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Risk of juvenile fibromyalgia among Taiwan adolescents: Nationwide population-based study from 2000 to 2010

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Abstract

Background: The incidence of juvenile fibromyalgia (JFM) in Taiwan has yet to be documented. As such, we investigated the incidence, risk factors, and comorbidities of JFM in this country.

Methods: We analyzed the 2000–2010 claims data of outpatients diagnosed with JFM (ICD-9-CM codes 729.1) from the National Health Insurance Research Database.

Results: A total of 9,808 females (52.38%) and 8,916 males (47.62%) were included in this study. The

male-to-female ratio was 0.99–0.95 among 16- to 18-year-old individuals. The JFM with the highest incidence was observed in the 15- to 18-year-old age group. The annual incidences of JFM peaked in 2004 (235.10 per 1,000 people/year). Comorbidities with all JFM included Signs, symptoms, and ill-defined conditions(65.29%) and Gastrointestinal conditions (17.86%). The incidence of JFM among the female patients with Signs, symptoms,and ill-defined conditions and Gastrointestinal conditions were significantly higher than that among the patients without JFM (OR = 1.09, 95% confidence interval (CI) = 1.03–1.16, $p <$ 0.003; OR = 1.10, 95% confidence interval (CI) = 1.01–1.20, $p <$0.026). The incidence of JFM among the male patients with Signs, symptoms, and ill-defined conditions was significantly higher than that among the patients without JFM (OR =1.09, 95% confidence interval (CI) = 1.03 –1.16, $p < 0.0062$).

Conclusions: Differences in comorbidities with JFM were observed. Additional multidisciplinary intervention strategies should be developed to detect and treat JFM.

Keywords: juvenile fibromyalgia, adolescents, pediatric, incidence, nationwide population-based study

Introduction:

Juvenile fibromyalgia (JFM) is characterized by generalized pain and chronic fatigue of unknown etiology. Previous studies reported the incidence of JFM among school children aged 9–15 years; approximately 1.2%–6.2% of these children suffer from JFM [1–3]. The condition is characterized by musculoskeletal pain and other associated symptoms, including morning stiffness, fatigue, sleep problem, lightheadedness, irritable bowel symptoms, dysautonomia, and mood disorders, such as anxiety, depression, and cognitive dysfunction[4–7]. Chronic pain in children is associated with a significantly negative effect on physical activity and social, emotional, and school functioning [1, 3, 8]. Patients with JFM experience significantly greater anxiety and depressive symptoms and emotional impairment than those without JFM; the lifetime prevalence of major depression is approximately 26% in children with JFM [2, 9–11]. In children that exhibit long school absences, severe limitations are observed in daily living activities, physical inactivity, or exacerbated social isolation; the absence from school can also adversely affect a child's quality of life and family relationships[3, 8, 12–14].

JFM is a chronic pain disorder that affects approximately 1.2%–6.2% of children and adolescents in a general population; the disorder occurs more frequently in females than in males[15–17]. JFM most frequently affects children aged approximately 10 years, with a male-to-female ratio of 1:4–8[18]. Most adolescent female patients and patients with JFM constitute 7%–15% of referrals to pediatric rheumatology clinics [6,7]. The condition has been found in 52% of female adolescents admitted for psychiatric treatment [5,19]. Epidemiologic studies have further revealed a high prevalence (25%–46%) of chronic pain in children and adolescents; the prevalence also increases with age [20–22]. Females are more likely diagnosed with JFM than males. JFM affects approximately 2% of the general population and is seven times more likely to occur in females than in males [23]. However, occurrence may be similar between females and males in younger age groups [24]. The prompt recognition of JFM may alleviate problems among pediatric patients with chronic pain, but the lack of familiarity regarding JFM of pediatric primary care providers can cause a delay in diagnosis [12].

In Taiwan, the National Health Insurance (NHI) program covers most of the population. The coverage rate in 2000 was 96.16%. Most medical institutions (93%) provide NHI, which is a large sample national health claims database. The majority of patients have likely been attended to by primary care physicians. The prevalence rate of JFM has been reported as 1.2%–6.2% of patientsI in previous studies[15–25]. However, the incidence of JFM among patients in Taiwan has yet to be documented. Therefore, we investigated the incidence of JFM among patients in Taiwan; we also determined the incidence, gender, age, and comorbidities associated with JFM.

