Musculo-skeletal phenotype of Costello syndrome and cardio-facio-cutaneous syndrome: insights on the functional assessment status

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Abstract

Background

Costello syndrome (CS) and cardio-facio-cutaneous syndrome (CFCS) belong to the RASopathies, a group of neurodevelopmental disorders with skeletal anomalies as associated features. Due to their rarity, the characterization of the musculo-skeletal phenotype in both CS and CFCS has been poorly characterized compared to other RASopathies.

Patients and methods

Herein we assessed a thorough evaluation of orthopedic findings in CS and CFCS in a monocentric cohort of patients, including information about their functional status. A total of 34 patients with molecularly confirmed diagnosis of CS (N=17) and CFCS (N=17) were recruited. Data on orthopedic findings were collected by filling in a comprehensive checklist of 100 items assessment. Functional and disability evaluations were performed by assessing the 6-minute walking test (6MWT) in patients with independent walking and Pediatric Outcomes Data Collection Instrument (PODCI). Genotype/phenotype correlations were assessed taking into account available data in the literature.

Results

Orthopedic manifestations are highly prevalent in CS and CFCS, and do overlap in the two disorders. Overall, patients with CS harboring the recurrent *HRAS* Gly12Ser substitution show a more severe skeletal phenotype compared to patients carrying the Gly12Ala and Gly13Cys variants. Among CFCS patients, those with *MAP2K1/2* mutations show different skeletal characteristics compared to *BRAF* variants, with a higher prevalence of orthopedic abnormalities. Generalized muscular hypotrophy is detected in most recruited patients. Functional assessment demonstrates that patients with CS and CFCS reach lower values compared to the general population with CFCS patients showing the lowest scores.

Conclusions

Orthopedic manifestations appear universal features of CS and CFCS and they can evolve along patients' life. Longitudinal assessment of disability status by using 6MWT and PODCI could be useful to evaluate the functional impact of orthopedic and neurological manifestations on patients' outcome, and help monitoring planning a tailored treatment of these comorbidities.

Background

Costello syndrome (CS, OMIM #218040) and cardiofaciocutaneous syndrome (CFCS, OMIM PS115150) are neurodevelopmental disorders caused by gain-of-function mutations in genes encoding components of the RAS/mitogen-activated protein kinase (MAPK) pathway, an intracellular signaling cascade playing a pivotal role in cell cycle regulation, differentiation, growth and senescence [1]. These conditions are grouped under the term RASopathies together with Noonan syndrome (NS) and neurofibromatosis type 1 (NF1) and other emerging clinically related disorders, due to a common pathogenetic mechanism resulting in dysregulation of the RAS/MAPK pathway [2]. Both CS and CFCS are ultra-rare conditions with approximately 300 individuals each reported worldwide [3-4]. CS is caused by heterozygous activating mutations in the *HRAS* gene, with a missense change resulting in the Gly12Ser substitution representing the most common event underlying the disorder. As a consequence, CS is characterized by a relatively homogeneous phenotype [3]. Conversely, CFCS is genetically heterogeneous, and caused by heterozygous activating mutations in the *BRAF, MAP2K1, MAP2K2* and *KRAS* genes, leading to a more variable clinical presentation [4]. Overall, key-features affecting RASopathies include a distinctive facial appearance, postnatal growth failure, a wide spectrum of cardiac defects, variable intellectual disability, skin manifestations and different signs of musculo-skeletal involvement. The musculo-skeletal profiling of NS and NF1 syndrome has previously been outlined in the medical literature [5-7], while incidence similar characterization is lacking for both CS and CFCS, possibly because their overall lower prevalence. Indeed, available data on skeletal anomalies in CS and CFCS have been collected during the International Costello Syndrome Conferences [8-13] and poor information is available about the function and disability level [8,14] or daily living activities in these patients [15].

The present study aimed to improve our general knowledge about the musculo-skeletal phenotype of CS and CFCS thorough a the assessment of a single, unselected and relatively large monocentric cohort of patients, and to add information about the functional status of such patients. Moreover, we present first genotype/phenotype correlations.

Patients And Methods

A prospective study was performed between May 2018 and January 2020. Patients with molecularly confirmed diagnosis of CS and CFCS followed in our Institution, were consecutively recruited. A written informed consent was obtained from all participating individuals and families. The study was approved by the local Ethics Committee. All individuals underwent pediatric, genetic, neurological and orthopedic evaluations by physicians experienced in the management of RASopathies. Patients' past medical history was reviewed in order to check for: i) congenital orthopedic malformations; ii) achievement of neuro-motor developmental milestones; iii) use of orthosis; iv) physical activity.

