/37	16.2
Hypertonia/hipereflexia	28/38	73.7
Pes planus	27/43	62.8
Premature greying	14/46	30.4
Normal sexual development	46/48	95.8
Hyperactivity	18/47	38.3

[a] Adolescent and adult patients (48 with terminal deletions and two with interstitial deletions) for whom the data were available. These patients include the 49 patients of Table 5.

3.7. Clinical features III

A malformation was present in 185 patients (159 with isolated deletions and 26 with unbalanced translocations resulting in 5p deletions) (Table 7). Both maximal and minimal percentages were always higher in patients with unbalanced translocations resulting in 5p deletions than in those with an isolated deletion; for the minimal percentage the difference was significant for cardiac, cerebral and renal anomalies ($P < 0.05$). The frequency of cardiac, cerebral, renal and gastrointestinal anomalies observed in all patients, independently of the type of deletion, was 19% in the period 1965–1983 and 66% in the period 1984–2002 ($P < 0.01$).

3.8. Medical problems

Data about medical problems, surgical operations and hospitalisation are reported in Table 8. One hundred fifty-nine patients with isolated deletions, for which data were available, were evaluated. There were no significant differences for 26 patients with unbalanced translocations resulting in 5p deletions.

3.9. Psychomotor development

The evaluation of the psychomotor development (Denver Test II [24,42]) was performed separately in 103 patients with an isolated deletion and in 13 with an unbalanced translocation. The results for 103 patients with isolated deletions are reported in Fig. 2. The youngest reported age of independent walking was 15 months, the median age was 3 years and all children learned to walk. Forty-four patients out of 103 (42.7%) were able to form sentences, the first at 18 months, 25% at 4.5 years, the median age was 5.5 years and 86.4% by 10 years of

Table 7
I.R. for CdCS. Clinical features (III) [a]

	Isolated deletion [b]	% max [c]	% min [d]	Malformations	Translo-cation [b]	% max [c]	% min [d]	Malformations
Congenital heart disease	29/81	35.8	18.2 [e]	IVD 14, IVD + IAD 1, IVD + aortic valve stenosis 1, PDA 6, IAD 3, IAD + pulmonary valve stenosis 1, Tetralogy of Fallot 1, aortic valve stenosis 1, not specified 1.	11/19	57.9	42.3	PDA 3, IAD 3, IVD 1, IVD + pulmonary valve stenosis 1, not specified 3.
Neurological abnormalities	17/57	29.8	10.7 [e]	H/ACC 5, ACC + scarce white matter myelination 1, ACC + brainstem hypoplasia 1; ACC + cerebellar hypoplasia 1, cerebral atrophy 5, cerebral + cerebellar atrophy 1, cerebral atrophy + hydrocephalus 1, cerebellar atrophy 1, periventricular leukomalacia 1	8/13	61.6	30.8	H/ACC 3, ACC + cerebellar anomalies 1, cerebellar atrophy 1, cerebellar atrophy + hydrocephalus 1, herniated cerebellum + meningocele + micropolygyria of the frontal lobes1, cerebral arteriovenous abnormality 1.
Renal	9/49	18.4	5.7 [e]	unilateral kidney 2, unilateral kidney + pelvic and renal ectasia 1, renal ectopia 2, horseshoe kidney 2, renal hypoplasia 1, hydronephrosis 1.	5/13	38.5	19.2	renal hypoplasia 2, hydronephrosis 2, renal ectopia 1
Gastrointestinal	6/28	21.4	3.8	congenital megacolon 3, anteriorly placed anus 3.	1/4	25.0	3.8	anteriorly placed anus 1.
Genital	20/159	/	12.6	cryptorchidism 14, external genitalia hypoplasia 3, phimosis 2, hypospadias 1.	4/26	/	15.4	cryptorchidism 3, cryptorchidism + external genitalia hypoplasia 1.
Feet	83/159	/	52.2	pes planus 30, pes planusvalgus 25, pes planusvarus 5, pes planus + overlapping toes 4, syndactyly +pes planus/ valgus/ varus/clubfoot/rocker-bottom 10, clubfoot 3, syndactyly 2, camptodactyly 2, short hallux 1, sandal sign 1.	16/26	/	61.5	pes planus 4, pes planusvalgus 5, pes planusvalgus +hammer hallux 1, clubfoot 3, clubfoot+hammer hallux 1, syndactyly 1, syndactyly + short hallux 1.
Hands	31/159	/	19.5	clinodactyly V finger 21, camptodactyly 3, syndactyly 2, preaxial polydactyly right thumb 1, ulnar polydactyly1, thumb laxity 1, trident hand 1, fingers ovelapping 1.	7/26	/	26.9	clinodactyly V finger 4, absent hand with five rough fingers 1, clubhand 1, thumb in hyperextension 1.

