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Characteristics of traditional Chinese medicine usage in children with precocious puberty: A nationwide population-based study

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ABSTRACT

Ethnopharmacological relevance: Precocious puberty (PP) occurs in children with the early onset of pubertal development leading to physical and psychological problems. Current medical treatment is expensive and has its side effects. However, little is known about the utilization of traditional Chinese medicine (TCM) among patients with PP. To characterize the application of TCM among these patients, we conducted a nationwide population-based study.

Materials and methods: We used the Taiwanese National Health Insurance Research Database (NHIRD), to perform a nationwide population-based study. The NHIRD has a derived dataset with the information for a randomly selected half of all insured children from 1997 to 2008 in Taiwan. We identified children < 18 years of age with newly diagnosed sexual precocity (ICD-9 CM code: 259.1). The subjects were categorized based on the inclusion of TCM in their treatment plan.

Results: Overall, 3495 newly diagnosed subjects with sexual precocity were included. Among these children, 1.86% (N=65) had used TCM. There were significantly more subjects with no treatment, 87.32% (N=3052), than those with treatment of TCM, western medicine, or both. Most of the TCM users received Chinese herbal remedies (98.25%), and only 1.75% received acupuncture or manipulative therapies. Zhi-Bai-Di-Huang-Wan was the most frequently prescribed TCM formulation (23.73%), while Mai-Ya (Fructus Hordei Germinatus) was the most commonly prescribed single herb (10.87%).

Conclusion: Our study identified the characteristics and prescription patterns of TCM for children with PP in Taiwan. Further basic mechanistic studies and clinical trials are needed to confirm the efficacy and mechanism.

1. Introduction

Puberty is a period when children undergo physiological and psychological progression to achieve sexual maturation. Precocious puberty (PP) means the early onset of puberty, such as the early development of secondary sexual characteristics, the occurrence of breast development in girls before 8 years old, and the occurrence of testicular enlargement in boys before 9 years old (Abreu and Kaiser, 2016a). The estimated incidence in American girls is 1 in 5000–10,000 (Latronico et al., 2016). The prevalence was 1 in 500 among Danish girls and the female-to-male ratio was approximately 10:1, based on national registries over a 9-year period (Teilmann et al., 2005). Additionally, a significant increase in the incidence of central PP (CPP) occurred among Korean girls from 2004 to 2010; the prevalence

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was 55.9 per 100,000 girls and 1.7 per 100,000 boys (Kim et al., 2015). Until now, there has been no integral epidemiology investigation of PP among Taiwanese children.

PP has substantial impact on children's biological, psychological, and long-term health (Cesario and Hughes, 2007). PP has been associated with the increased risks of metabolic disorders and cardiovascular diseases (Lakshman et al., 2009; Prentice and Viner, 2013). Additionally, some evidence has suggested that there is an increased emotional problems in children with PP (Latronico et al., 2016). It is basically categorized into central (gonadotrophin-dependent) or peripheral (gonadotrophin-independent) type. Most cases of PP in girls and most cases in boys without a detectable pathologic cause belong to idiopathic precocious puberty (Carel and Leger, 2008; Cesario and Hughes, 2007; Hwang, 2012). The first-line therapy for central PP is depot gonadotropin-releasing hormone (GnRH), analogs, which desensitize the pituitary and inhibit luteinizing hormone and follicle-stimulating hormone (Pienkowski and Tauber, 2016). GnRHa therapy delays the maturation of epiphyseal plate and thus may improve the final adult height (Willemsen et al., 2014). However, side effects of GnRH analogs have been reported such as local erythema, hyperlipidemia, central obesity, temporary vaginal bleeding, and loss of bone density. Moreover, GnRH analogs are expensive and cost approximately $150 U.S. dollars every month in Taiwan (Yu et al., 2014). However, without treatment, early skeletal maturation and the early closure of the epiphyses may lead to a shorter adult height and adverse psychological outcomes.

Because of the increase in the incidence of PP and limitations of treatment, it is a critical and urgent problem to be solved to find a safe, complementary and alternative treatment for children with PP. In Asian countries, traditional Chinese medicine (TCM) is a form of complementary medicine that has been widely applied for centuries. In Taiwan, TCM is a widely used form of medical treatment for various diseases in children (Huang et al., 2014), such as asthma (Huang et al., 2013), allergic rhinitis (Yen et al., 2015), atopic dermatitis (Lin et al., 2014), diabetes mellitus (Lien et al., 2016) and cerebral palsy (Liao et al., 2017). In the aspect of growth and development, most of the ancient TCM pediatric literatures emphasize treatment for children with delayed growth and development. Information regarding the treatment for children with PP was very little. It was until last century, some TCM pediatricians proposed that, in terms of TCM theory, the pathogenesis of PP is due to the unbalance of Yin and Yang in Kidney and Liver, which further induces hyper-function of ministerial fire (Lin et al., 2013b; Shi YM, 1981).