A standardized musculo-skeletal physical examination was carried out by filling in a comprehensive checklist, including 100 items assessment (**Table 1 supplementary data**). Coxa valga subluxans (CVS) was radiologically diagnosed when femoral neck-shaft angle was >140°. Functional and disability evaluations were performed by assessing the 6-minute walking test (6MWT) [16] in all patients with independent walking and by using the Pediatric Outcomes Data Collection Instrument (PODCI) [14,17-18]. The 6MWT was used to measure the distance covered on a flat and hard surface in a total of six minutes, to monitor overtime worsening of general status and deambulation [16]. 6MWT data were normalized taking into account sex, age, body mass index and height [19-20]. PODCI was used to assess the global (functional and psychological) profile of the orthopedic patient. Based on the global level of intellectual

disability, PODCI was filled in by patients' parents or caregivers; data on all PODCI domains (physical functions, transfer and basic mobility, sports, comfort, pain, happiness and satisfaction, global function) were collected.

Study data were analyzed with GraphPad PRISM software (version 5.1; GraphPad Software. Inc., San Diego CA, USA). Descriptive analysis was expressed as mean ± standard deviation (SD) and percentages. According to the cut-off age identified by PODCI, the whole sample was divided into two groups: children (when <11 years) and adolescents (if ≥11 years). The nonparametric Mann Whitney test was used to compare CS and CFCS PODCI scores with normative values [18]. A *p* value <0.05 was considered statistically significant.

Results

A total of 34 patients with molecularly confirmed diagnosis of CS (N=17) and CFCS (N=17) were recruited in the study (CS: age range 4-36 years; CFCS: age range 5-35 years) (**Table 1**). Prevalence of congenital malformations detected at birth was very low (hip dysplasia 3/34, 9%; clubfoot 2/34, 6%) (**Table 2**). All patients experienced a delay in the neuromotor developmental milestones, which was treated with dedicated physical therapy, requiring the use of orthosis (mostly insoles, orthopedic shoes and ankle foot orthosis or AFO) in 15 (88%) CS patients and 13 (76%) CFCS patients (**Table 2**). At the time of clinical evaluation, all patients with CS reached head and trunk control, and they achieved an independent walking. In contrast, 6 (35%) patients with CFCS needed some kind of support for standing an upright position and/or deambulation (orthosis and/or wheelchair for long distances). Most of patients had some kind of physical activities at the time of clinical evaluation (14/17, 82% CS; 13/17, 76% CFCS) (**Table 2**). The standardized checklist to detect musculo-skeletal manifestations revealed that most patients were affected by a variable combination of deformities; the most frequent osteo-articular abnormalities are shown in **Table 3**. The most frequent skeletal findings in CS were scoliosis, anterior chest anomalies, ulnar deviation of fingers, elbows contractures, cubitus valgus, feet anomalies (metatarsus varus, pes planus or cavus), Achille's tight heelcord and small joint laxity. Overall, patients with CS harboring the Gly12Ser variant showed a more severe skeletal phenotype compared to patients carrying other HRAS mutations (e.g., Gly12Ala and Gly13Cys). Scoliosis in CFCS was more prevalent compared to CS; other frequent skeletal findings were pectus anomalies and pterigium colli. Ulnar deviation of fingers, elbows contractures and cubitus valgus were also present, but they were less prevalent than in CS. Hip and knees contractures and feet anomalies (mostly characterized by pes valgus and planus) were also frequent. In the CFCS group, patients with *MAP2K1/2* mutations showed different skeletal characteristics compared to those carrying *BRAF* variants, with a higher prevalence of scoliosis, pectus anomalies, upper limbs anomalies, hip contractures and pes valgus compared to *BRAF* mutations. At the time of clinical evaluation, coxa valga subluxans was radiologically documented in 7/8 patients with CS (88%) and 3/11 patients with CFCS and *BRAF* mutations (27%). However, one patient with CS (Gly12Ser) was radiologically negative for hip subluxation at the time of recruitment, though she was surgically treated at the age of 5 years for this problem. Generalized muscular hypotrophy (small and flabby muscles both in upper al lower limbs) was detected in most of patients with CS and CFCS, with a higher prevalence in CS (**Table 3**).