(continued)

Table 7 *(continued)*

	Isolated deletion [b]	% max [c]	% min [d]	Malformations	Translo-cation [b]	% max [c]	% min [d]	Malformations
Muscoloskeletal	40/159	/	25.2	inguinal hernia 17, joint hypermobility 9, joint hypermobility + hiatal hernia 1, joint hypermobility + tibia and knee vari 1, tibia vara/knee varus/valgus 7, tibia vara/knee varus/valgus + umbilical hernia 1, hip dysplasia 2, hip valgus 1, hiatal hernia 1.	9/26	/	34.6	inguinal hernia 4, inguinal hernia + joint hypermobility 1, joint hypermobilityn 2, hip dysplasia 2
Others	32/159	/	20.1	preauricular tag/fistula 13, preauricular tag/fistula + bifid uvula 1, preauricular tag/fistula + cutaneous aplasia 1, bifid uvula 4, angioma 3, angioma + hemihypertrophy 1, angioma + epitrochlear and suprapatellar fovea 1, microphtalmia 3, bilateral choanal atresia 2, polyotia 1, auditory canal stenosis 1, cleft lip 1.	5/26	/	19.2	preauricular tag/fistula 3, bifid uvula 1, hypodontia 1.

IVD: interventricular defect, IAD: interatrial defect, PDA: patent ductus arteriosus, H/ACC: hypoplasia/agenesis of corpus callosum.

[a] 185 patients for which the data were available, 159 with isolated deletions (152 with terminal deletions + 7 with interstitial deletions) and 26 with unbalanced translocations resulting in 5p deletions.

[b] The denominator refers to the number of patients in whom clinical manifestations and instrumental examinations were referred to.

[c] The patients without referred clinical manifestations and instrumental examinations were not considered (e.g. neurological abnormalities: 17/57 = 29.8% (%max)).

[d] The patients without referred clinical manifestations and instrumental examinations were considered negative or normal (e.g. neurological abnormalities: 17/159 = 10.7% (%min)).

[e] $P < 0.05$.

Table 8
I.R. for CdCS. Medical problems [a]

	Frequency	%
Neonatal [b]		
- Asphyxia/cianosis	32	26.9
- Feeding difficulties	52	43.7
Anesthesiological [b]	1	0.8
Respiratory infections	83	52.2
Other infections [b]		
- Otitis	18	15.1
- Gastrointestinal	9	7.6
- Urinary	4	3.4
Orthopedic		
- Pes planus/valgus/varus/equinus/clubfoot	75	47.2
- Scoliosis	34	21.4
Dental		
- Malocclusion	61	38.4
- Caries	7	4.4
- Not specified	19	11.9
Ocular		
- Strabismus	57	35.8
- Myopia	13	8.2
- Astigmatism	7	4.4
- Retinopathy	7	4.4
- Blindness	4	2.5
- Cataract	2	1.3
Gastrointestinal [b]		
- Constipation	28	23.5
- GER/regurgitation/esophagitis/vomit	15	12.6
Seizures	25	15.7
Allergies [b]		
- Cutaneous	4	3.4
- Food allergy	3	2.5
- Respiratory	3	2.5
Other clinical problems		
Hospitalisations [b]		
- Surgery operation	56	47.1
- Respiratory infection	9	7.7
- Gastrointestinal infection	5	4.2
Surgery operations [b]		
- Inguinal hernia	9	7.7
- Cryptorchidism	8	6.7
- Congenital heart defects	7	5.9
- Strabismus	4	3.4
- Other	28	23.5

GER: gastroesophageal reflux.
[a] Data available for 159 patients with isolated deletions (152 with terminal deletions and seven with interstitial deletions).
[b] Data available for 119 out of 159 patients.

