ORIGINAL PAPER

Congenital penile curvature as a possible risk factor for the onset of Peyronie's disease, and psychological consequences of penile curvature

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__Summary__ *Objective: To investigate a possible relation-*
ship between a history of congenital penile
curvature (CPC) and Peyronie's disease (PD), and to character-
ize the psychological profile of patients suffering from PD, with
or without concomitant CPC.
Methods: We included 519 patients with Peyronie's disease
(PD), of which 73 were found to have underlaying CPC. As a
comparator population, we selected 2166 patients without PD,
referring to our tertiary care clinic. In this population we
detected 15 subjects with CPC. All patients completed the GAD-
7 (Generalized-Anxiety-Disorder - 7 questions) and the PHQ-9
(Patient-Health-Questionnaire - 9 questions) questionnaires.
Results: The overall prevalence of CPC in PD-patients was
14.07%, compared to a prevalence of 0.69% in the non-PD con-
trol population (p < 0.00001). Moderate-to-severe anxiety was
found to be present in 89.4% of all PD-patients.
Significantly higher proportions of patients with CPC associated
with PD showed severe anxiety, compared to patients with PD
alone (57.5% vs. 36.7%, respectively, p = 0.0008). Moderate-
severe depression was found to be present in 57.8% of all PD-
patients. Significantly higher proportions of PD patients with a
history of CPC showed severe depression, compared to patients
with PD alone (13.6% vs. 3.36%, respectively, p < 0.0002).
GAD-7 median scores were significantly higher in patients with
more severe penile curvatures (> 45°; p = 0.029). We did not
detect a statistically significant difference between PHQ-9 medi-
an scores based on the severity of PD (p = 0.53). Analysis of
PHQ-9 and GAD-7 median scores showed significantly worse
depressive and anxious symptoms in younger patients
(p < 0.001 and p = 0.0013, respectively).
Conclusions: The presence of congenital-penile-curvature may
represent a risk factor for the subsequent onset of Peyronie's
disease. Moderate/severe anxiety and moderate/severe depres-
sion were reported in a high fraction of cases. Anxiety was sig-
nificantly higher in patients with more severe penile-curvatures,
and depression was present independently of the degree of
penile curvature. Depression and anxiety were found to be more
severe in younger subjects.

KEY WORDS: *Congenital penile curvature; Peyronie's disease;*
Risk factors.

INTRODUCTION

Congenital Penile Curvature (CPC) is a genetically inherited condition characterized by the presence of penile curvature. This malformation, already present at birth, is evident during erection and manifests in the absence of a demonstrable organic penile pathology. The pathogenesis of CPC is unknown (1, 2). However, it has been proposed that CPC may be caused by local androgen insufficiency determined by fetal androgen deficiency. Alternatively, local deficiency of 5-alpha reductase, capable of causing penile malformation, has been proposed (3, 4). An ultrastructural study of the tunica albuginea, performed on tissue samples belonging to the '*lozenge*' removed during Nesbit's corrective surgery at the level of the external curvature (the zone of the concave angle), demonstrated the presence in this area of disruption of the tunica albuginea, associated with a chaotic alignment of collagen fibers, able to interfere with the normal mechanical properties of the same albuginea (*Darewicz et al.*, 2001) (5). In the frame of the same study, the authors analyzed microscopically the tissue contralateral to the lesions, at the inner side of the curvature, on the side of the convex angle. Normal extension of the fibroblasts and blood vessels was demonstrated. Moreover, in the latter tissue collagen fibers were shown to be normal both in quantity and in quality and organization. The Authors concluded that the diseased area which causes the curvature is located at the level of the tunica albuginea on the external side, i.e. at the level of the great curvature, whereas the "*diseased*" albuginea is more yielding and extensible, causing this side of the penis to curve towards the opposite side (5).