Our previous hospital-based observational study found that TCM therapy might be beneficial for children with PP in Taiwan (Huang et al., 2014). However, there is no large-scale study of TCM treatment for PP so far. The aim of our study was to investigate the characteristics of TCM use in children with PP. We enrolled Taiwanese children who were registered as having PP in the NHI program. The results of this study could offer ethnopharmacological information of the utilization of TCM among Taiwanese children with PP.

2. Method

2.1. Data source

TCM and western medicine are both covered by the National Health Insurance (NHI) program, which is a government-run, single-payer program that covers more than 99% of residents in Taiwan (NHIA, 2015). Although Western medicine is the mainstream therapy in Taiwan, approximately 30% of Taiwanese residents also utilized TCM (Yen, 2013). TCM therapy, including Chinese herbal remedies, acupuncture and manipulative therapy has gained popularity as a choice of therapies for many chronic diseases in Taiwan (Chang et al., 2016; Lee et al., 2016a; Weng et al., 2016; Wu et al., 2017). Two kinds of Chinese herbal remedies are reimbursed, Chinese herbal formulas and single herbs. Each Chinese herbal formula contains single herbs with fixed proportions strictly based on the TCM classics, and each herbal formula can be combined with other herbal formula or single herb. In addition to private clinical settings, many of the public hospitals and university-affiliated teaching hospitals have TCM clinics. TCM doctors received TCM education either at the bachelor program (7 or 8-year M.D. program) or the post-baccalaureate TCM programs (5-year M.D. program). Until 2014, there are approximately 6000 board-certified TCM doctors serving 23 million people in Taiwan. More than 90% of Taiwanese hospitals and clinics are contracted with the NHI Program (NHIA, 2015). We analyzed the datasets from the National Health Insurance Research Database (NHIRD). Taiwan launched the NHI Program in 1995 and has reimbursed both Western medical services and TCM outpatient service since 1995 and 1996, respectively (NHIA, 2015). The registry and claim data of the program was sent to the National Health Research Institutes to establish and maintain the NHIRD. The data files were de-identified to ensure the protection of the privacy of the patients and healthcare providers. This study used children's files derived from the NHRID with the information for half of the population of children (aged < 18 years) in Taiwan who were insured from 1997 to 2008. The study was approved by the Institutional Review Board of the China Medical University Hospital (CRREC-103-048). The diagnosis were made based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes.

2.2. Study subjects and variables

The study subjects were selected and enrolled in the following manner. First, all of the children (N =6966) who had a diagnosis of PP (ICD-9-CM code: 259.1) between January 1997 and December 2008 were included in this study. Because PP was defined as the early onset of puberty before 8 years old in girls, and before 9 years old in boys (Abreu and Kaiser, 2016a), children older than 8 years of age for girls or older than 9 years of age for boys were excluded for this study. Overall, 3495 children whose ages are younger than 8 years old in girls or 9 years old in boys with PP were included in the study cohort. Children with TCM treatment were defined as TCM users; children with western medicine treatment were defined as WM users; children with both TCM and western medicine treatments were defined as both users; children with no treatment were defined as NT users. Comorbidities were determined based on ICD-9-CM diagnosis in the electronic medical records of the inpatient hospitalization and/or outpatient clinical visits. Comorbidities including cancer (ICD-9-CM code: 140–208), allergic rhinitis (ICD-9-CM code: 477), asthma (ICD-9-CM code: 493), atopic dermatitis (ICD-9-CM code: 691), attention deficit hyperactivity disorder (ICD-9-CM code: 341), anxiety (ICD-9-CM code: 300.00), and Tourette syndrome/tic disorder (ICD-9-CM code: 307.2 and 333.3) were defined as diseases diagnosed during the study period. Additionally, to investigate the differences between urban and rural areas, we used the definition of urbanization of the residence area that was described in previous studies (Lin et al., 2013c; Yen et al., in press). The residence area of the Taiwan townships was divided into 4 levels of urbanization. Level 1 had the highest degree of urbanization, and level 4 had the lowest degree. These 4 levels were categorized by the population density (people/km^2), population ratio of different educational levels, ratio of elderly people, ratio of agricultural workers, and number of physicians per 100,000 people. Urbanization levels 1 and 2 were defined as urban areas, and levels 3 and 4 were defined as rural areas. Herbal formulas were listed in the order of pin-yin name and English name. Single herbs were listed in the order of pin-yin name, Latin name and botanical plant name. The TCM indications of the Chinese herbal formulas and single herbs were based on TCM theory (Bensky et al., 2004; Scheid et al., 2009). The full botanical names comply with the rules of the *International Plant Names List* (IPNI; http://www.ipni.org) and *The Plant List* (http://www.