CASE REPORT

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Endocrine Evaluation and Homeostatic Model Assessment in Patients with Cornelia de Lange Syndrome

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What is already known on this topic?

Cornelia de Lange syndrome (CdLS) is a rare developmental genetic disorder associated with short stature and delayed puberty. However, research on other hormonal assessments in this condition, such as high homeostatic model assessments of insulin resistance (HOMA-IR), is scarce.

What this study adds?

Three of seven prepubertal patients with CdLS had high HOMA-IR values but no metabolic risk factors, suggesting insulin resistance in this population. Two of the 17 postpubescent patients had altered HOMA-IR values associated with increased body mass index, which to the best of our knowledge, has not been published before. These findings highlight the importance of endocrine follow-up in these patients.

Abstract

The aim of this study was to expand knowledge about endocrine disorders in individuals with Cornelia de Lange syndrome (CdLS), a rare developmental genetic disorder with anomalies in multiple organs and systems. Hormone levels, clinical scores, anthropometric measurements, and molecular analysis were assessed in 24 individuals with CdLS. Hyperprolactinemia was the most common endocrine disorder. Three patients showed subclinical hypothyroidism. Concerning the gonadotropic axis, mildly delayed puberty was observed, as well as genital anomalies, such as cryptorchidism. Despite short stature, levels of insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 tended to be normal. Three prepubertal individuals without risk factors had higher than normal values for the homeostatic model assessment of insulin resistance (HOMA-IR) and for insulinemia, suggesting insulin resistance. Furthermore, two adults had elevated body mass indexes associated with HOMA-IR values over the cut-off values. CdLS may lead to dysregulation of the endocrine system, particularly in patients with high HOMA-IR values and insulinemia who are at risk of insulin resistance. Therefore, clinical follow-up with comprehensive hormonal assessment appears warranted in individuals with CdLS.

Keywords: Cornelia de Lange syndrome, HOMA-index, insulin resistance, endocrine evaluation and hypothalamic-pituitary axis

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Introduction

Cornelia de Lange syndrome (CdLS) [(OMIM) #122470, 300590, 300882, 610759 and 614701)] is a congenital malformation syndrome characterized by distinctive facial features, microcephaly, growth retardation, and anomalies in multiple organs and systems. The prevalence of CdLS is estimated to be below 1:30000 live births (1). The onset of this syndrome has been linked to mutations involving proteins associated with the cohesin complex, which is a basic regulator of chromosomal biology. Eight causal genes (*NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8, ANKRD11,* and *MAU2*) (2,3,4,5) and several candidate genes have been identified. Mosaicism and splicing mutations are relatively frequent (6,7,8). Thus, a broad phenotypic spectrum (9) has been described, and a clinical score (2) has been developed.

Recently, small-fibre neuropathy and changes in body composition have been associated with CdLS (10,11). Abraham and Schlesinger (12,13) performed the first endocrine studies, Kline et al. (14) reported CdLS-specific growth charts, and Schwartz et al. (15) published a pituitary study of five patients. In 2007, an extensive study including comprehensive endocrinological work-ups on 49 patients with CdLS reported mildly delayed puberty (1), and these findings were included in a CdLS consensus paper published in 2018 (2). However, a thorough endocrine evaluation of patients with CdLS has rarely been reported. Thus, the aim of this study was to expand the knowledge of endocrine findings in patients with CdLS.

Patients

A descriptive study of 24 Spanish individuals aged 2-37 years, seven (29.2%) of whom were prepubescent and the remaining 17 postpubescent patients, with CdLS was performed. All subjects were evaluated by a paediatrician or a clinical geneticist with experience in CdLS. After comprehensive and detailed clinical and auxologic evaluations, patients were classified based on recently published CdLS consensus criteria (2). Pubertal development in children was assessed by an expert endocrinologist using Tanner staging (16). Adult participants completed a questionnaire reporting the time of onset of main secondary sexual characteristics. All data were confirmed by checking levels of gonadotropic and sex steroid hormones. Informed consent from participants, their parents, or legal guardians was obtained before entry into the study.

