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Views on pediatric migraine of classification and traditional Chinese medicine treatment.

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Abstract

In 2004, the International Headache Society (IHS) published the 2nd edition of International Classification of Headache Disorders, which is of significant meaning for the diagnosis of migraine in children, including 1.3 childhood periodic syndromes that are commonly precursors of migraine". Based on 43 years from Professor Chen Bao-tian who invented the national renowned headache pills "Zhengtian Pill", he realized that there are three types of among the pediatric migraine cases in our country: I complete type, the "childhood periodic syndromes that are commonly precursors of migraine" listed in ICHD-II. Since there is completely no symptom of headache, it is called the complete type, which could be further subdivided into several derivative types including vomiting type, abdominal pain type, vertigo type etc; II incomplete type, which is between the complete type and adult type, manifested as prodromal syndromes associated with episodic headache; III adult type, which is called the adult type since its manifestation is identical with the migraine in adult cases. Based years practices and experiences, Chen found that the classification and traditional Chinese medicine of pediatric migraine should be completely consistent with the adult migraine. Several representative examples were listed in the article in order to arouse people pay attention to the pediatric migraine.

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Introduction

In 2004, the International Headache Society (IHS) published the 2nd edition of International Classification of Headache Disorders, which is of significant meaning for the diagnosis of migraine in children, including 1.3 childhood periodic syndromes that are commonly precursors of migraine", which was further divided into several derivative categories including "1.3.1 cyclic vomiting syndrome (CVS)", "1.3.2 abdominal migraine (AM), and 1.33 benign paroxysmal vertigo of childhood (BPVC)". Based on 43 years from Professor Chen Bao-tian who invented the national renowned headache pills "Zhengtian Pill", he realized that there are three types of among the pediatric migraine cases in our country: I complete type, the "childhood periodic syndromes that are commonly precursors of migraine" listed in ICHD-II. Since there is completely no symptom of headache, it is called the complete type, which could be further subdivided into several derivative types including vomiting type, abdominal pain type, vertigo type etc; II incomplete type, which is between the complete type and adult type, manifested as prodromal syndromes associated with episodic headache; III adult type, which is called the adult type since its manifestation is identical with the migraine in adult cases. Developing relationship exists among the three types, that is, "I complete type" can develop into" II incomplete type ", and eventually into "III adult type". Each type can also stand alone. Rare aura could be observed for all three types. Based years practices and experiences, Pro.

Traditional Chinese Medicine (TCM) is the Chinese constitution concept which constructs to serve as part of an explanatory model with understand on various aspects of life and physical wellbeing. Ti-zhi, well used term in China for constitution in which ti means body and zhi is the quality or substance. Global and dynamic view of human differences is took part in TCM that believes the constitution as partially genetically determined and partially acquired. The individuals' constitution is classified into nine types of Chinese medical theory, multidisciplinary studies, and clinical practice [1]. Based on the shape of human body, function, psychology, and other characteristics and individual constitution is assessed in Chinese Medicine Questionnaire (CCMQ). TCM theory

constitution provides personalized services for all women in three different way. Initially different constitutions are hold by the people even in the presence of similar demographic and medical characteristics in them. Different treatments like food, food properties; guidance on work and rest and on exercise regimen, Chinese herbs is required by different constitutions. Finally similar nutrients are provided by different foods that have same TCM natures due to different food properties and the better foods are chosen based on their constitutions.

Headache is a universal symptom occurred for daily living. Partial document is made on the headache epidemiology and its public health impact. For many number of primary headache disorders, most commonly migraine and Tension-Type Headache (TTH) the headache will be the symptom. Cluster headache is important due to the severe connected pain. Migraine headache ranges between 4 and 72 hours with characteristics such as unilateral location; pulsating quality; moderate or severe intensity and aggravation by routine physical activity like walking or climbing stairs. Headaches go with the nausea and/or sensitivity to light and sound. International Headache Society says that migraine is diagnosed if a person has at least five attacks fulfilling these criteria. Tension-type headache is very common than migraine. Bilateral pain of mild-to-moderate intensity is caused by the TTH. This pain is named as a pressing or dull ache with attacks ranging between 30 minutes to 7 days. Nausea or aggravation by physical activity won't accomplish these attacks. For TTH detection, the patient must experience at least10 headache episodes [2].