Methods

Data collection

We performed a population-based retrospective cohort study. The Taiwanese National Health Insurance Bureau (NHIB) provides electronic data, including patients' gender and birth date, classification codes of diagnosed diseases, health services, and clinic or hospital codes. In March 1995, the NHI service was initiated in Taiwan to provide comprehensive medical care to the public. According to the NHI annual statistics report, the coverage rate of NHI in 2007 was approximately 98.6% of the entire population of Taiwan, with more than 25 million individuals enrolled in the program. The JFM case data from 2000 to 2010 were collected from the Taiwanese NHIB, and 1 million cases were considered for this longitudinal study.

The general population employed in this study included 9,808 females and 8,916 males. The JFM cases (ICD-9-CM: 729.1) from 2000 to 2010 were identified from the NHIRD by ICD-9-CM. We excluded patients with diseases that differed from fibromyalgia; such conditions were rheumatic or collagen diseases, including juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, Sjoegren syndrome, and vasculitis syndrome, particularly Takayasu's aortitis. The average age-specific incidences in the target period were further compared and analyzed. This study protocol was approved by the Institutional Review Board Committee of China Medical University Hospital (CMUH103-REC1-088).

Comorbidities

The following criteria were based on the diagnostic guide for juvenile primary fibromyalgia: 1, generalized musculoskeletal aching for at least 3 months; 2, more than 11 of 18 tender points; and 3, laboratory findings, including inflammatory markers, such as white blood cell counts, erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, within the normal range. Anti-nuclear antibody, rheumatoid factor, and anti-SSA/Ro antibody can be either positive or negative. 4, Absence of an underlying condition or cause, such as juvenile idiopathic arthritis, juvenile dermatomyositis, Sjoegren syndrome, systemic lupus erythematosus, mixed connective tissue disease, and others. Ascertainment is as follows. I. Clinical manifestations: 1. Hypothermia (<36 ℃), 2. Chronic sense of fatigue, 3. Sleep disturbance (hard to go to sleep, frequent arousal during the night), 4. Chronic headaches and/or lumbago 5. Irritable bowel syndrome, 6. School absences (school rejection syndrome), 7. Autonomic signs (dyshidrosis, hypotension, and car sickness), 8. Allodynia, 9. Pain modulation by weather factors, 10. Chronic anxiety or tension. II. Specific personality traits: 1. so-called "good kid," 2. Perfectionist, 3. Neatness fanatic, 4. Intransigent, 5. Communication disorder, 6. Too much concern for other people [16]. We analyzed the JFM-associated comorbidities, includingsigns, symptoms, ill-defined conditions, gastrointestinal conditions, sleep disorders, mental disorders, and fatigue-related conditions. The JFM cases from 2000 to 2010 were identified from the NHIRD by ICD-9-CM (Table 3).

Statistical analyses

Age- and gender-specific incidence rates were calculated on the basis of year by using the NHIRD population. The annual incidences of JFM and hospital characteristics, comorbidities, OR, and 95% CIs were calculated. The annual incidence was calculated by dividing the

number of new cases in a specific period by the number of individuals in the population at risk at the beginning of the study. A two tailed $p < 0.05$ was considered statistically significant. Data were analyzed with SPSS version 17.0.

Results

A total of 18,724 patients with JFM (9,806 females and 8,9816 males) from 2000 to 2010 were enrolled in the study. The average ages of the females and males were 13.96 and 14.36 years, respectively. Among the male and female age groups, the 18-year-old group exhibited the highest incidence of JFM [11,17]. The percentage of female subjects compared with male subjects was 52.38% versus 47.62% [odds ratio (OR) = 6.21, 95% confidence interval (CI) = 5.31– 7.26, $p < 0.0001$). The female-to-male ratio was 0.86–1.38. A female-to-male ratio of 0.99–0.95 was found among 16- to 18-year-old subjects (Table 1).

Table 2 shows that all JFM of the annual incidence was 145.27–257.97 per 1,000 people/year. The annual incidences of females with JFM increased from 2002 (226.08per 1,000 people/year) to 2004 (248.78per 1,000 people/year) and peaked in 2004 year. The annual incidences of males with JFM increased from 2002 (243.03per 1,000 people/year) to 2004 (267.51per 1,000 people/year) and peaked in 2004 year.