Hormonal Studies

Venous blood samples were drawn and centrifuged, and plasma or serum was separated. Levels of insulin, thyrotropin, thyroxine, prolactin, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle-stimulating hormone, 17-beta-estradiol, and total testosterone were measured using specific electrochemiluminescence assays in a Cobas e601 autoanalyzer (Roche Diagnostic, Mannheim, Germany). Serum glucose was analysed using an enzymatic spectrophotometric method with the Cobas 8000 autoanalyzer (Roche Diagnostic). Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) levels were measured using chemiluminescent immunometric assays (Immulite 2000Xpi, Siemens Healthcare Diagnostics, Los Angeles, CA, USA). After ruling out comorbidities, analyses were performed while participants were fasting and in a resting state for 20-30 minutes.

Weight was measured in kilograms (kg) using an AMGI-IMSA model and height in centimetres (cm) using a Harpenden Tallimeter. Body mass index (BMI) was calculated as weight (kg) divided by height in metres squared (m^2). The obtained value was expressed as a Z-score, according to the reference graphs in a Carrascosa Lezcano et al. (17) (2010) Spanish Growth Study. Insulin resistance was calculated by means of the homeostatic model assessment of insulin resistance (HOMA-IR), defined according to the following equation: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5 (18). All molecular analyses for each individual were performed using a custom, targeted gene panel including *NIPBL, SMC1A, SMC3, RAD21, HDAC8, BRD4, ANKRD11,* and *MAU2* (19). Chromosomal studies were performed using standard methods.

Ethics Committee Approval: The ethical guidelines for human research outlined by the Declaration of Helsinki and revised by Fortaleza (2013) were followed. The Ethics Committee of Clinical Research from the Government of Aragón (CEICA; PI15/00707) and the subjects approved the study protocol.

Results

Study participants totalled 24 Spanish patients with CdLS, of whom nine (37.5%) were male. The patients were aged 2-37 years and seven (29.2%) were prepubescent with the remaining 17 being postpubescent. Most had mild involvement of most endocrine axes. In the thyroid axis, three participants had normal or low thyrotropin level and low thyroxine level. Hyperprolactinemia was the most common endocrine disorder, affecting half of the participants (P1, P2, P4, P6, P9, P13, P14, P15, P16, P18, P20, and P22). Regarding pubertal and gonadal function, two male and one female patient had mildly delayed puberty, and four of the nine males had bilateral cryptorchidism.

Four females (P15, P16, P19, and P21) reported having irregular menstrual cycles; a 16-year-old participant (P17) showed absence of menarche and no breast development. Chromosomal studies were normal in all cases. Among all 24 participants, 63% had prenatal growth retardation, and 80% had postnatal growth retardation. Finally, the HOMA-IR values in three prepubertal (P5, P7, and P8) and two adult participants (P21 and P22) exceeded the cut-off points. Tables 1 and 2 summarize these results.

Discussion

Although individuals with CdLS rarely develop severe endocrine disorders, the endocrinological work-ups reported here suggest a mild involvement of most axes. Decreased thyroxine values and normal thyrotropin levels might suggest a central subclinical hypothyroidism; however, no abnormalities were detected on brain imaging. Hyperprolactinemia was the most frequent endocrine disorder, occurring in 50% of participants, among whom P9, P13, P14, P18, P20, and P22 were taking antipsychotic drugs that may explain this increase, but P1, P2, P4, P6, P15, and P16 were not undergoing any treatment. Furthermore, six had normal adrenocorticotropic hormone and cortisol levels, thus ruling out acute stress as a cause of their hyperprolactinemia.

Regarding gonadal function, cryptorchidism (14) was observed in two prepubertal participants (P1 and P6) and two pubertal ones (P14 and P18), suggesting that dysfunction of the pituitary-gonadal axis could be present in early gestation. In addition, P14 and P18 had delayed puberty, as diagnosed by the absence of testicular development at age 14 years and no progression of secondary sexual characteristics at more than two years after pubertal onset. Seven female participants reported irregular menstruation and one (P17) reported delayed puberty and lack of breast development at age 13 years. In these patients, gonadotropins were not elevated, suggesting a possible central origin of the disorder. Regardless of LH levels, clinically there is often a pubertal delay, and LH values suggest that central hypogonadism may be transitory or permanent depending on the evolution, thus requiring close clinical follow-up.