International Classification of Headache Dis-orders (ICHD) classifies TTH into episodic and chronic TTH forms. Episodic TTH attack experience less than 15 times per month (infrequent episodic: <1 attack per month; frequent episodic: 1–14 attacks per month). Chronic condition will occur when the headaches comes more frequently than 15 or more days per month and last for longer than 4 hours. Diagnosis for chronic headache is complicated one and the pain quality and features of these headaches be likely to be distinctly different. Chen found that the classification and traditional Chinese medicine of pediatric migraine should be completely consistent with the adult migraine. Several representative examples were listed in the article in order to arouse people pay attention to the pediatric migraine.

Literature Survey

Pediatric migraine variants, named as childhood periodic syndromes, migraine equivalents, or migraine precursors, are the group of periodic or paroxysmal disorders occurred in patients who also have migraine with or without aura, or who have an increased likelihood of developing migraine. Lagman-Bartolome and Lay [3] made a review on pathophysiology, evaluation, and management of the pediatric migraine variants with abdominal migraine, benign paroxysmal vertigo, cyclic vomiting syndrome, benign paroxysmal torticollis and episodic syndromes that leads to migraine, infantile colic, alternating hemiplegia of childhood, and vestibular migraine. Ren et al. [4] made an evaluation on an inclusion of TCM related information in Western medicine Clinical Practice Guidelines (CPGs) developed in China and high level evidence is adopted. From the China Guideline Clearinghouse (CGC), all CPG s were identified in which the main Chinese organization maintains the guidelines issued by the Ministry of Health of China, the Chinese Medical Association and the Chinese Medical Doctor's Association. TCM-related contents were extracted from all the CPGs identified. Extracted information comprised the institution issuing the guideline, date of issue, disease, recommendations relating to TCM, evidence level of the recommended content and references supports recommendations.

Jaiswal et al. [5] made a discussion on the histories of Ayurveda and TCM, the common medicinal plants species, the drug processing strategies used, and the current statuses of these TSM. A new perspective was provided to herbal drug researchers which expands and improves the utilization of botanical drugs and their therapeutic applications. A bibliographic investigation of Chinese and Indian pharmacopoeias, monographs and official websites was performed. Information was obtained from scientific databases on ethnobotany and ethno medicines. Li et al. [6] made an investigation on the Resting-State Functional Connectivity (RS-FC) of the right Fronto-Parietal Network (rFPN) between migraineurs and Healthy Controls (HCs) to determine how the rFPN RS-FC is modulated by effective treatment. Employed one hundred patients and 46 matched HCs. Migraineurs were randomized to verum acupuncture, sham acupuncture, and waiting list groups. Before and after longitudinal treatments, resting-state functional magnetic resonance imaging data was collected. In data analysis, an independent component analysis was applied. Results show that migraineurs were associated with abnormal rFPN RS-FC. Acupuncture, an effective treatment which relieve symptoms by strengthening the cognitive adaptation/coping process. Elucidation of the adaptation/coping mechanisms was opened up a new window for migraine management.

Case Report

Case report 1

1) Basic information: Hong Zhang, male, 12 years old. Cellphone: 13822855999 (Father, Zhang Man-cheng)

2) Characteristics of the case: First admission on 2014.09.25. The Patient was admitted in our headache treatment center due to episode of binocular flash, dark spots, and visual fuzziness for more than 1 year. From July, 2013, the patient start to experience repeated visual flashes, bright spot, and visual fuzziness without an obvious cause, with the symptoms gradually appear and disappear automatically after lasting for 20 to 50 minutes. No limb numbness, speech difficulties, voice disorders, dizziness, tinnitus, walking instability was reported, which was not accompanied by nausea, vomiting or other symptoms. No headache occurred during and after the above symptoms. The patient suffered 2 to 4 episodes every month,

with identical characteristics each time. The binocular vision and visual field of patient were normal at the interval of episodes. No special medical history was reported, or family history of migraine. No abnormal sign was observed during physical check of internal medicine and the nervous system. The MRI and EEG of the patient obtained during onset in our hospital appeared to be normal.