In the Taiwanese population, the incidence rate of females with JFM was higher than that of males with JFM from 2000 to 2010. In 2002,2006 and 2007, the incidence rate of females was also higher than that of males (OR = 6.16, 95% CI = 3.02–12.56, $p < 0.0001$;OR = 2.68, 95% CI = 2.03–3.53, $p < 0.0001$; OR = 4.15, 95% CI = 3.18–5.42, $p < 0.0001$(Table 2).

Table 3 shows the percentage of comorbidities in patients with JFM and the relative occurrence of the disease between the gender groups. We also examined the association between all JFM and the following comorbidities: signs, symptoms, and ill-defined conditions, including headache ,chest pain, abdominal pain, and anxiety-related symptoms (65.29%); gastrointestinal conditions (17.86%); sleep disorders (11.20%); fatigue-related conditions (3.44%) and mental disorders (2.22%). These conditions were also the leading comorbidities affecting all JFM patients. The female-to-male ratios of gastrointestinal conditions, sleep and mental disorders were 2.81, 2.18 and 2.15, respectively (Table 3).

Table 4 shows a comparison of the clinical-related comorbidities between patients with and without JFM. The incidence of JFM among the female patients with Signs, symptoms, and

ill-defined conditions and Gastrointestinal conditions were significantly higher than that among the patients without JFM (OR = 1.09, 95% confidence interval (CI) = 1.03–1.16, $p <$ 0.003; OR = 1.10, 95% confidence interval (CI) = 1.01–1.20, $p <$0.026). The incidence of JFM among the male patients with Signs, symptoms, and ill-defined conditions was significantly higher than that among the patients without JFM (OR =1.09, 95% confidence interval (CI) = 1.03 –1.16, $p < 0.0062$).

Discussion

We performed the first large sample population-based epidemiological study on JFM in Taiwan. In Taiwan, the high annual incidence of all JFM among outpatients is 145.27–257.97 per 1,000 people/year, and an increasing is observed in patients aged 13–18 years [5]. The female-to-male ratio of 16- to 18-year-old patients was 0.99–0.95. This study reported that the disorder was most prevalent in females[2]. The female-to-male ratios of gastrointestinal conditions, sleep and mental disorders were 2. 81,2. 18, and 2.15, respectively.

In a population-based cohort, the male-to-female ratio was 0.73–1.9. Females exhibited a higher incidence of JFM than males, and this result is similar to that obtained from previous studies [3]. In the present study, the age group with the highest incidence rate was 18 years old [26–28]. Among Taiwanese males, the incidence of JFM reached the peak when they were 18 years old; by contrast, the incidence of JFM among Taiwanese females increased more remarkably when they were older than 14 years[20].

Pediatric JFM is a severe condition affecting children and adolescents in a crucial stage of their physical and emotional development [6]. Most patients also experience other symptoms, such as neuropsychiatric problems, functional bowel disturbances, debilitating fatigue, disrupted or non-restorative sleep, anxiety, and depression.The incidence of JFM among the female patients with signs, symptoms,and ill-defined conditions and gastrointestinal conditions were significantly higher than that among the patients without JFM (OR = 1.09; OR = 1.10). The incidence of JFM among the male patients with signs, symptoms, and ill-defined conditions was significantly higher than that among the patients without JFM (OR =1.09). The incidence of JFM among female and male patients with signs, symptoms, and ill-defined conditions was significantly higher than among patients without JFM, there was fatigue, headache, sore throat, abdominal pain, depression, lymph node pain symptoms[29].The distortion of biological rhythms may have contributed to the major complaints, such as fatigue

and sleep disturbances, experienced by patients with JFM. Most adolescent female patients and patients with JFM constitute a substantial 52% of female adolescents admitted for patient psychiatric treatment [5, 19].

This study is limited by several important individual demographics in the NHI medical care database; these factors included absence from school, effect on a child's quality of life and family relationships, and environmental situations. In conclusion, the findings of this study strengthened previous reports that described JFM as a commonly observed condition in the clinical populations of adolescent patients. This study demonstrated that the highest incidence of JFM in males was found in the 13- to 18-year-old group. The large nationwide cohort represents the common phenotypes of JFM comorbidities. Our results indicated a large proportion of patients with JFM among Taiwanese adolescents. Considering that this condition largely contributes to the disease burden, we emphasized the need to develop passive lifestyle modification for patients with JFM and population level strategies to detect and treat JFM.