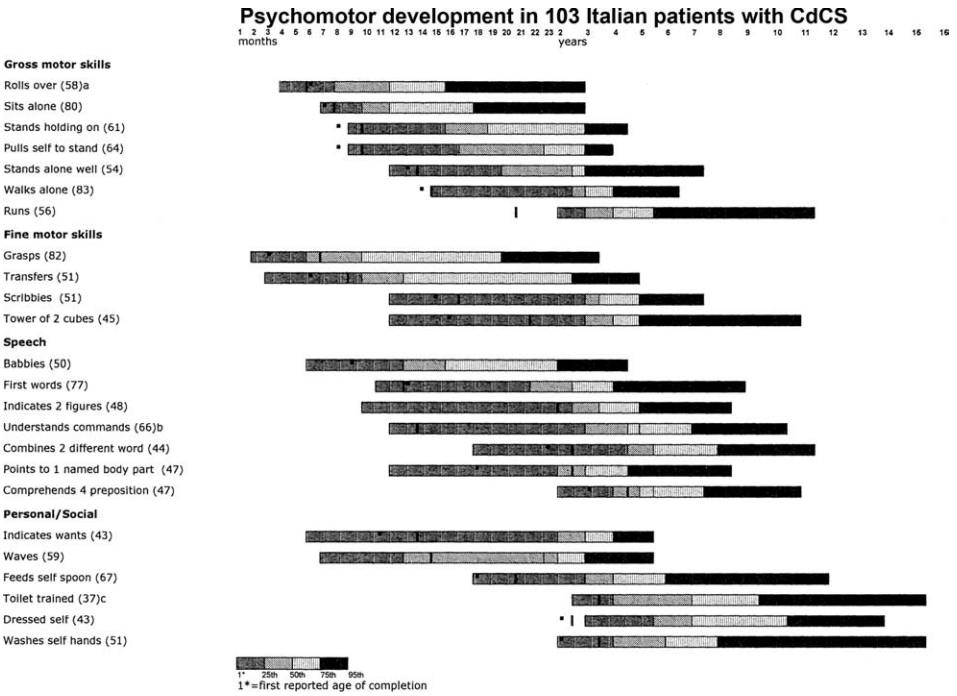

Fig. 2. | = 90th of normal American population (Denver Developmental Screening Test II) [24]. ▪ = 90th of the normal Italian population for the available milestones [42]. [a] Number of informative cases in brackets. [b, c] Skills not screened for on the DDST II [24], see in Cerruti Mainardi et al. [9].

age. With regard to autonomy, the youngest age by which a child learned to eat by himself was 18 months, the median age was 4 years. The youngest age for dressing oneself was 3 years, median age was 7 years. The number of patients with an unbalanced translocation who achieved the milestones below the 25th centile was lower compared to those with isolated deletions for 17/24 skills but the difference never reached statistical significance. If the size of the sample were twice as big, statistical significance would be reached for "sits alone" and "walks alone" ($P < 0.05$).

The correlation between the beginning of physiotherapy and the achievement of developmental skills was evaluated in 95 patients with an isolated deletion. Most patients started therapy before the age of one year: ≤ 1 year (68/95 = 71.6%), 1–3 years (21/95 = 22.1%), > 3 years (6/95 = 6.3%). Of 95 patients, 28 (29.5%) were born in the period 1965–1983 and 67 (70.5%) in the period 1984–2002. Only 14 out of the 28 patients (50.0%) born in the period 1964–1983 started physiotherapy before one year, while 54 of 67 patients (80.6%) born in the period 1984–2002 ($P < 0.01$) did so. Patients who attained the skills below the 25th centile (e.g. a child who rolled over before 8 months, achieved the milestone below the 25th centile (Fig. 2) were more frequent in the group who started the therapy ≤ 1 year of life than in the group who started the therapy > 1 year for only 11 of 24 skills and the difference never reached statistical significance.