Functional and disability evaluation was performed by using the 6MWT and PODCI scale, respectively. A total of 24 patients were able to perform the 6MWT (12/17 CS and 12/17 with CFCS). Among the five patients with CS who did not perform the test, a single individual had not reached independent walking at the time of clinical evaluation, two subjects had undergone surgical interventions, and two patients showed hip dislocation. In the CFCS subcohort, the five patients who were not able to perform the 6MWT showed multiple musculo-skeletal deformities associated with loss of walking ability and severe epilepsy. Overall, the CS and CFCS groups covered on average 49% and 46% of the expected distance, respectively. No significant differences occurred between genetic analysis, phenotypes, gender or age of assessment (**Figure 1**). The average PODCI scores for CFCS (both children and adolescents) were constantly lower compared to CS population (**Figure 2**). Statistically significant differences were recorded in the upper-extremities mobility (children *p*=0.04, adolescents *p*=0.01), transfer and basic mobility (children *p*=0.04, adolescents *p*=0.03) and global functioning domains (adolescents *p*=0.02). When compared to normative values, the CFCS group (both children and adolescents' sub-groups) reached significantly lower scores in all domains, with the exception of comfort and pain in the group of children (*p*=0.2). Significant differences between CS and normative values were detected in all domains, with the exception of happiness both in children (*p*=0.3) and adolescents (*p*=0.08) (**Fig 3**). The prevalence of main orthopedic findings and the comparison with literature data are shown in the **Table 4**.

Discussion

In the present study, the musculo-skeletal phenotype and functional status of CS and CFCS were assessed considering a single, unselected and relatively large monocentric cohort of patients, and genotype/phenotype correlations were explored. We report that orthopedic manifestations are highly prevalent in both disorders. Compared with previously reported observations, the different prevalence of these features could be related to the different ages of patients recruited in the cohorts [8-13]. As demonstrated by the need of orthosis and surgical intervention, the musculo-skeletal phenotype of CS and CFCS evolves with age.

Genotype/phenotype correlation analyses documented that CS patients carrying the Gly12Ser variant show a higher prevalence of orthopedic abnormalities compared to subjects with different mutations in *HRAS*. Conversely, in patients affected by CFCS, those harboring the *MEK1/2* gene mutations generally show a more severe skeletal phenotype compared to other CFCS patients, with a higher prevalence of scoliosis and multiple joint contractures. Future studies on larger cohorts including patients carrying the less frequent variants of *HRAS* and *MAP2K1/2* genes are necessary, to confirm the present findings.

The prevalence of congenital bone deformities detected in our sample was low; although the high prevalence of coxa valga subluxans in our CS population suggests that orthopedic phenotype may evolve in the long-term, highlighting the importance to perform a hip X-ray since infancy to rule out this possible finding. In our sample, some deformities, such as pes planus and tigh Achille's heelcord, were surgically treated during patients' life and therefore some specific items could be underestimated.

Both CFCS and CS patients frequently required use of orthosis and postural/mobility devices to improve posture and facilitate acquisition of neurodevelopmental milestones. In particular, CFCS patients reported a higher need of stroller and corset, as they had a higher incidence of scoliosis and lower limb contractures (especially knee and hip contractures), as already reported in the medical literature [11]. In our cohort, these deformities showed a progressive and worsening pattern, needing surgical intervention in some cases and compromising the independent walking.

Generalized muscular hypotrophy and hypotonia were detected in most patients. Skeletal muscle hypotonia of varying degree is a universal finding in CS and CFCS, and some authors speculated that this could be related to myopathy [21]. Tidyman et al., reported muscle biopsies in a limited number of CS and CFCS patients, describing the presence of abnormal muscle fiber size and variability as one of the potential mechanisms leading to hypotonia. Due to the small number of biopsies available, the same authors concluded that since overall muscle tissue's architecture was relatively intact, experiments on animal models would be essential to better define this myopathy *in vivo* [21]. As it has been demonstrated the vital role of the RAS/MAPK pathway in the myogenesis regulation, mainly in myoblast differentiation and proliferation [21-22], we speculate that decreased muscle fiber size and hypotonia in CS and CFCS could result from inhibition of myoblast differentiation during early muscle development, and this could explain both the muscle hypotrophy found in our patients and their functional status.