Prenatal and postnatal growth retardation is a common feature in individuals with CdLS (14,15,20). In the present study, 20 of the 24 patients had heights >2 standard deviation (SD) below the means for age and sex, and 15 were born small for gestational age (>2 SD below means for birth weight or birth length), indicating a prenatal origin. In addition, 80% did not show catch-up growth at four years of age. However, levels of IGF-1 and IGFBP-3 were normal for all, except in P5, whose low BMI could indicate malnutrition associated with secondary IGF-1 deficiency.

One research objective of this study was to evaluate carbohydrate metabolism in these patients. Although the euglycemic-hyperinsulinemic clamp method is considered the gold standard technique to estimate insulin sensitivity, this approach can be invasive for patients with intellectual disabilities and behavioural disorders. Therefore, it is more appropriate to use a simple and indirect method, such as the HOMA-IR index (21), which estimates insulin resistance using a simple equation. However, the cut-off point for insulin resistance on this index remains a matter of controversy. In adults, more invasive techniques have confirmed a cut-off point of 3.8 (22). In children, such studies are more difficult and ethically controversial. However, a previous study in a Spanish cohort of 372 individuals established 3.42 as the cut-off point (23), and a recent meta-analysis of populations of various ethnicities indicated cut-off points between 2.30 and 3.54 (24).

Five participants, or approximately 21% of the study population, had HOMA-IR levels exceeding the respective 3.54 cut-off for insulin resistance in children (25) and the 3.8 cut-off for adults. Prepubertal participants P5, P7, and P8 had HOMA-IR values of 4.53, 5.54, and 7.2, respectively. Adults P21 and P22 had HOMA-IR values of 6.23 and 10.7, respectively. These results could be related to obesity and increased BMI, particularly in adults. However, the three prepubertal patients all had normal BMI and no family history or risk factors, such as hypertension or obesity, suggesting that CdLS may be associated with increased insulin resistance. Notably, a fasting insulin value above 16 µU/mL in children and adults is considered suggestive of hyperinsulinemia (22,25). Thus, all participants with elevated HOMA-IR values also had high blood insulin levels.

To the best of our knowledge, this is the first study to associate CdLS with elevated insulin and HOMA-IR values. It therefore seems reasonable to recommend follow-up assessments of carbohydrate metabolism in these patients. Close endocrinological follow-up is also necessary to assess nutritional status, growth, and pubertal development in patients with CdLS so that severe endocrinological alterations of central origin, such as hypothyroidism and/or hypogonadism, can receive appropriate treatment as soon as possible.

Limitations of this study include the low incidence of this rare disease and the absence of elderly participants. The method of measuring insulin resistance may also be considered a limitation although HOMA-IR is widely used as it is more practical. In most cases, hyperglycaemic/euglycemic clamp is the gold standard for quantifying *in vivo* insulin action, secretion, and disposal, but clamp studies are expensive to conduct and invasive, which raises ethical concerns

Table 1. Anthropometric values, clinical score and affected gene in individuals with CdLS patients

Patient	*P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age	2	2	3	3	3	4	5	5	7	8
Gender	M	M	M	M	F	M	F	F	M	F
Gene*	*H*	*N*	*N*	*N*	*N*	*N*	*R*	*S*	*N*	*N*
Clinical score*	11	14	7	14	15	13	8	5	6	13
Pubertal stage (Tanner)	I	I	I	I	I	I	I	I	I	I
Birth weight (SDS)	-1.24	-1.15	-1.08	-1.09	**-2.31**	**-2.17**	0.44	-1.04	-0.69	-1.9
Birth length (SDS)	**-2.57**	**-2.39**	-0.97	**-2.18**	-1.27	**-3.45**	-0.28	0.57	1.69	-1.96
Weight (kg)	10.2	9.9	14	9.8	6.63	12.1	11.5	20	19.2	16.8
Weight (SDS)	-2.12	**-2.66**	-1.29	**-2.6**	**-4.02**	**-2.23**	**-2.47**	-0.11	-1.3	-2.09
Height (cm)	78.2	81	95.2	87.2	78	93.3	98	108.8	115.2	111.1
Height (SDS)	**-3.93**	**-3.82**	**-2.09**	-3.47	**-5.49**	**-4.8**	**-2.98**	-0.98	-1.58	-3.61
BMI (kg/m^2)	16.6	15.09	15.45	12.89	10.8	13.9	11.9	16.9	14.47	13.6
BMI (SDS)	0.09	-1	-0.33	-1.75	**-2.88**	-1.04	-1.91	0.49	-0.89	-1.34
Waist circumference (cm)	-	-	-	39.7	-	-	43.2	57.7	-	45.4
Waist circumference (SDS)	-	-	-	**-2.66**	-	-	-3.15	0.39	-	-1.66