The prevalence of congenital penile curvature is very low and ranges between 0.04 and 0.6% (6-8) of the total population. The incidence of the various types of curvature shows minor variations among different authors: ventral curvatures occur in about 50% of cases, lateral ones in about 25% of cases (20% left, 5% right), mixed ventral/lateral ones in about 20-23% of cases, whereas dorsal curvatures are found in about 5% of cases (6, 9, 10).

The incidence of the different degrees of curvature varies between different studies. According to various – and sometimes diverging – opinions, curvatures between 30 and 60 degrees show incidences ranging between 44 and 74%, whereas curvatures above 60 degrees are found by

some in about 32% of cases. Alterations of 90 degrees show incidences of about 25%, whereas curvatures below 30 degrees are found in about 40% of cases (6, 9, 10).
CPC (also referred to by some authors as "*penile chordee*") is often associated with hypospadias, as only 4-10% of cases are not associated with this condition (11).
Corporoplasty is the surgical treatment indicated for CPC (1). The most frequently used corporoplasty techniques include the Nesbit procedure and its modifications, albuginea plication techniques, or techniques exploiting the insertion of grafts, aimed at lengthening the penis (10, 12-17).
Peyronie's disease (PD) is an acquired penile curvature consisting of a chronic inflammation of the tunica albuginea of penile corpora cavernosa (18). Although a genetic origin of the disease has been demonstrated, there is not unanimous agreement on its pathogenesis. Trauma appears to be the triggering cause of the onset of the disease, which finally results in deformation of the penis (curvature, hourglass shape, shortening, etc.). The condition is also associated with penile pain, erectile dysfunction and depression (19-22). The incidence of the disease ranges between 3.2% and 13% (23-25). The pathogenesis of PD occurs in two main phases. Initially, an active inflammatory phase takes place, whereby the plaque is formed, subsequently progressing to fibrosis and possible calcification. This stage is characterized by pain and by the progressive worsening of the deformation. In the second stage (the stabilization phase), pain has disappeared, and the deformation has stabilized. During the first phase, conservative medical treatment is indicated, including oral antioxidants, Vitamin E, non-steroidal anti-inflammatory drugs, penile injections with various drugs (verapamil, interferon-α2b, cortisone, pentoxifylline, collagenase, hyaluronic acid, etc.), and physical therapies (SWT, iontophoresis, vacuum penile and traction devices) (26-28). The surgical treatment is indicated in the second phase of the disease, when the curvature is severe and/or when severe erectile dysfunction occurs. The surgical techniques for PD differ according to the specific clinical condition and consist of corporoplasty (simple or with use of grafts), with or without application of penile prostheses (29-31).

Psychological consequences of congenital or acquired penile curvature

The presence of a deformation of the penis showing different degrees of severity can affect the psychological equilibrium and the psycho-social relationships of the patients, resulting in a negative impact on the *quality of life* (QoL). It has been documented that depression may occur in 48% of cases of Peyronie's disease, and in 65% of cases of congenital penile curvature (22, 32). Patients with penile deviation may show erectile dysfunction caused by sexual performance anxiety. This may be associated with a loss of personal body image, with reduced self-esteem and with a lack of confidence in the ability to achieve a satisfactory sexual intercourse (32). In this respect, surgical treatments have been shown to drastically improve the psychological state and the QoL of patients (2, 32, 33).
It is established that a diagnosis of PD is associated with alterations of the psycho-social functioning of affected subjects, who may show an array of conditions linked to each other and able to reinforce each other, including depressive symptoms, social isolation, stigmatization and sexual difficulties (34, 35).
Considering that PD does not affect all males, but only a fraction of those who are genetically predisposed, it may be hypothesized that congenital penile curvature could represent a risk factor for males genetically predisposed to PD. According to this hypothesis, CPC would favor traumatic events of different degrees of severity during coitus (36-38). In fact, repeated intercoital thrusts can cause microtraumas in the context of the tunica albuginea of the corpora cavernosa, thus giving rise to the events underlying the formation of the plaque: delamination of the tunica albuginea, micro-hematoma, accumulation of fibrin, recruitment of macrophages, lymphocytes, platelets and fibroblasts, production of pro-inflammatory cytokines, and production and accumulation of collagen (26, 39).
The present study was aimed at studying the relationship between a history of congenital penile curvature and Peyronie's disease. The psychological impact of PD, in the presence of absence of concomitant CPC, was also investigated in depth.