As expected, CS and CFCS patients showed a worse functional performance and level of disability assessed by both 6MWT and PODCI scales, compared to normative values. All patients able to walk performed 6MWT, covering less than 50% of the expected distance. Overall, the walked distance decreased proportionally to the patient's age and, in particular, patients with CFCS showed worse performances compared to CS. This finding has been also confirmed by the PODCI scale. Overall, CS patients older than 11 years reached higher scores in PODCI domains compared to younger patients, contrarily to CFCS individuals in whom stable or lower PODCI values were detected in the older ones. Global functioning items between children with CS and CFCS was not significantly different, and we speculate that this could be related to the high level of global care assistance needed by children with these genetic conditions. The lower PODCI scale scores collected in CS and CFCS compared to normative data suggest how cognitive impairment, complex clinical history, neurological condition and musculo-skeletal deformities have a great impact on the disability in RASopathies. Data on functional and disability status published by Johnson et al. detected lower scores in CS compared to CFCS [14]. Interestingly, both Johnson's and our study did not detect a significant difference in the comfort and pain domains between syndromic patients and normative values. We believe that parents' report could represent a crucial bias since detection of pain in patients with intellectual disability is quite challenging [23]. On the same way, the absence of significant differences between happiness domain in CS *versus* normative values could be related to the friendly behavior shown by patients with CS [24].

Overall, the musculo-skeletal manifestations in CS and CFCS should be included in a more comprehensive clinical assessment, in which growth and neurodevelopmental delay have to be considered as universal features. We speculate that worsening of the neurological profile in term of behavioral pattern and epilepsy in CFCS [25], the abnormal posture and bone health in CS [26-27], may play an important role in terms of adult outcome, justifying the lower PODCI scores found in our patients compared to CS. Results of the 6MWT and PODCI scales underscore how the routinely assessment of disability status could be useful to evaluate the functional impact of orthopedic and neurological manifestations on patients' outcome to monitoring their worsening and planning a tailored treatment of comorbidities.

The adequate classification of musculo-skeletal deformities, their overtime monitoring together with disability status assessment could represent good clinical data to be monitored in the frame of future clinical trials.

Conclusions

Our study confirms the clinical relevance of musculo-skeletal involvement in CS and CFCS, which leads to functional impairment, as demonstrated by the 6MWT and PODCI assessments. The routinely use of both these instruments would be relevant to monitor the impact of orthopedic malformations on the functional status along life and plan a timely treatment (conservative or surgical). An early use of the orthosis is also suggested to reduce the progressive onset and worsening of contractures, especially in the lower limbs, and consequently reduce surgical indications. When necessary, surgical treatment should be performed as early as possible to allow for minimally invasive or low impact surgical techniques; in fact, the severe progressive worsening of such deformities may lead to complex orthopedic surgery often unsustainable for these fragile patients. In this view, the precocious classification of musculo-skeletal deformities and their careful monitoring over time is of crucial relevance.

Abbreviations

CS: Costello syndrome; CFCS: cardiofaciocutanoeus syndrome; NS: Noonan syndrome; 6MWT: 6-minute walking test; PODCI: Pediatric Outcomes Data Collection Instrument;

Declarations

Acknowledgments

Authors' contribution

Dr Leoni conceptualized and designed the study and data collection instruments, interpreted data, wrote the manuscript, revised the manuscript for important intellectual content. Dr Romeo analysed and interpreted data, reviewed results and drafted the article. Drs Pelliccioni, Di Già, Onesimo and Giorgio collected,

interpreted data, and reviewed the manuscript. Drs Flex and Tartaglia interpreted clinical data and drafted the article. Dr Rigante analysed data and thoroughly reviewed the manuscript. Dr Valassina conceptualized the study, acquired and interpreted data, reviewed the manuscript for important intellectual content. Dr Zampino conceptualized the study and critically revised the manuscript for important intellectual content.

All authors approved the final version of the manuscript as submitted and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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Availability of data and materials

Data available from the corresponding author on request from the physicians

Ethics approval and consent to participate

The study was approved by our Institutional Ethic Committee. Parents' patients signed a written informed consent

Conflict of interest

None

Consent for publication

Not applicable

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Tables

Table 1: Demographic and body mass index characteristics of the study population						
Phenotype		Gene variant	N° of patients	Total		BMI
CS	(mean 18.6±9.3SD)	HRAS (p.Gly12Ser)	14 (4 M; 10 F)	17	(6 M; 11 F)	
		HRAS (p.Gly12Ala)	1 (1 M; 0 F)			19.0±2.9
		HRAS (p.Gly13Cys)	2 (1 M; 1 F)			
CFCS	(mean 14.5±7.9SD)	BRAF (all variants)	13 (3 M; 10 F)	17	(6 M; 11 F)	
		MAP2K1(all variants)	3 (2 M; 1 F)			16.5±2.4
		MAP2K2(p.Ala62Pro)	1 (1 M; 0 F)			