3) Diagnosis: Typical aura without headache.

4) Treatment: Twenty one (21) doses of the new Headache No. 1, with no recurrence reported up to now.

Case report 2

1) Basic information: Male, 18 years old, admitted to the neurology department of South University on 2014.07.24, diagnosed as "brainstem migraine" by Chief Su-yue Pan (13556184981), who was then referred to our headache treatment center by Chief Jian-ting Chen in the department of spine, South Hospital (13602890333).

2) Characteristics of the case: The patient suffered paroxysmal headache for 5 years, and was firstly admitted half-a-year after aggravation of the condition. Patient experienced the first onset at the age of 13, manifested as initial eyes flash with bright spot, and visual fuzziness, darkness, and numbness of limbs in a few minutes, with the numbness of the right limbs more severe, along with slurred speech and dizziness. The above symptoms lasted for about 30 to 60 minutes before disappearance, followed by headache, left temporal pulse with needle-stabbing headache, with visual analogue score (VAS score) of 9, accompanied by nausea, vomiting, photophobia, and phonophobia. The patient felt comfort when lying down, with the headache disappeared after sleeping and resting, and the headache usually lasts for about 12 hours. The patient experience repeated episodes at frequency of 1 to 2 times a month. The frequency and duration of headache attack are worsened in the past half a year, with headache in 15 to 20 days each month, each onset lasting for 12 to 24 hours, which is mostly migraine, which would aggravate in case of polygenetic mood swings. No special medical history or family history was reported. No abnormal sign was observed during body check of internal medicine and the nervous system. The MRI and EEG of the patient obtained during episodes in our hospital appeared to be normal.

3) Diagnosis: 1.2.6 basilar migraine 1.5.1 chronic migraine.

4) Treatment: 7 doses of new headache No. 1, which was discontinued due to significant gastrointestinal reactions of the patient with relative severe vomiting. This case was lost during follow-up.

Case report 3

1) Basic information: Jia-pei Zhang, female, 18 years old, address: Jie dong County, Jie yang city, Guangdong province. The patient was firstly admitted into headache treatment center of our hospital on 2014-10-21, who was then hospitalized in the department of traditional Chinese medicine of our hospital for treatment.

2) Characteristics of the case: The patient suffered repeated unilateral limb weakness with headache for more than 2 years, who was then admitted into our headache treatment center. Two years ago, without apparent cause, the patient started to gradually experience eyes flash, bright spot, unilateral limb weakness, difficulty to stand alone and speak, chewing and swallowing weakness, and sweating, which would last for about half an hour, with the flash and bright spot disappeared, followed by headache, pain at top of the head and right tempor, visual analogue score (VAS) score of 9, without nausea, vomiting, photohobia or phonophobia. The headache could last for about 10 hours before disappearance, with the slurred speech, difficulty to swallow, and limb weakness extended to 2 to 3 days before gradual recovery. Since the first attack, the patient suffered 1 to 2 episodes per month, with similar symptoms, and the headache lasted for 10 to 16h, which could be partially relieved by resting and ibuprofen. The patient received multiple acupuncture treatment at local clinic after onset of the condition, but symptoms such as hemilaterial limb weakness and headache still repeatedly attacks. In the last six months, the headache aggravated, and the patient was admitted into the third affiliated school of the Sun Yat-sim Univerisity due to the onset of hemiplegia, headache and other symptoms again in January, with the head MRI showing: small lesion at right frontal lobe with no other obvious abnormalities. The EEG appeared to be normal. The headache was relieved after treatment, but other symptoms such as slurred speech and weakness of the upper limb persisted. On 2014-10-21, the patient was admitted in our headache treatment center for the first time. At the first visit, the patient complained about headache, blurred vision, slurred speech, unilaterial limb weakness, walking difficulties, difficulties in swallowing and chewing, and so on. The body check revealed bilateral Babinski sign (+), right upper limb muscle strength of 3, right lower limb muscle strength of 3, and normal muscle strength of the left upper and lower limbs. No obvious abnormality was found in bilateral muscle tension. No motor weakness with migraine aura was found in the first or second degree relatives of the patient.