4. Discussion

This study on 220 Italian patients enabled us to confirm and to expand the literature data on this rare disease. Cytogenetic and molecular-cytogenetic analyses showed a large variability of the deletions with breakpoints ranging from 5p15.2 to 5p11 (Fig. 1). This study confirmed the high percentage of terminal deletions (81.8%; about 80% in Niebuhr [37] data). A lower percentage (77.7%) was present in 112 out of 220 patients studied with FISH analysis, which enabled the identification of five interstitial deletions, one de novo unbalanced translocation and one mosaicism not correctly diagnosed by standard cytogenetics. Therefore the importance of FISH for a correct diagnosis of 5p deletions must be underlined, as it allows the breakpoint to be established with greater precision, and this is useful for a more personalised evaluation of the patient [10,32].

The number of patients included in the I.R. is lower than that expected because our I.R is hospital-based and not population-based. However, it should be pointed out that for the period 1984–2002 the number is much closer to the expected value (53.2%) than in the period 1965–1983 (36.1%) and this difference is significant. This may be partly due to diffusion of knowledge about the syndrome, home-rearing and to the Italian Cri du Chat Children's Association.

In most cases, the diagnosis was made in the first year of life (81.9%) but only 9.1% within the first 3 months, while for 18.1% (35 patients) the diagnosis was made at an age ranging from 13 months to 47 years. As foreseeable, in the period 1984–2002 the number of diagnoses made in the first month of life was higher than in the period 1965–1983 ($P < 0.05$). Nevertheless, even in the more recent period, still 14 patients out of 35 were diagnosed after the first year of life. In two cases a 5p deletion failed to be identified at prenatal diagnosis for advanced maternal age. In these last cases, it is possible that the chromosomal anomalies were not identified because of a small terminal deletion in one case (breakpoint in 5p15.1) and a familial unbalanced translocation resulting in 5p deletion in the other, which "apparently" did not modify the morphology of the involved chromosomes.

Of the 35 patients diagnosed after the first year of life, 10 were born shortly after the syndrome had been described, four were institutionalised (three born in the period 1965–1983 (period I), one in the period 1984–2002 (period II)), five had an unbalanced translocation resulting in 5p deletion (four I, one II), five a small terminal deletion in 5p15 (two I, three II), two an interstitial deletion (II), two had other associated pathologies (two II: one a severe prematurity, one a West syndrome), for three, preliminary karyotype results appeared to be normal (two I, one II). For four other patients (II) there is not enough data to explain the delay in diagnosis. These observations show the importance of knowing the clinical features at birth and their changes in time in order to perform karyotype analysis more often and, in doubtful cases perform FISH analysis. Early diagnosis is important for a correct evaluation of medical problems (e.g. possible intubation difficulties in the early months of life because of larynx anomalies) and for genetic counselling on the reproductive risk, more particularly to identify patients with a deletion caused by familial rearrangements which have a higher recurrence risk [8,22]. Moreover, late diagnosis prevents the early access to adequate information and psychological support, increasing the bewilderment of the family.

Mean maternal age at birth (period I) overlapped with data reported by Niebuhr [37] and that of the Italian general population (27 years) of the same period. In the second period maternal age at birth increased, like that of Italian general population (29 years) reflecting the present trend to conceive later. The neonatal parameters (gestational age, weight, length and head

circumference) are similar to those reported by Niebuhr [37]. Mortality, already quite low in previous studies, has decreased in time: 9.67% in 1978 [37], 8.75% in 1983 [51], and 6.36% in the present study. In the series from Niebuhr [37] 75% of deaths occurred in the first month and 90% in the first year of life. In the present study this decreased to 35.7% ($P < 0.05$) and 64.3%, respectively (almost statistically significant). Mortality in patients with unbalanced translocations resulting in 5p deletions was higher than in those with isolated deletions ($P < 0.05$) as already observed by Wilkins [51]. The number of deaths in period I (10.4%) was four times greater than that in period II (2.6%) ($P < 0.05$). This reduction can probably be ascribed to improvements in neonatal and paediatric care.