Table 2: Relevant medical findings						
	CS	N=17	(%)	CFCS	N=17	(%)
Congenital orthopedic malformation						
Congenital hip dysplasia	2 (12)			1 (6)		
Clubfoot	1 (6)			1 (6)		
Neuro-motor abilities°						
Head control	17 (100)			17 (100)		
Trunk control	17 (100)			16 (94)		
Autonomous deambulation*	17 (100)			11 (65)		
Assisted Walking*	0 (0)			6 (35)		
Past use of orthosis	15 (88)			13 (76)		
Use of orthosis*						
DAFO/AFO	5 (29)			4 (24)		
Postural Stroller	1 (6)			6 (35)		
Corset/Belt/Brace	0 (0)			3 (18)		
Orthopedic Insole	8 (47)			8 (47)		
Physycal activity#	14 (82)			13 (76)		
Physical therapy	4 (24)			13 (76)		
Sport	5 (29)			10 (59)		
°Prevalence data refers to acquired neuro-motor ability at time of clinical evaluation; * Data showed at time of clinical evaluation; # We cosidered physical therapy or sport played ≥ 2 times per week						

Table 3: Muscle-skeletal findings							
	CS N=17 (%)	HRAS Gly12Ser (N=14)	HRAS Gly12Ala (N=1)	HRAS Gly13Cys (N=2)	CFCS N=17 (%)	BRAF all variants (N=13)	MAP2K1/2 all variants (N=4)
Axial							
Scoliosis	5 (29)	5 (36)	0 (0)	0 (0)	6 (35)	4 (31)	2 (50)
Pectus Carinatum/excavatum	8 (47)	8 (57)	0 (0)	0 (0)	9 (53)	6 (46)	3 (75)
Dorsal Hyperkyphosis	3 (18)	2 (14)	0 (0)	1 (50)	3 (18)	3 (23)	0 (0)
Stiff Back	3 (18)	2 (14)	0 (0)	1 (50)	3 (18)	3 (23)	0 (0)
Pterigium colli	0 (0)	0 (0)	0 (0)	0 (0)	6 (35)	5 (38)	1 (25)
Lumbar hyperlordosis	1 (6)	1 (7)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Upper limbs							
Fingers' ulnar deviation	14 (82)	13 (93)	1 (100)	0 (0)	7 (41)	3 (23)	4 (100)
Elbows contractures	9 (53)	8 (57)	0 (0)	1 (50)	6 (35)	4 (31)	2 (50)
Cubitus valgus	6 (35)	4 (29)	0 (0)	2 (100)	4 (24)	3 (23)	1 (25)
Wrist contractures	2 (12)	2 (14)	0 (0)	0 (0)	1 (6)	0 (0)	1 (25)
Fingers' radial deviation	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Lower limbs							
Coxa valga subluxans*	8 (89)	7 (87)	1 (100)	-	3 (27)	3 (33)	0 (0)
Hip contractures	2 (12)	2 (14)	0 (0)	0 (0)	6 (35)	2 (15)	3 (75)
Adducted hip	2 (12)	1 (7)	0 (0)	1 (50)	3 (18)	1 (8)	2 (50)
Knees contractures	3 (18)	3 (21)	0 (0)	0 (0)	6 (35)	4 (31)	2 (50)
Genu valgum	5 (29)	5 (36)	0 (0)	0 (0)	3 (18)	1 (8)	2 (50)
Genu varum	0 (0)	0 (0)	0 (0)	0 (0)	2 (12)	1 (8)	1 (25)
Metatarsus varus	8 (47)	7 (50)	0 (0)	1 (50)	6 (35)	4 (31)	2 (50)
Pes valgus	4 (24)	4 (29)	0 (0)	0 (0)	9 (53)	6 (46)	3 (75)
Pes planus	6 (35)	5 (36)	1 (100)	0 (0)	6 (35)	4 (31)	2 (50)
Pes cavus	6 (35)	4 (29)	0 (0)	2 (100)	1 (6)	0 (0)	1 (25)
Hallux valgus	4 (24)	4 (29)	0 (0)	0 (0)	2 (12)	1 (8)	1 (25)
Foot heelcord contractures	3 (18)[§]	2 (14)	1 (100)	0 (0)	3 (18)	3 (23)	0 (0)
Equinovarus foot	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Supinated foot	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Clino-/syn-/campto-dactyly	6 (35)	6 (43)	0 (0)	0 (0)	4 (24)	3 (23)	1 (25)
Others							
Small joint laxity	7 (41)	5 (36)	1 (100)	1 (50)	5 (29)	4 (31)	1 (25)
Congenital hip Dislocation	2 (12)	2 (14)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Talipes	1 (6)	1 (7)	0 (0)	0 (0)	1 (6)	1 (8)	0 (0)
Generalized muscular hipotrophy	14 (82)	12 (86)	0 (0)	2 (100)	12 (71)	8 (62)	4 (100)