3) Diagnosis: 1.2.5 Sporadic hemiplegia migraine

4)Treatment: After 14 doses of New Headache No. 1 formula, the patient reported significantly improved chewing and swallowing weakness.

Case report 4

1) Basic information: Zi-shan Lin, female, 19 years old, address: Bridgehead fruit shop, South Medical University, phone: 13265055428, first visit time: 2014-10-31.

2) Characteristics of the case: the patient was admitted into our headache treatment center due to “recurrent abdominal pain for more than 7 years, which was aggravated for 2 years”. The patient started to suffer abdominal pain 7 years ago without apparent cause, mainly dull pain around the umbilici,

which makes the patient cry and roll on the ground when the pain extremes, with visual analogue score (VAS) score of 10, accompanied by pale color, sweating, nausea, vomiting of stomach contents, but without headache, dizziness, diarrhea, followed by spontaneous remission after about three hours, and the patient would feel fatigue. The episode repeatedly attacks 1 to 3 times a month, mainly in the early morning, with the abdominal pain lasts for about 2 to 4h, with spontaneous remission after resting. The patient appeared normal during onset interval. In the past 2 years, the onset frequency of abdominal pain increased, with the abdominal pain onset for 5 to 7 times daily when the condition was aggravated. The patient was treated at department of digestive diseases, pediatric and surgical treatment in the South hospital. No obvious abnormality was observed in the three conventional physical check, with monitoring of erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and pH, color doppler ultrasound of liver, gallbladder, pancreas, spleen, and kidney, hydrogen breath test, endoscopy, and CT/MRI imaging examination. Repeated onset of abdominal pain persists after stomach protection and gastrointestinal motility promotion and other drug treatment. The patient was referred to our headache treatment center on 2014.10.31.

3) Diagnosis: 1.3.2 abdominal migraine.

4) Treatment: The abdominal pain was relieved after 14 doses of New Headache No. 1 formula, with no recurrence reported up to now.

Case report 5

1) Basic information: Mei Liu, female, 14 years old, Tel: 15521232388. The patient firstly visited the headache treatment center of South Hospital on 2015-4-8.

2) Characteristics of the case: The patients suffers paroxysmal headache for 2 years. The patient experienced first onset 2 years ago, manifested as linear flash, bright seen by the left eye, gradually blurred vision of the left eye in about 10 minutes, resulting in blackouts. The right eye can see normal with the left eye blindfolded. No numbness or weakness, speech disorder, structure dysarthria, dizziness, or tinnitus was reported. The amaurosis fugax of the left eye lasted for about half an hour before disappearance, followed by headache, pulse like and needle like headache at the frontal and left temporal, accompanied by light pain swelling pain at the left orbit, without conjunctival hyperemia, tears, or runny nose. The extent of headache is quite severe, with visual analogue score (visual analogue score, VAS) of 8, accompanied by nausea, vomiting, photophobia and phonophobia. The headache would aggravate with exercise, which would spontaneous remiss after about 5 h quite resting. The patient suffered in total 6 onsets at the time of first visit to our center, with each headache onset lasted 5 to 8h, and the degree of headache and the duration of each attack increased. No special history or family history of migraine was reported. No abnormal signs were found in the nervous system examination. The brain MRI, cerebral artery imaging, fundus, intraocular pressure and other examinations of patient taken in our hospital (South Hospital) during headache onset did not show any abnormality.

3) Diagnosis: 1.4 retinal migraine.