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Table(1): Age percentage of juvenile fibromyalgia among Taiwan adolescents between 2000 and 2010

Age (years)/ gender	Female N (%)	male N (%)	Total N (%)	Female/male ratio	OR (95% CI)*	*p* value
8	371 (3.49%)	320 (3.34%)	691 (3.42%)	1.16	1.25 (1.04–1.51)	0.02
9	502 (4.72%)	396 (4.13%)	898 (4.44%)	1.27	1.54 (1.29–1.84)	0.0001
10	692 (6.51%)	554 (5.78%)	1246 (6.16%)	1.25	1.81 (1.51–2.17)	0.0001
11	780 (7.33%)	573 (5.98%)	1353 (6.69%)	1.36	2.64 (2.17–3.21)	0.0001
12	941 (8.85%)	681 (7.11%)	1622 (8.02%)	1.38	7.24 (5.39–9.72)	0.0001
13	889 (8.36%)	685 (7.15%)	1574 (7.78%)	1.30	3.68 (2.90–4.67)	0.0001
14	963 (9.05%)	817 (8.52%)	1780 (8.80%)	1.18	5.83 (4.05–8.40)	0.0001
15	1,040 (9.78%)	999 (10.42%)	2039 (10.08%)	1.04	1.05 (0.96–1.15)	0.34
16	1,093 (10.28%)	1,103 (11.51%)	2196 (10.86%)	0.99	0.99 (0.91–1.09)	0.82
17	1,123 (10.56%)	1,306 (13.63%)	2429 (12.01%)	0.86	0.84 (0.77–0.92)	0.0001
18	1,414 (13.29%)	1,482 (15.46%)	2896 (14.32%)	0.95	0.95 (0.87–1.02)	0.17
Total	9808 (100.00%)	8916 (100.00%)	18724 (100.00%)	1.10	6.21 (5.31–7.26)	0.0001

* OR = odds ratio, CI = confidence interval

Table (2): Annual incidence* of juvenile fibromyalgia among Taiwan adolescents from 2000 to 2010

Year/ gender	Female N (incidence)	Male N (incidence)	Total N (incidence)	OR (95% CI)**	*p* value
2000	722 (158.10)	662 (182.03)	1,384 (169.79)	1.33 (1.09–1.60)	0.0037
2001	569 (139.57)	573 (151.24)	1,142 (145.27)	0.98 (0.82–1.17)	0.12
2002	991 (226.08)	947 (243.03)	1,938 (234.38)	6.16 (3.02–12.56)	0.0001
2003	1,032 (227.87)	993 (246.37)	2,025 (236.95)	1.04 (0.96–1.15)	0.3606
2004	1,109 (248.78)	1,091 (267.51)	2,200 (257.97)	1.02 (0.93–1.11)	0.6842
2005	1,078 (200.47)	873 (259.31)	1,951 (229.39)	1.26 (1.15–1.39)	0.0001
2006	918 (182.21)	807 (214.15)	1,725(197.90)	2.68 (2.03–3.53)	0.0001
2007	919 (160.16)	732 (209.65)	1,651 (184.48)	4.15 (3.18–5.42)	0.0001
2008	827 (153.66)	730 (179.90)	1,557 (166.55)	1.77 (1.43–2.19)	0.0001

Year/ gender	Female N (incidence)	Male N (incidence)	Total N (incidence)	OR (95% CI)**	*p* value
2009	808 (164.44)	781 (175.85)	1,589 (170.04)	1.18 (0.95–1.47)	0.1354
2010	835 (153.13)	727 (181.83)	1,562 (167.22)	1.90 (1.53–2.36)	0.0001
Total	9808(190.00)	8916(170.00)	18724(180.00)	6.21 (5.31–7.26)	0.0001

*Annual incidence (per 1,000 people/year) is the number of new fibromyalgia cases among patients divided by the size of the population at risk each year.