*Genes: *H (HDC8). N (NIPBL). R (RAD21). S (SMC1A). A (ANKRD11).*

Reference levels have been used according to age. sex and pubertal stage. Abnormal values are highlighted in bold. *HDC8, RAD21, SMC1A* and *ANKRD11* genes are highlighted in gray. *Clinical Score: According to Kline et al. (2) (2018) Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet; 19:649-666. Anthropometric values have been expressed in Z-scores according to the reference graphs [Spanish Growth Study 2010, Carrascosa Lezcano et al. (17)].

Abnormal values are highlighted in bold. *P: patient abbreviation.

CH: carbohydrate, IUGR: intrauterine growth restriction, BMI: body mass index, CdLS: Cornelia de Lange syndrome, SDS: standard deviation score

Table 2. Endocrine assessment in twenty four individuals with CdLS

Patient		*P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age		2	2	3	3	3	4	5	5	7	8
Gender		M	M	M	M	F	M	F	F	M	F
Thyroid axis/ prolactin	Thyrotropin	**5.94**	2.04	1.1	1.83	**0.26**	1.4	1.74	2.76	2.89	1.57
	Free thyroxine	1.23	1.41	0.99	1.28	1.28	1.24	1.6	1.07	1.22	1.25
	Prolactin	**38**	**90.6**	13.7	27	4.37	**28.9**	15.4	12.3	37.6	16.7
	Neuroleptic tx	-	-	-	-	-	-	-	-	+	-
Adrenal axis	Adreno-corticotropic hormone	50.4	-	17	32.9	19.3	46.9	17.4	30.7	21	16.8
	Cortisol	7.47	-	-	13.7	11.9	< 0.3	7.53	12.3	-	10.2
Gonadal axis	Luteinizing hormone	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3	< 0.3
	Follicle-stimulating hormone	1.35	2.1	0.87	0.56	0.75	0.48	1.97	1.58	0.4	1.48
	17-beta-estradiol	-	-	-	-	< 20	-	< 20	< 20	-	-
	Total testosterone	< 0.2	< 0.2	< 0.2	< 0.2	-	< 0.2	-	-	< 0.2	-
Growth axis	IGF-1	87.8	94.8	53.4	66.6	< 15	151	78.1	116	145	119
	Insulin-like growth factor-binding protein 3	2.71	3.2	2.32	2.15	1.85	4.61	3.08	3.6	3.95	4.67
Carbohydrate metabolism	Glucose	71	87	105	84	90	82	107	90	93	72
	Insulin	**15.2**	2	7.5	**14.3**	**20.4**	2.1	**17.2**	**32.4**	7.48	2
	HOMA-IR	2.66	0.42	1.95	2.96	**4.53**	0.42	**4.54**	**7.2**	1.71	0.36