4) Treatment: After taking 21 doses of new Headache No.1, the self-reported extent of pain during headache was significantly alleviated, and the patient continued to take the medication.

Case report 6

1) Basic information: Ying-qi He, 11 years old. The patient was hospitalized in the First Affiliated Hospital of Guangzhou Medical College, with registration number of 0000369017, who visited the headache treatment center of the department of Chinese Medicine in South Hospital for the first time on 2014-06-20.

2) Characteristics of the case: The patient has suffered headache with weakness in the right limb and slurred speech for more than 2 years. With no obvious cause, the patient started to experience headache, mainly frontotemporal pain, with nausea, vomiting, photophobia, phonophobia, palpitations, paleness, and sweating from 2 years ago. Typical premonitory symptoms such as eyes flash, bright spot would last more than 1 week before ev onset; the headache was accompanied with hemiparesis, impaired activity, and slurred speech. Each time the headache would last for 2-3 days and spontaneously remiss, with 4-6 onsets per month. In the past 6 months, the frequency of headache onset was increased, and each time the symptoms of right hemiplegia were aggravated. In July of 2014, the patient was hospitalized in the First Affiliated Hospital of Guangzhou Medical College (No. 0000369017) with the enhanced MRI scan showing scattered multiple small focal ischemia below the bilateral corona radiata, semioval center, and parietal cortex. After blood vessels extension, circulation improvement and pain-releasing treatment, headache and hemiplegia symptoms still repeatedly occurred. The patient visited the headache treatment center of our department for the first time on 2014-6-20, and the body check revealed right limb muscle strength of grade 4, with normal muscle tension and no abnormal signs in other physical parameters.

3) Diagnosis: migraine-type cerebral infarction.

4) Treatment: after taking 60 doses of new headache No. 1, the headache and weakness of right side of the body of the patient haven't recur again.

Case report 7

1) Basic information: Lei Fu, female, 13 years old. Address: No. 123 Tianhe Tangxia, Tel: 13794431908. The patient visited the headache treatment center of the department of Chinese Medicine in South Hospital on 2014-03-08 for the first time.

2) Characteristic of the case: the patient visited the hospital due to recurrent tics of the limbs associated with consciousness disorders for more than 2 years. 2 years ago, without apparent

cause, the patient started to experience binocular lines or spot-like flash and dark spots in visual field, like colorful pieces of glass in front of eyes, also accompanied by dizziness, blurred vision, abdominal pain, and limb tics with foaming in the mouth, superduction, loss of consciousness in 5 min, which would last for approximately 3 min before relieving. The symptoms attacked for 7 times in the past 2 years. There was no obvious abnormality shown the plain scan of MRI in our hospital. TCD: morphology of the skull, both the wave shape of the temporal window and pillow window are normal. ECG showed paroxysmal spike slow wave complex in the right center of the parietal occipital region, suggesting that artery blood flow of the right side of the anterior cerebral was too fast. The patient was diagnosed with epilepsy by the neurology department of western medicine, and treated with anti-epileptic drugs (Sodium Valproate), which showed poor efficacy. The patient visited Professor Chen for the first time on 2014-03-08.

3) Diagnosis: 1.5.5 Migraine-induced epileptic seizures.

4) Treatment: Abdominal pain, vomiting has never recurred after taking Sodium Valproate and new Headache No.1 for one month. EGG showed mild abnormality. After taking new headache No.1 for 2 months, the ECG examination showed normal EEG, with no recurrence of epileptic seizure up to now.

Case report 8

1) Basic information: Lei Cheng, female, 20 years old, address: Xinshi Tong kok, Baiyun District, Guangzhou City. Telephone: 15112026281. The patient visited the headache treatment center of the department of Chinese Medicine in South Hospital for the first time on 2013-12-16.