**OR = odds ratio, CI = confidence interval

Table(3): Comparison between adolescents and non-adolescents with juvenile fibromyalgia exhibiting clinical-related comorbidities

System/gender	JFM									
	Female (N)	%	Rank	Male (N)	%	Rank	Total (N)	%	Rank	Female/male ratio
Signs, symptoms, and ill-defined conditions	3246	59.60	1	2701	73.70	1	5947	65.29	1	1.20
Gastrointestinal conditions	1200	22.03	2	427	11.65	2	1627	17.86	2	2.81
Sleep disorders	700	12.85	3	320	8.73	3	1020	11.20	3	2.18
Fatigue-related conditions	162	2.97	4	153	4.17	4	313	3.44	4	1.05
Mental disorders	138	2.53	5	64	1.75	5	202	2.22	5	2.15
Total	5446	100.00		9877	100.00		9109	100.00		1.49

Denominator (Number of occurrences): 98,274; Female Denominator (Number of occurrences): 59,058; Male Denominator (Number of occurrences): 39,216.

ICD-9-CM, 9th revision of the International Classification of Diseases, Clinical Modification.

Signs, symptoms, and ill-defined conditions, including headache 784.0X.Chest pain 786.5X. Abdominal pain 789.0X. Anxiety-related symptoms 780.4, 785.0, 785.1, 786.01, 786.05, 786.09. Gastric-related symptoms 787.0, 787.01–787.03, 787.1–787.3, 787.9, 787.91, 787.99. Others 780.02–780.39, 780.6, 780.8–783.9, 784.1–784.9,785.2–786.00, 786.02–786.04, 786.06, 786.07,786.1–786.4, 786.6–786.9, 787.4–787.7, 788.0–788.9, 789.1–796.9, 799. X. Car sickness 994.6. Gastrointestinal conditions, including irritable bowel syndrome 564.1. Gastroesophageal reflux disease 530.11, 530.81.Gastritis 535.00–535.5X. others 520.5–530.10, 530.19–530.7, 530.82–534.91, 535.60–537. X, 540.0–543. X, 550.00–553.XX,555.0–558. X, 560. XX, 562. XX, 564.2–579. X. Sleep disorders, including insomnia/sleep disorders 780.5X, 307.4X, 347.0X, 347.1X,V69.4. Sleep apnea 780.51, 780.53, 780.57. Cardiovascular disorders, including hypotension 458.0, 458.1, 458.2, 458.21, 458.29, 458.8, 458.9, hyperlipidemia 272.0, 272.1, 272.2, 272.4, coronary heart disease 410.XX–414.XX, congestive heart failure 428.0,peripheral vascular disease 440.2X, 440.3X, 443.89, 443.9. Mental disorders, including depression 296.2X, 296.3X, 300.4, 311, anxiety 300.00, 300.5, 300.09, 300.20, 300.22, 300.23, 300.29, 300.3, 308.3, bipolar disorder 296.4X, 296.5X, 296.6X, 296.7, generalized anxiety disorder 300.02, panic disorder 300.01, 300.21, post-traumatic stress disorder 309.81. Fatigue-related conditions, including chronic fatigue syndrome 780.71, other malaise, and fatigue 780.79.

Table(4): Comparison of the related comorbidities of juvenile fibromyalgia and non-juvenile fibromyalgia among Taiwan adolescents from 2000 to 2010

Comorbidities /gender	**Signs, symptoms, and ill-defined conditions**	**Gastrointestinal conditions**	**Sleep disorders**	**Mental disorders**	**Fatigue-related conditions**
Female					
FM	3246	1200	700	138	162
NON-FM	3053	1100	1715	396	2634
OR(95% CI)*	1.09 (1.03 –1.16)	1.10 (1.01–1.20)	0.37 (0.33–0.39)	0.24 (0.19–0.34)	0.046 (0.039–0.054)
P value	0.003	0.026	0.0001	0.0001	0.0001
Male					

Comorbidities /gender	Signs, symptoms, and ill-defined conditions	Gastrointestinal conditions	Sleep disorders	Mental disorders	Fatigue-related conditions
FM	2701	427	320	5	151
NON-FM	2531	8967	1,580	58	4563
OR(95% CI)*	1.09 (1.03 –1.16)	0.0021 (0.0019–0.0024)	0.24 (0.22–0.28)	0.1022 (0.038–0.2749)	0.04 (0.038–0.052)
P value	0.0062	0.0001	0.0001	0.0001	0.0001

*OR = odds ratio, CI = confidence interval

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