*Coxa valga subluxans diagnosed by X-Rays; §Of note 8/17 patients already performed Achille's heel cord lengthening at time of clinical evaluation

	Present data		Reinker 2011 (CS)			Detweiler 2013	White 2005	Yassir 2003	Armour 2008
	CS N=17 (%)	CFCS N=17 (%)	CS N=2 (%)*	CFCS (%)*	N=32	CS N=43 (%)	CS N=17 (%)[‡]	CS N=18 (%)[‡]	CFCS N=38 (%)
Spine									
Scoliosis	5 (29)	6 (35)	1 (50)	8 (25)		25/40 (36)	10 (59)	3/18 (17)	11/33 (33)
Kyphosis	3 (18)	3 (18)	0 (0)	6 (19)		23/40 (58)	3 (18)	3/18 (17)	6/26 (23)
Lordosis	1 (6)	1 (6)	0 (0)	1 (3)		6/32 (19)	NA	NA	NA
Upper extremities									
Cubitus valgus	5 (29)	4 (24)	1 (50)	0 (0)		NA	NA	NA	NA
Elbow contracture	9 (53)	5 (30)	1 (50)	4 (12)		21/38 (55)	NA	10/16 (63)	NA
Ulnar Deviation	14 (82)	6 (35)	NA	NA		26/41 (63)	NA	4/18 (22)	NA
Lower extremities									
Hip dysplasia	8/9 (89)[§]	3 (27)[§]	0 (0)	5 (16)		17/38 (45)	NA	3/18 (17)[§]	NA
Genu valgum	5 (29)	3 (18)	NA	NA		7/28 (25)	NA	NA	NA
Knee contracture	3 (18)	6 (35)	1 (50)	7 (22)		13/40 (33)	NA	NA	NA
Vertical talus	0 (0)	0 (0)	NA	NA		7/41 (17)	4 (24)	5/18 (28)	NA
Bilateral talipes equinovarus	0 (0)	3 (18)	0 (0/2)	5 (16)		1/41 (2)	1 (6)	NA	NA
Pes planus	6 (35)	6 (35)	1 (50)	20 (62)		19/36 (53)	NA	7/16 (44)	5/38 (13)
Pes cavus	6 (35)	1 (6)	0 (0)	2 (6)		3/40 (8)	4/17 (24)	NA	NA
Clino-/Syn-/Campto-dactyly	6 (35)	4 (24)	0 (0)	4 (12)		11/41 (27)	NA	6/16 (38)	8/38 (21)
Metatarsus varus	8 (47)	6 (35)	0 (0)	2 (6)		NA	NA	NA	NA
Hallux valgus	4 (24)	2 (12)	0 (0)	2 (6)		3/39 (8)	NA	NA	NA
Others									
Pectus excavatum/carinatum	9 (53)	8 (47)	0 (0)	4 (12)		12/40 (30)	8/13 (62)	1/16 (6)	19/29 (63)
Joint Laxity	7 (41)	5 (29)	NA	4 (12)		35/41 (85)	3/3 (100)	16/16 (100)	17/27 (63)
Achille tendon release	8 (47)	1 (6)	NA	NA		17/43 (40)	14/17 (82)	8/18 (44)†	NA