PATIENTS AND METHODS

We performed a retrospective analysis of the clinical database of a single andrology clinic. From the database we extracted two separate cohorts of patients referring to a single urology/andrology clinic between January 2013 and December 2022. One cohort included patients diagnosed with *Peyronie's disease* (PD). As a comparator population, we extracted a cohort of urological patients without PD. All data were obtained from the available patient records.
This retrospective observational study was conducted in compliance with the principles contained in the Declaration of Helsinki (*Fortaleza, 2013*) (40): all study subjects were contacted and gave their informed consent to the study. Sensitive data have in any case been anonymized in respect of privacy according to Legislative Decree 10 August 2018, n. 101 adapted to the GDPR (*Official Gazette of the Italian Republic, General Series n.205, dated 04-09-2018*).
Inclusion criteria for the study were an age between 18 and 75 and the completion of two validated psychometric tests: the *Generalized Anxiety Disorder - 7 questions* (GAD-7) and the *Patient Health Questionnaire - 9 questions* (PHQ-9) (41, 42). A diagnosis of CPC was not an exclusion criterion for the present study.
The specific inclusion criterion for the PD cohort was a documented diagnosis of Peyronie's disease.
The exclusion criteria for the comparator control cohort were a diagnosis of Peyronie's disease or *erectile dysfunction* (ED).
The primary endpoint of the study was the association between a history of CPC and the occurrence of PD in a patient population referring to a single tertiary care andrology center.
Secondary endpoints were the impact of the degree of penile curvature or of the age on the psychological profile of patients showing PD and/or CPC, assessed with the GAD-7 and PHQ-9 tests.

Statistical analysis

To investigate an association between PD and a history of CPC, we calculated the Pearson's Chi-squared test with Yates' continuity correction. Statistical analysis was performed on the 'R' software environment for statistical computing and graphics.

We performed a post-hoc analysis of the statistical power achieved for the crude odds-ratio calculation using the G*Power 3.1 software (43).

We investigated by the Mann-Whitney-Wilcoxon test the impact of the degree of the penile curve on the median scores of the GAD-7 or PHQ-9 questionnaires in patients stratified in two groups (Group A, curve between 0-45 degrees; Group B, curve > 45 degrees).

We analyzed by the Mann-Whitney-Wilcoxon test the impact of the age of patients on the median scores of the GAD-7 or PHQ-9 questionnaires in patients stratified in two groups (Group A, age up to 40 years; Group B, age > 40 years).

The significance of differences between prevalences/proportions was analyzed by a Z-test.

Statistical analysis was performed on the 'R' software environment for statistical computing and graphics. Two-sided crude odds ratios and 95% confidence intervals (95% CIs) were calculated using the 'Epitools' package for 'R'.

All statistical analyses were two-tailed. A 5% threshold for an alpha error was used to define statistical significance (significant P-value < 0.05).

RESULTS

We extracted from our database 519 patients meeting the inclusion criteria for this study, consecutively diagnosed with *Peyronie's disease* (PD) between January 2013 and December 2022. As a comparator population, we extracted 2166 patients without PD and/or ED and meeting our inclusion criteria, referring to our tertiary care clinic for urological diseases.

Characteristics of congenital penile curvature

The characteristics of the of CPC detected in 88 patients with or without PD, the prevalence and the degree of the different types of penile curvature are presented in Table 1. The curvature angle was found to vary between 5 and 45 degrees. Of the 73 patients with CPC who subsequently developed PD, 32 (43.8%) reported significant penile trauma in the weeks/months preceding the onset of the disease.