2) Characteristics of the case: The patient suffered recurrent headache with limb convulsions and consciousness disorders for more than 4 years. Manifestation of the first episode was as follows: binocular flash, dark spots firstly occurred, with gradually blurred vision, followed by onset of headache, with mainly pulsatile pain at two temples, which was severe and unbearable, with visual analogue score (VAS) of 9, accompanied by photophobia, phonophobia, nausea, and vomiting. The headache lasted for half an hour with sudden occurrence of limb tics, foaming in the mouth, and consciousness disturbance, which lasted for 5-10 minutes before the patient regained consciousness, stopped twitching limbs, and the headache was subsequently relieved. The whole process from foreboding of headache to seizures attack and relieving of headache lasted for about two hours. The patient suffered 6-10 episodes per month on average. Characteristics of each attack are similar. The ECG obtained in our hospital showed symmetrical image, with the slow activity of 7-8C/ S30-80uV as the basic rhythm, poor rhythm regulation and mixed low amplitude β activity .Visual response: a wave was suppressed. H.V: no obvious change. The patient visited the headache treatment center of our department for the first time on 2013-12-16.

3) Diagnosis: 1.5.5 Migraine-induced epileptic seizures.

4) Treatment: After taking Sodium Valproate and new Headache No.1 for one month, the onset of above symptoms was significantly reduced. Re-exmination demonstrated mild abnormality in EEG. The patient was treated continuously with the original medicine with periodic EEG reexamination.

Preliminary Study on Pediatric Migraine

1). Pro. Chen realized that there are three types of pediatric migraine in China, the “complete type”, “incomplete type”, and the “adult type”. The first one is precursor syndrome without headache, and the second one mainly manifested as headache, and the third one is precursor syndrome with accidental headache. Therefore, considering the causes of disease onset, the pediatric migraine was divided into "complete type", "incomplete type" and "adult type”. We collected 237 cases of adult migraine [7], studying their whole medical history, and found that more than half of the cases (51.9%) were developed from pediatric migraine, showing developing trend from the "complete type" to "incomplete type", and eventually "adult type", which proved the rationality behind the classification of pediatric migraine. The data of medical history study suggested that pediatric migraine tended to develop into adult migraine, which also have a tendency of developing from abdomen to head. And the average onset age of migraine headache and vertigo was older than those of abdominal pain and vomiting [8].

There were also three kinds of natural history of pediatric migraine: one is manifested as precursor syndrome at the onset of the disease, which would disappear for a period of time, and then the patient would experience migraine symptoms with or without aura; the second one is that after precursor Syndromes has appeared for a period of time (a few days to a few years), the patient started to suffer syndrome with episodic headache, and then after the precursor syndrome disappeared for a period of time (usually a few years later), the patient starts to experience typical aura or non-aura migraine symptoms; the third one appears as typical migraine symptoms with or without aura. When studying medical history, it was observed that precursor symptoms such as abdominal pain, dizziness and vomiting may occur alone or in combination, with different cycles for as short as a few days or as long as a few years. There is a clear transition period from the "periodic syndrome "to" migraine with or without "aura", which is consistent with domestic/foreign studies. The study by Walker et al. [9] showed that functional abdominal pain in children and adolescents increased the risk of chronic pain and headache in adulthood. The study by Paker [10] showed that migraine appears in 13% "equipotential syndrome" of migraine (1.3 pediatric periodic syndromes that may be the precursor of the migraine) with the gradual emergence of the condition. Dignan [11] followed up 54 cases of AM children for 7-10 years, among which 38 AM patients also suffered headache symptoms, consistent with the diagnostic criteria of IHS, therefore AM was considered the precursor symptoms of migraine. Studies have shown that more than 50% of children with AM and CVS will develop typical migraine, while

patients with other subtypes of migraine "equipotential syndrome" and benign paroxysmal vertigo, benign paroxysmal torticollis, non-headache migraine and acute confusional migraine have only 25% chance of developing typical migraine . However, the ICHD-II diagnostic criteria lack the description of such "transitional period", which is unfavorable for the comprehensive and dynamic understanding of pediatric migraine, objective and accurate diagnosis, and avoiding misdiagnosis. Therefore, we proposed a new classification of pediatric migraine.