The examination of clinical features confirms that the cat-like cry represents the most typical sign of the syndrome, not only at birth and in the first years of life, but also later. The timbre of the voice (shrill, sometimes hoarse) remains abnormal in most adolescents and adults [5,7,30,37,43,49]. Kjaer and Niebuhr [29] recently suggested that the developmental connection between the malformations in the rhomboencephalic cranial base-brainstem region and the laryngeal region responsible for the cry in CdC patients is related to the course of migration of the neurons to the larynx. The main facial features are not specific, but their combination produces a well recognisable facial gestalt [37,52] (Figs. 3 and 4). A longitudinal study carried out in 49 patients showed that the round face generally disappeared, prominent metopic bossing became less evident, palpebral fissures frequently became horizontal. The other features persisted in most patients and the short philtrum became more evident. Changes of facial dysmorphism in adolescent and adult age have been described [3,7,20,35,49]; the present study indicates the presence of a narrow face, long coarse nose, full lower lip, dental malocclusion (open bite), short metacarpals and metatarsals. However, the phenotype remains recognisable in most patients (Figs. 3 and 4). The muscle hypotonia, present in infancy, is replaced by hypertonia, evidenced by a hyperactive patellar reflex [7,37]. Premature greying was already seen after 15 years, normal sexual development was observed in most patients. Hyperactivity was present in 66.7% of patients from 10 to 15 years and in 38.3% of patients over 15 years; both percentages were lower than those reported in previous studies: 80% in Dykens and Clarke [23] (age range 2–40 years, mean age 12 years), 90% in Cornish et al. [16] (age range 4–16 years, mean age 7.6 years), likely because of different age range of patients considered. This finding can also be due to the decrease of hyperactivity with age, as already suggested [19], and it is of prognostic relevance. However, precocious educational interventions can improve the behaviour of CdC children [50] considering that hyperactivity is the most striking problem in CdCS [5,23,50]. Hyperactivity and distractibility are considered specific characteristics of this syndrome in comparison to others as Prader–Willi and Smith–Magenis syndrome [14].

The clinical features are present in most patients who had a deletion involving the critical region in 5p15.2 [39], but there is a variability of frequency and expression related to size and type of the deletion [10]. The facial dysmorphism is particularly mild in patients with a deletion in 5p15.1 and in 5p15.2 (Figs. 3 and 4). Moreover, the patients with interstitial deletions which do not include the critical regions for the cry [39] or the language [12,13], have not the typical cry or have a better development of the language, respectively [10, 12, 13. 39, 53, 56]. In the patients with unbalanced translocations resulting in 5p deletions (not evaluated in the examination of the facial features) the phenotype may be influenced by the partial trisomy of the other chromosome involved [8,39,51], and a different phenotype can be present in the patients with more rare rearrangements. Two patients, one with an interstitial deletion and one