Notably, patients with CPC of the lateral type remember their previous penile trauma more frequently.

Prevalence of CPC in PD vs. non-PD patients

In the cohort of 519 patients diagnosed with PD, 73 had a documented history of CPC (14.07%), whereas in the comparator population (n = 2166) CPC was reported in 15 cases (0.69%).

The chi-square value for the comparison between frequencies of CPC in the PD and control cohorts was 201.65 (p < 0.0001). The Z ratio was 15.4 (p < 0.001).

We generated a contingency table comparing the presence/absence of a history of CPC in patients diagnosed or not with PD. The resulting significant crude odds ratio for CPC was 23.23 (95% CI, 13.57 to 42.51, p < 0.0001). Post-hoc analysis showed an achieved power equal to 0.99 for the magnitude of effect (odds ratio) and 95% CI shown above.

Psychological profile of patients with PD with or without CPC

The prevalence of anxiety in PD patients with or without CPC was assessed with the GAD-7 test. Moderate to severe anxiety (GAD-7 score > 9) was reported in 89.4% of total patients (Table 2). Significantly higher proportions of patients with CPC associated with PD showed severe anxiety, compared to patients with PD alone (57.5% *vs.* 36.7%, respectively, p = 0.0008).

Conversely, moderate anxiety was reported more frequently in patients with PD alone than in subjects with CPC associated with PD (52.2% *vs* 34.2%, respectively; p = 0.004).

Table 1.

Typology of congenital penile curves and their characteristics in CPC patients with or without PD.

	Type of congenital penile curvature	Number of cases (%)	Degrees of penile curvature	No. and (%) of cases with memory of previous penile trauma
Patients with PD	Lateral	48 (65.7)	5-40	20 (27.39)
	- left side	35 (47.9)	5-30	13 (17.8)
	- right side	13 (17.8)	5-40	7 (9.58)
	Ventral	11 (15.06)	10-40	5 (6.8)
	Ventral and left side	3 (4.1)	5-10	1 (1.3)
	Dorsal	9 (12.3)	10-45	5 (6.8)
	Dorsal and left side	2 (2.7)	5-10	1 (1.3)
	Total	73	-	32 (43.8)
Patients without PD (control cohort)	Lateral	13 (86.6)	5-45	0
	- left side	10 (66.6)	10-30	0
	- right side	3 (20.0)	5-45	0
	Ventral	1 (6.6)	10	0
	Ventral and left side	-	-	-
	Dorsal	-	-	-
	Dorsal and left side	1 (6.6)	15	0
	Total	15		0

Table 2.

Prevalence of anxiety in PD patients with or without CPC, assessed with the GAD-7 test.

	GAD-7 Score range	No. total cases (%)	No. cases with PD and CPC (%)	No. cases with PD alone (%)	Z-ratio (P)
No anxiety	0	2 (0.38)	2 (2.7)	0 (0)	Not assessable
Minimal or mild anxiety	1-9	53 (10.2)	4 (5.4)	49 (10.9)	-1.073 (0.28)
Moderate-severe anxiety	10-21	464 (89.4)	67 (91.7)	397 (85.5)	0.71 (0.47)
- Moderate anxiety	10-14	258 (42.0)	25 (34.2)	233 (52.2)	-2.85 (0.004)
- Severe anxiety	15-21	206 (39.6)	42 (57.5)	164 (36.7)	3.36 (0.0008)
Total		519	73	446	

The prevalence of depression in PD patients with or without CPC was assessed with the PHQ-9 test. Moderate to severe depression (PHQ-9 score > 9) was reported in 57.8% of total patients (Table 3). Significantly higher proportions of PD patients with a history of CPC showed severe depression, compared to patients with PD alone (13.6% *vs.* 3.36%, respectively, p < 0.0002).