Table 4: Actual main orthopedic findings and literature data review

* In this population 1/2 patients with CS and 19/32 patients with CFCS, received a molecular confirmation; [‡]Patients without genetic confirmation; [§]coxa valg̲ subluxans based on X-Rays, †5 surgically treated and 3 with serial casting.
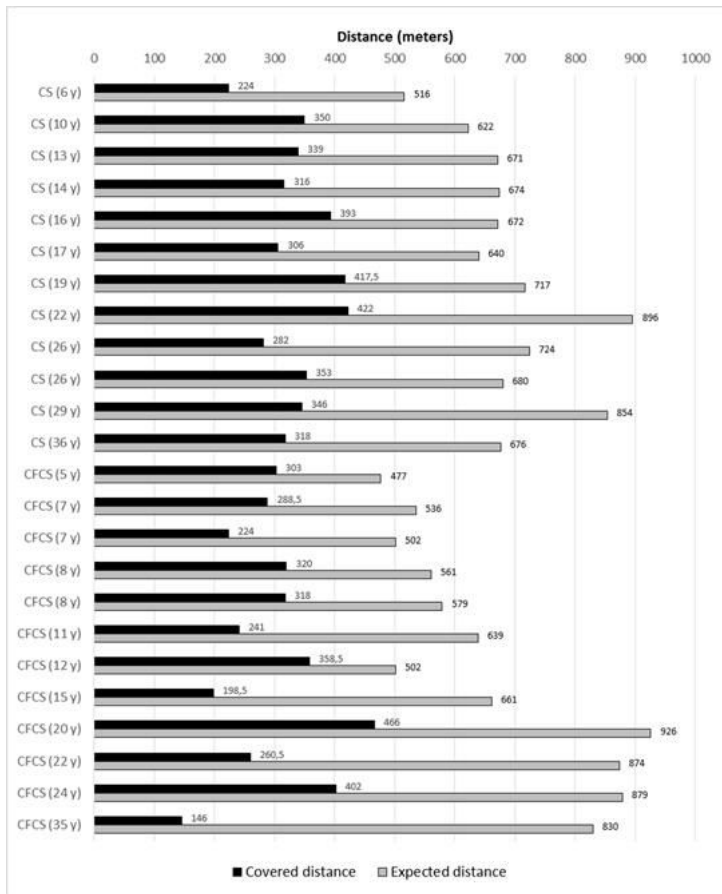
Figures