2). **In-depth exploration of pediatric migraine:** the classification and traditional Chinese medicine of pediatric migraine should be identical with the classification of adult migraine. In ICHD- II, "1.3 childhood periodic syndrome" is also called "equipotential syndrome of migraine". The periodic syndromes such as periodic vomiting, episodic abdominal pain, children benign paroxysmal vertigo paroxysm syndrome, are regarded as "equipotential syndrome of migraine". Childhood periodic syndrome is not a special disease independent of migraine, but a period in the development of migraine. For the diagnosis of pediatric migraine, it is of equally important value as the typical headache symptoms. Therefore, although pediatric migraine has certain characteristics of its own, its essence is consistent with adult migraine, with "1.1 migraine without aura" and "1.2 migraine with aura" as the most basic category. Long-term practice in a large number of clinical cases also confirmed such standpoint: the treated pediatric migraine patients almost covered all the 1.1-1.6 types of headache listed in ICHD-II headache spectrum, with some of the typical cases cited in the manuscript as examples. Since the essence of pediatric migraine is identical with the adult migraine, their classification and treatment should also be the same.

3). **Traditional Chinese medicine treatment of pediatric migraine:** the treatment of pediatric migraine is identical with the adult cases. There is no radical therapy of migraine in western medicine. However, traditional chinese medicine can achieve radical treatment effect, completely relieving the pain of migraine patients. Our experimental study showed that: Zhengtian pill group and model group rat trigeminal nerve TCC P2X 3 receptor and its mRNA expression level was higher than the control group ($P<0.05$); Zhengtian pill group rat trigeminal TCC of P2X 3 receptor and its mRNA expression level was significantly lower than that in the model group reduced ($P<0.05$). As a consequence, therapeutic effect of Zhengtian Pill on migraine may be related to the can inhibit trigeminal nerve secondary neuronal P2X 3 receptor upregulation, and promote blood vessel contraction, improve the regulation of vascular systolic and diastolic blood pressure and systolic function to relieve migraine [12,13].

During the process of treating migraine and developing Zhengtian pill, we have acquired new understanding the etiology and pathogenesis of headache, which are complicated but not unitary. We proposed a new migraine etiology theory: "excessive wind, blood stasis, dampness and deficiency at the head, the mixture of which caused the headache". "Excessive wind at the head": migraine onset is of sudden attack and sudden disappearance, in accordance with the characteristics of the wind evil: mobile and caprice. Head is the intersection of multiple “Yang”, with the “Tai Yang” running at the back of the head, and “Shao Yang” running at the side of the head, both of which lack Qi and blood. Wind is Yang evil, which is light and can reach the summit, "this must be due to the two deficiencies, but off the form", so "harms by wind start from the top" and therefore manifested as headache. "Shengji Zonglu" said: "migraine is caused by occupation of yang channels by wind, which becomes the yang weak. The evil concentrates at one side, causing pain at frontal angle, which lasts for a long time, so called migraine." Therefore "excessive wind at head" is an important etiology and pathogenesis of chronic headache disease. "blood stasis at head": head is vulnerable to be hit and develop blood stasis due to its position; head is covered by liver and gallbladder channel. Liver channel runs by the side of the head, while gallbladder channel runs at the top of the head, in charge of catharsis, the disorders of which would lead to blood stasis; chronic illness gets into the collateral channels, chronic pain also gets into the collateral channels, leading to the blood stasis, "obstruction leads to pain". Therefore, "blood stasis at head "is another important etiology and pathogenesis of headache. "Excessive dampness at head": the Qi of “Jue Yin” carried up the phlegm and dampness caused by spleen deficiency, as indicated by "Shanghan Lun" article 378 "retching, spit saliva, headache, should be treated by Wuzhuyu Decoction". Therefore, onset of headache is usually accompanied by nausea, vomiting and vertigo, indicating excessive phlegm and dampness in the head. “Deficiency in the head”: head is the intersection of multiple “Yang”, is a “Yang” position, which is hard to be reached by “Yin” blood, therefore with vertigo, and visual aura such as flash and scotoma; Liver and gallbladder are partners, blood deficiency of liver will lead to insufficient “Qi” in gallbladder, and asthenia of gallbladder would lead to cowardice. Therefore, headache is usually accompanied with other symptoms such as photophobia and phonophobia, etc. "deficiency in head" usually refers to the deficiency of liver blood, which is another important pathogenesis of headache.