The impact of the severity of the penile curvature on the profile of anxiety or depression of PD patients was further investigated by dividing PD patients (irrespectively of concomitant CPC) in two groups, using 45 degrees as a curve cutoff value (Group A, ≤ 45 degrees; Group B, > 45 degrees). GAD-7 median scores were significantly higher in patients with more severe penile curvatures (p = 0.029, Table 4). Conversely, we did not detect a statistically significant difference between PHQ-9 median scores based on the severity of penile curvature (p = 0.53, Table 4). These results indicate that in PD patients depression can manifest independently of the degree of penile curvature. In addition, we investigated the impact of age on the median scores of both the GAD-7 and PHQ-9 questionnaires, by dividing PD patients (irrespectively of concomitant CPC) into two main age categories, using 40 years as cutoff value (Group A, ≤ 40 years; Group B, > 40 years). PHQ-9 median scores were significantly higher in younger patients (p < 0.001, Table 5). Despite identical median values of GAD-7 scores, a significant intergroup difference was found with the Mann-Whitney-Wilcoxon test (0.0013). Most likely, and similarly to the PHQ-9 analysis, younger patients show a higher degree of anxiety, since GAD-7 mean values were higher (16.21 ± 3.99) than the mean values assessed in older individuals (14.66 ± 4.66). These results indicate that younger PD patients may have a more pronounced anxious profile.

DISCUSSION

A large number of studies have demonstrated the existence of several risk factors that can increase the possibility of developing PD. These risk factors include penile trauma, smoking, diabetes mellitus, hypertension, Dupuytren's disease, alcohol consumption, erectile dysfunction, obesity, dyslipidemia, psoriasis, psoriatic arthritis, and rheumatoid arthritis (44-49).

To our knowledge, this is the first study investigating the association between PD and CPC. Our results show that the overall prevalence of CPC in patients with PD was significantly higher (14.07%), compared to the prevalence in a non-PD control population (0.69%). These data suggest that the presence of *congenital penile curvature* (CPC) may represent a risk factor for the subsequent onset of *Peyronie's disease* (PD).

A search in the scientific literature retrieved a single article that approaches on the subject (50).

In presenting the results of their study, the Authors made no reference to CPC as a possible risk factor for PD. The study included a sample of 60 patients who had already undergone tunica albuginea plication surgery (50). The authors specified that 21 patients reported worsening over time of the original congenital curve. The Authors also added that these patients were older (mean age 34 years) and showed signs of Peyronie's disease (penile shortening, history of penile trauma, palpable penile plaque, etc).

In our study we diagnosed various types of congenital penile curves, although, unlike other authors we detected more frequently lateral congenital curves instead of ventral congenital curves (6, 9, 10).

Our results revealed that severe or moderate anxiety was present in 89.4% of PD patients. Although in the literature there is no precise data regarding the incidence of anxiety symptoms during PD, *Smith and co-workers* reported that 81% of PD patients included in their study reported '*emotional difficulties*' (51). We also found that severe anxiety is more prevalent in PD patients showing the concomitant presence of CPC, compared to PD alone (57.5 *vs.* 36.7, respectively).

Table 3.
Prevalence of depression in PD patients with or without CPC, assessed with the PHQ-9 test.

	PHQ-9 Score range	No. total cases (%)	No. cases with PD and CPC (%)	No. cases with PD alone (%)	Z-ratio (P)
No depression	0	2 (0.38)	2 (2.7)	0 (0)	Not assessable
Minimal or mild depression	1-9	217 (41.8)	26 (35.6)	191 (42.8)	-1.15 (0.24)
Moderate-severe depression	10-27	300 (57.8)	45 (61.6)	255 (57.1)	0.71 (0.47)
- Moderate depression	10-14	186 (35.8)	25 (34.2)	161 (36.09)	-0.31 (0.75)
- Moderately severe depression	15-19	89 (17.1)	10 (13.6)	79 (17.7)	-0.84 (0.39)
- Severe depression	20-27	25 (4.8)	10 (13.6)	15 (3.36)	3.92 (< 0.0002)
Total		519	73	446	

Table 4.
GAD-7 and PHQ-9 median scores in patients stratified according to penile curvature angles.