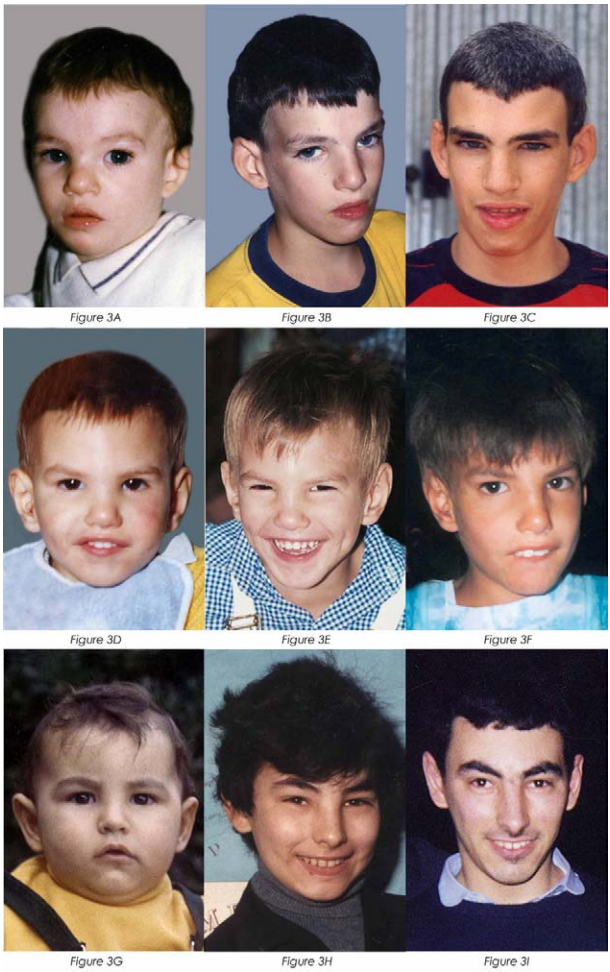

Fig. 3. (A) Patient 103 at age 10 months, (B) 7 years, (C) 14 years. Diagnosis at 5 months, del(5)(p14.1). (D) Patient 111 at age 2 years, (E) 4 years, (F) 9 years. Diagnosis at 2 months, del(5)(p15.1). (G) Patient 104 at age 1 year, (H) 10 years, (I) 28 years. Diagnosis at 13 years, del(5)(p15.2). All the patients show terminal deletions.

with a small terminal deletion neither of which included the critical region in 5p15.2 [39], had mild facial dysmorphism (not typical of CdCS) and mild mental retardation. The patient with a small terminal deletion had the typical cry because he lost the more distal cat-like cry critical region. These two patients were not included in the present study and they confirm that not all the 5p deletions can be considered CdCS [1,2,10,12,13,18,25,26,39,45,53,56]. This variability must be kept in mind for a precocious diagnosis and in order to permit a more precise prognostic evaluation.

As regards major malformations, many patients, in particular the oldest ones, did not undergo instrumental investigations. Available data shows that congenital heart diseases were the most frequent, followed by cerebral, renal and gastrointestinal anomalies. The most prevalent cardiac defects were ventricular and atrial septal defects and patent ductus arteriosus. There was one case of tetralogy of Fallot. In addition to microcephaly, brain anomalies such as hy-

Fig. 4. (A) Patient 186 at age 4 months (B, C) 14 years. Diagnosis at 4 years, del(5)(p15.2). (D) Patient 69 at age 2 years, (E, F) 23 years. Diagnosis at 14 months, del(5)(p15.2). (G) Patient 110 at age 2 years and 8 months, (H, I) 20 years. Diagnosis at birth, del(5)(p14.1). (J) Patient 71 at age 7 years, (K, L) 25 years. Diagnosis at birth, del(5)(p14.1). All the patients show terminal deletions.

poplasia or agenesis of the corpus callosum, cerebral atrophy and cerebellar hypoplasia or atrophy were recorded. Renal anomalies included renal agenesis or hypoplasia, renal ectopia, horseshoe kidney and hydronephrosis. Three cases of congenital megacolon were reported. Anomalies of foot, hand and muscle-skeletal, were frequent. Among the other malformations preauricular tags or fistulae were not rare. In a previous study Wilkins et al. [51] found a higher frequency of malformations in patients with unbalanced translocations resulting in 5p deletions than in those with a simple deletion; our study confirms this for cardiac, cerebral and renal anomalies ($P < 0.05$). The evaluation of the frequency of cardiac, cerebral, renal and gastrointestinal malformations in the period 1965–1983 (19.0%) and 1984–2002 (66.0%), without distinction between patients with isolated deletions and those with unbalanced translocations resulting in 5p deletions, showed a significant increase in the second period ($P < 0.01$), probably due to the more frequent and detailed instrumental investigations in recent years.

A previous collaborative study [33] about growth confirmed the existence of pre- and postnatal growth retardation of weight, height and head circumference. Difficulties in feeding, frequently reported during the first years of life, can be the cause of the low weight. But reduced weight in adolescent and adult patients may also be explained by constitutional factors related to the syndrome [7,38]. Microcephaly was not present in all patients at birth. In our previous study [10] microcephaly at birth was shown to be correlated to deletion size, therefore this data is of prognostic relevance. Almost all patients became microcephalic with age, but the most severe microcephaly was found in patients with largest deletions. Specific growth charts for CdCS [33] are useful for a correct evaluation of development compared with a population of CdCS children and to avoid unnecessary interventions.