Normal values: Glucose (60-100 mg/dL); insulin in children/adolescents (Tanner I: 0.62-11.57 µU/mL. Tanner II: 0.69-13.75 µU/mL. Tanner III: 3.42-16.28 µU/mL. Tanner IV-V: 2.02-20.76 µU/mL). Insulin < 15 µU/mL; thyrotropin (0.6-4.84 mU/L); thyroxine libre (0.97-1.67 ng/dL); prolactin: Male (4.04-15.2 ng/mL). Female (4.79-23.2 ng/mL); IGF-1 Tanner I (53-332 ng/mL). Tanner II (84-431 ng/mL). Tanner III (114-773 ng/mL) Tanner IV (217-843 ng/mL). Tanner V (147-842 ng/mL). adults 20-30 years (116-358 ng/mL). 30-40 years (109-307 ng/mL); IGF-BP3: Tanner I (1.3-6.3 microgr/mL). Tanner II (2.4-6.7 µg/mL). Tanner III (3.3-9.1 µg/mL). Tanner IV (3.5-8.6 µg/mL). Tanner V (2.7-8.9 µg/mL). Adults 20-30 years (3.4-7.8 µg/mL). 30-40 years (3.5-7 µg/mL); adrenocorticotropic hormone (0-46 pg/mL); cortisol (5-25 mcg/dL); luteinizing hormone prepubertal < 0.3 UI/L. pubertal: Male (1.7-8.6) UI/L. Female: follicular phase (2.4-12.6 UI/L). Ovulation phase (14.0-95.6 UI/L), luteal phase (1-11.4 UI/L); follicle-stimulating hormone prepubertal: Male (< 0.3-3) UI/L. Female (< 0.3-4) UI/L; pubertal: Male (15-12.4) UI/L. Female: follicular phase (3.5-12.5 UI/L). Ovulation phase (4.7-21.5 UI/L). Luteal phase (1.7-7.7 UI/L); 17-beta-estradiol: male (0-56) pg/mL. Female: prepuberal < 20 pg/mL puberal > 20 pg/mL; total testosterone: prepuberal < 0.2 ng/mL. Puberal > 0.2 ng/mL. Abnormal values are highlighted in bold. Tx: treatment abbreviation. *P: patient abbreviation

M: male, F: female, IGF-1: insulin-like growth factor-1, HOMA-IR: homeostatic model assessments of insulin resistance, CdLS: Cornelia de Lange syndrome

Table 1. Continued

Patient	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24
Age	9	11	11	14	15	15	16	17	20	23	25	30	31	37
Gender	F	F	F	M	F	F	F	M	F	M	F	F	F	F
Gene*	*N*	*N*	*S*	*N*	*N*	-	*N*	*N*	*N*	*N*	*N*	*A*	*N*	*N*
Clinical score*	-	14	14	14	7	11	15	14	16	13	-	9	9	13
Pubertal stage (Tanner)	II	II	III	I	V	V	III	III	V	V	V	V	V	V
Birth weight (SDS)	-0.07	-1.15	-1.98	**-2.45**	0.34	-0.87	**-3.44**	**-2.03**	**-3.78**	**-2.91**	**-2.1**	**-3.61**	**-0.83**	**-2.06**
Birth length (SDS)	**-5.11**	-1.61	-2.21	**-4.48**	-0.77	-0.44	-1.7	**-2.04**	**-5.73**	**-3.84**	**-2.9**	**-5.73**	-1.25	**-5.2**
Weight (kg)	20.6	18.8	26.5	43	58.8	40.2	24	50.5	22.8	43.3	96.2	54.8	36	62.8
Weight (SDS)	-1.83	**-2.42**	-1.91	-1.23	0.24	-1.5	-3.47	-1.65	-	-	-	-	-	-
Height (cm)	114.8	114	135	134	155.8	148.8	118	166.1	107	153.6	140.3	138.4	142.8	148.3
Height (SDS)	**-3.75**	**-4.8**	**-2.28**	**-3.79**	-1.01	**-2.04**	**-6.98**	1.44	-	-	-	-	-	-
BMI (kg/m^2)	15.6	14.4	14.54	23.95	24.22	18.16	17.2	18.3	19.9	18.31	**48.87**	**28.61**	17.65	**28.55**
BMI (SDS)	-0.82	-1.35	-1.47	0.74	0.87	-0.86	-1.39	-1.25	-	-	-	-	-	-
Waist circumference (cm)	56.4	49.8	-	76.8	73.8	63.5	-	70.4	-	67.2	-	76.6	57.8	86.5
Waist circumference (SDS)	-1.19	**-2.14**	-	0.14	1.39	-0.66	-	-0.35	-	**-2.11**	-	0.73	-1.79	**3.92**