Questionnaires administered	Group A (n = 449) angle of penile curvature ≤ 45 degrees	Group B (n = 70) angle of penile curvature > 45 degrees	P-value (Mann-Whitney-Wilcoxon)
PHQ-9 Median, IQR (mean ± SD)	10 (8) (10.68 ± 4.99)	12 (6) (11.14 ± 5.09)	0.53
GAD-7 Median, IQR (mean ± SD)	14 (7) (14.89 ± 4.49)	14.5 (8) (15.94 ± 4.86)	0.029

IQR: Interquartile range; SD: Standard deviation.

Table 5.
GAD-7 and PHQ-9 median scores in PD patients stratified by age.

Questionnaires administered	Group A (n = 126) angle of penile curvature ≤ 40 degrees	Group B (n = 393) angle of penile curvature > 40 degrees	P-value (Mann-Whitney-Wilcoxon)
PHQ-9 Median, IQR (mean ± SD)	12.6 (13 ± 5.04)	10.8 (10.02 ± 4.78)	< 0.0001
GAD-7 Median, IQR (mean ± SD)	14.7 (16.21 ± 3.99)	14.7 (14.66 ± 4.66)	0.0013

IQR: Interquartile range; SD: Standard deviation.

In a study about the chronology of depression and distress in men with Peyronie's disease, *Nelson and coworkers* demonstrated that 48% of patients show clinically meaningful depression, assessed with the *Center for Epidemiologic Studies Depression Scale* (CES-D) (22). In our study moderate to severe depression was reported in a higher fraction of patients (57.8%). However, a direct comparison is hampered by the different psychometric scales used in the two studies. Beside corroborating the available evidence, our study suggests that, if not investigated in patients with PD by means of specific questionnaires, depressive and anxious symptoms may generally be underestimated in terms of severity and prevalence.

In addition to the data in the overall PD population, we have also found that severe depression was present in a significantly higher fraction of patients with PD and concomitant CPC (13.6%) compared to patients with PD alone (3.36%).

In our study we have shown that patients with more pronounced penile curves (> 45 degrees) show a higher degree of anxiety. Conversely, analysis of PHQ-9 median scores using the 45-degree cutoff showed that PD patients develop various degrees of depression independently of the degree of penile curvature. Articles containing similar considerations are present in the literature (34, 52-54).

Furthermore, when we investigated a possible relationship between the scores of the GAD-7 and PHQ-9 questionnaires and the age of patients (age cutoff, 40 years) we noticed that younger patients show more severe depressive and anxious profiles.

Since age and the degree of penile curvature are potential factors for the development of psychological difficulties, it is deemed necessary to refine the diagnostic profiling of PD patients; a deeper understanding of these aspects may lead to the improvement of therapy protocols and their outcomes.

CONCLUSIONS

The presence of congenital penile curvature may represent a risk factor for the subsequent onset of Peyronie's disease. Although the present study presents the limitations of a retrospective analysis of a patient database, the magnitude of the effect size, its statistical significance and the achieved power support the relative robustness of our results.

Nevertheless, further studies are needed to confirm CPC as a risk factor for PD, and also to investigate in depth the psychological effects of penile curvature.

Patients with PD and CPC showed a significantly higher prevalence of more severe depression and anxiety.

Patients with more pronounced penile curves show a higher degree of anxiety, compared with subjects showing a less severe curvature.

Depression and anxiety appear to be age-related, as their severity was shown to be higher in younger subjects.

In the uro-andrological clinical practice a multidisciplinary approach with the involvement of psychologists would be desirable, in order to offer PD patients psychological support treatment, which can in turn prevent or attenuate the psychological impact of this disease, which has been defined by some eminent authors a psychologically and physically devastating disorder (55-59).

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