In 159 patients with isolated deletions, the most frequent medical problems in neonatal age were asphyxia/cyanosis and difficulties in feeding, usually resolved in regular neonataly ward and only occasionally requiring admission to a neonatal intensive care unit. Feeding difficulties may persist during the first months or year of life. There were difficulties (but also few attempts) in breast-feeding. In recent years the number of newborns receiving breast milk is increasing, helping to establish a good mother-child relationship. A correct communication of the diagnosis is important as a psychological support to the families, as is information about physiotheraphy which should be started right from the first weeks of life (to improve suction and swallowing). Even though genetic counselling indicates that the risk of recurrence is no higher than that of the general population, some couples do not wish additional children because of the heavy psychological impact.

In neonatal age and in the first months of life it is important to highlight the risk of the anaesthetic problems (difficulties in intubation), linked to larynx and epiglottis abnormalities. This problem was previously reported for four patients [4,54]: a newborn and three patients aged 7 weeks, 33 months and 48 months, respectively (one died, three survived). Two patients in this study aged 1 month and 3 months needed a tracheotomy after intubation. At an older age a considerable number of our patients have undergone total anaesthesia for surgery without problems. Surgery was usually for congenital heart defects, inguinal hernia, cryptorchidism and strabismus. Respiratory infections (bronchitis and bronco-pneumonia) were frequent (52.2%) but only in the first years of life. Neither clinical nor serological evidence of a higher sensibility to infections are reported [44]. All compulsory and recommended vaccinations are advised.

Gastroesophageal reflux and vomiting are frequently reported in the first year of life, and constipation is often present later. Examinations for ocular and orthopaedic problems are re-

commended. Strabismus is frequent and usually divergent, and has been surgically treated with success in four patients. Seizures are rare at all ages even if more frequent in this study (15.7%) than in the Niebuhr [37] series (2.7%) ($P < 0.05$). Dental malocclusion (open bite) was present in 36.8% of children and adolescents; dental and orthodontic treatments are possible. Hospitalisations were most frequently for surgery, respiratory and gastrointestinal infections. A higher frequency of hospitalisation for acute illness (respiratory infections) and surgery, noticed by Wilkins et al. [51] in patients with unbalanced translocations resulting in 5p deletions was not observed in this study.

Psychomotor delay was present in all patients. Nevertheless our data confirm a better prognosis in home-reared patients [5,9,15,17,50]. The comparison between patients with isolated deletions and those with unbalanced translocations resulting in 5p deletions showed that the latter achieved developmental skills later, confirming the report by Wilkins et al. [50], even though the difference did not reach statistical significance because of the small sample size. Patients with isolated deletions achieved developmental milestones earlier than observed by Wilkins et al. [50], (36% of patients walked alone at age 3 [50] and 50% in the present study) and all children learned to walk unlike previous studies [37,50]. Language delay was severe in most patients, but 27% managed to form sentences before age 10 in Wilkins et al. [50], compared to 86% in the present study ($P < 0.01$).

With regard to the importance of early physiotherapy, Wilkins et al. [50], reported that most patients started the therapy above age 3, while in the present study most patients, born mostly in the period 1984–2002, started the therapy within the first year. Starting physiotherapy early certainly contributed to the better results, even though there was no significant difference between the two groups in the timing of achievement of skills. This finding shows the existence of variability also for psychomotor development. In our previous genotype-phenotype study in patients with deletions [10], we found that the severity of psychomotor retardation was related to the size of the deletion, as noticed by others [18,29,51]. In the present study we found a more severe clinical picture in patients with unbalanced translocations resulting in 5p deletions. Recently Zhang et al. [56] in a large study using array CGH analysis confirmed a correlation between mental retardation and size and type of deletion. Therefore several genetic and environmental factors can influence the psychomotor development. However, our results showed an improvement in comparison with the past. In addition to the factors previously considered (home-rearing, early starting of physiotherapy), early education, the use of information technology and sport (Fig. 4), have certainly contributed to this result, also improving social insertion. The collected data shows a less pessimistic picture than in the past which ought to encourage caregivers and parents to work together in order to improve the quality of life of children and their families.

Electronic database information Online Mendelian Inheritance in man (OMIM): http://www.ncbi.nlm.nih.gov/Omim.

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