Table 2. Continued

Patient		P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24
Age		9	11	11	14	15	15	16	17	20	23	25	30	31	37
Gender		F	F	F	M	F	F	F	M	F	M	F	F	F	F
Thyroid axis/ prolactin	Thyrotropin	2.23	2.39	0.94	1.18	2.09	2.07	0.78	1.57	1.33	0.74	0.69	1.57	1.29	1.04
	Free thyroxine	1.08	1.44	1.2	1.2	0.92	1.21	1.13	1.21	**0.84**	1.18	1.59	**0.94**	1.27	0.98
	Prolactin	20.8	5.37	**33.6**	**40.4**	**26.5**	**29.6**	9.06	**34.6**	12.4	60	12.5	**29.6**	14	11.3
	Neuroleptic tx	-	-	+	+	-	-	-	+	-	+	+	+	-	-
Adrenal axis	Adreno-corticotropic hormone	**182**	13.3	10.6	60	13.7	35.7	10.9	28.9	-	11	16.9	9.6	6.33	7.61
	Cortisol	13	7.66	9.16	16.6	8.2	9.89	7.35	14.7	-	7.28	9.27	3.46	6.44	9.15
Gonadal axis	Luteinizing hormone	1.82	**0.58**	13.1	4.74	11.3	3.05	3.68	5.52	9.82	4.31	10.2	4.78	12.6	2.66
	Follicle-stimulating hormone	3.87	6.95	4.08	8.76	5.3	2.14	4.65	7.48	4.44	5.58	6.45	5.71	6.96	4.25
	17-beta-estradiol	61.4	41.6	73.7	-	112	143	32.1	-	-	-	54.5	35.5	108	73.9
	Total testosterone	-	0.58	-	0.4	-	-	-	3.22	-	3.98	-	-	-	-
Growth axis	IGF-1	245	164	266	213	279	282	194	259	-	157	214	118	124	164
	Insulin-like growth factor-binding protein 3	6.34	4.6	4.81	5.89	6.62	6.36	5.56	5.6	-	4.81	4.77	3.68	3.5	5.94
Carbohydrate metabolism	Glucose	94	86	91	90	82	79	75	87	86	**102**	85	**115**	80	87
	Insulin	9.32	8.57	7.85	8.36	9.38	14.6	14.4	9.3	-	14.7	**29.7**	**37.8**	16.6	9.36
	HOMA-IR	2.16	1.82	1.76	1.85	1.89	2.84	2.66	1.99	-	3.7	**6.23**	**10.7**	3.27	2.01

for populations with physical, cognitive, and medical challenges, such as those with CdLS. Less invasive methods were used to evaluate axis integrity, including the luteinizing hormone-releasing hormone response test and thyrotropin-releasing hormone test, and the HOMA-IR index was used as a surrogate marker of insulin resistance.

Conclusion

Individuals on the CdLS spectrum may have dysregulation of the endocrine system, especially altered prolactin levels and also mildly delayed puberty, cryptorchidism, and short stature. In addition, some of the HOMA-IR assessments of patients in this study suggest early development of insulin resistance. Therefore, clinical follow-up with comprehensive hormonal assessment appears warranted in individuals with CdLS.

Ethics

Informed Consent: Informed consent from participants, their parents, or legal guardians was obtained before entry into the study.

Authorship Contributions

Surgical and Medical Practices: Ángela Ascaso, Ana Latorre-Pellicer, Beatriz Puisac, María Arnedo, Ilaria Parenti, Elena Llorente, Juan José Puente-Lanzarote, Ángel Matute-Llorente, Ariadna Ayerza-Casas, Frank J. Kaiser, Concept: Feliciano J. Ramos, Juan Pié Juste, Gloria Bueno-Lozano, Design: Feliciano J. Ramos, Juan Pié Juste, Gloria Bueno-Lozano, Data Collection or Processing: Ángela Ascaso, Laura Trujillano, María Arnedo, Juan José Puente-Lanzarote, Ángel Matute-Llorente, Analysis or Interpretation: Ángela Ascaso, Ana Latorre-Pellicer, Beatriz Puisac, Laura Trujillano, Juan Pié Juste, Gloria Bueno-Lozano, Literature Search: Ángela Ascaso, Ana Latorre-Pellicer, Juan Pié Juste, Gloria Bueno-Lozano, Writing: Ángela Ascaso, Beatriz Puisac, Laura Trujillano, María Arnedo, Juan José Puente-Lanzarote, Ariadna Ayerza-Casas, Frank J. Kaiser, Feliciano J. Ramos, Juan Pié Juste, Gloria Bueno-Lozano.

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