Figure 1

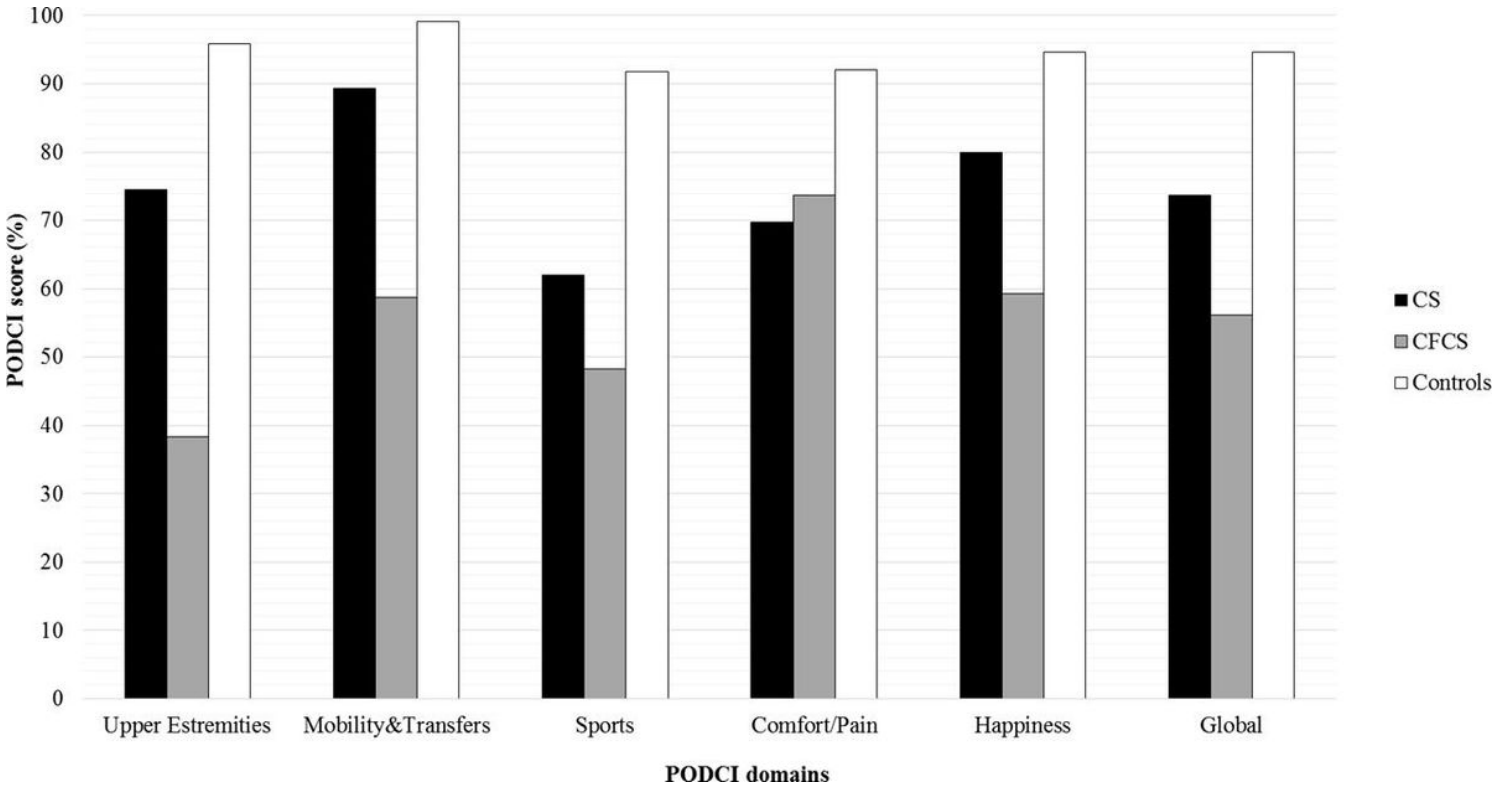Six minute walk test in CS and CFCS

Figure 2

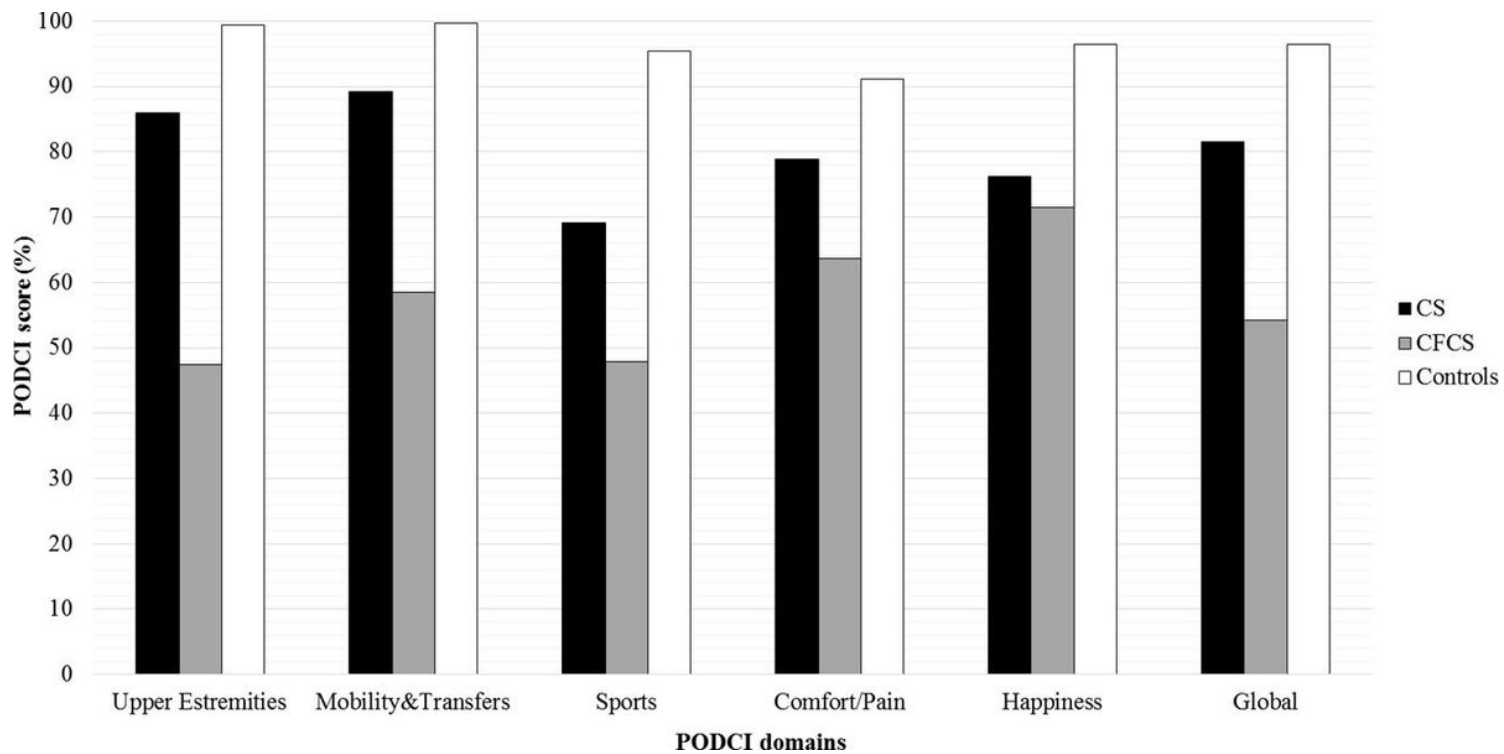PODCI scores in Children (population under 11 years of age)

Figure 3

PODCI scores in Adolescents (population over 11 years of age)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1Ssupplementarymaterial.xlsx