Discussion

With reference to epidemic febrile diseases, the Chinese classics of medicine and medical records abound. A heavy burden was applied along with the famine due to crop failures, droughts, floods and wars on Chinese populations throughout the ages. By pathogenic cold and wind to the invasion of the body the early classics of medicine credits the epidemic diseases by classifying them into category of “cold damage disorders”. A new conception of epidemic diseases is developed by creating the “School of Warm Diseases” which is the distinction between “warm diseases” and “cold damage disorders, role of a warm “epidemic (or pestilential) qi ” or “epidemic toxin” in their existence, body invasion through the mouth and nose, high contagiousness, specificity of the epidemic qi based on the species (human or animal) and the nature of the epidemic disease, favors the role of severe

climatic and environmental conditions in their emergence, etc. An evolution of medical perceptions on epidemic diseases was reviewed through Chinese classics of medicine. Importance of the growing awareness of variations was strains in local and regional environments with their climatic, epidemiological and medical specificities in refashioning of discourses and practices relative to epidemic diseases in Chinese medicine [14].

According to the new pathogenesis of headache "excessive wind, blood stasis, dampness and deficiency at the head, the mixture of which causes the headache", the specific migraine medication “Zhengtian Pill” was developed with the following composition: Rhizoma et Radix Notopterygii, Radix Angelicae Pubescentis, Radix Saposhnikoviae, Radix Angelicae Dahuricae, Herba Asari, Herba Ephedrae, Semen Juplandis, Flos Carthami, Radix Rehmanniae, Rhizoma Chuanxiong, Radix Paeoniae Alba, Radix Angelicae Sinensis, Caulis Spatholobi, Os Draconis, Concha Ostreae, Uncariae Cum Uncis, and Radix Aconiti Lateralis Preparata, etc. Aiming at the "excessive wind in the head", wind-eliminating herbs such as Rhizoma et Radix Notopterygii, Radix Angelicae Pubescentis, Radix Saposhnikoviae, and Radix Angelicae Dahuricae were used to expel the wind. Wind always comes with cold, therefore, Herba Asari, Herba Ephedrae and Radix Aconiti Lateralis Preparata were used to disperse the cold; for the blood stasis in the head, obstruction leads to pain, therefore Taohong Siwu decoction was used to promote blood circulation and remove blood stasis, activating meridians to stop pain; for the "excessive dampness in head ", since" wind beats dampness", the plenty of wind medicine can eliminate the dampness without any additional herbs. For the “deficiency in head", the Yin blood deficiency make it difficult to reach the Yang position, therefore Siwu decoction was used to nourish yin and blood.

The “Zhengtian Pill” was used to treat 350 cases for clinical observation, with total effective rate of 98%, and cure rate of 33% [15] observed. After launching, it is highly praised by both domestic and foreign patients. In China, Zhengtian pill has become the best seller among the similar proprietary Chinese medicine for headache treatment. In the last 20 years, with deepening understanding of migraine, we have developed Zhengtian pill, as well as New Headache No. 1 on the basis of Zhengtian Pill, which could achieve a cure rate as high as 45%. Considering that pediatric migraine and adult migraine are essentially the same disease, their treatment method should also be identical. Clinical practice has also confirmed such theory. And the treatment circle of pediatric migraine is usually shorter than that of the adult migraine with less recurrence, indicating that early detection and treatment of pediatric migraine is of great importance. With both innovated and traditional theory and continuously new drug development, we achieved remarkable curative effects of both adult and pediatric migraine. By sharing the mature treatment program, we hope to benefit more migraine patients.

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