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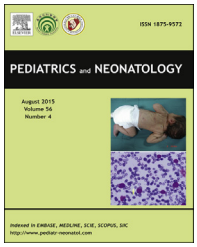

REVIEW ARTICLE

Genetic Evaluation of Children with Global Developmental Delay—Current Status of Network Systems in Taiwan

Yong-Lin Foo [a], Julie Chi Chow [a], Ming-Chi Lai [a], Wen-Hui Tsai [b], Li-Chen Tung [c], Mei-Chin Kuo [a,b], Shio-Jean Lin [c,*]

[a] *Division of Pediatric Neurology, Department of Pediatrics, Chi Mei Foundation Hospital, Tainan 710, Taiwan*
[b] *Genetic Counseling Center, Chi Mei Foundation Hospital, Tainan 710, Taiwan*
[c] *Department of Physical Medicine and Rehabilitation, Chi Mei Medical Center, Tainan 710, Taiwan*

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This review article aims to introduce the screening and referral network of genetic evaluation for children with developmental delay in Taiwan. For these children, integrated systems provide services from the medical, educational, and social welfare sectors. All cities and counties in Taiwan have established a network for screening, detection, referral, evaluation, and intervention services. Increased awareness improves early detection and intervention. There remains a gap between supply and demand, especially with regard to financial resources and professional manpower. Genetic etiology has a major role in prenatal causes of developmental delay. A summary of reports on some related genetic disorders in the Taiwanese population is included in this review. Genetic diagnosis allows counseling with regard to recurrence risk and prevention. Networking with neonatal screening, laboratory diagnosis, genetic counseling, and orphan drugs logistics systems can provide effective treatment for patients. In Taiwan, several laboratories provide genetic tests for clinical diagnosis. Accessibility to advanced expensive tests such as gene chips or whole exome sequencing is limited because of funding problems; however, the service system in Taiwan can still operate in a relatively cost-effective manner. This experience in Taiwan may serve as a reference for other countries.

* Corresponding author. Genetic Counseling Center, Chi Mei Medical Center, Taiwan, Number 901, Zhonghua Road., Yongkang District, Tainan City 710, Taiwan.
E-mail address: shiojean@gmail.com (S.-J. Lin).

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1. Definitions

Intellectual disability (ID) is defined as an intelligence quotient (IQ) of 70 or less with an onset prior to the age of 18 years.[1,2] Before ID is diagnosed by a standard test, developmental delay (DD) is considered for younger children under 6 years old who perform two standard deviations (SD) below their age-matched peers in development. Many of them also demonstrate ID.[1,2] Developmental delay can be further classified by severity (i.e., "mild", "moderate", "severe"), by functional dimensions, and by associated physical anomalies or dysmorphic features (i.e., syndromic or nonsyndromic). Global developmental delay (GDD) can be defined as a significant delay in two or more developmental domains: gross and fine motor; speech and language; cognition; personal and social development; or activities of daily living. These factors are two or more SDs below the mean on developmental screening or assessment tests. Developmental disability is attributable to a mental or physical impairment, or a combination of both, which manifests before the person attains adulthood. To reduce the scope for review, this discussion will focus on the genetic evaluation of GDD.

2. Epidemiology in Taiwan

Intellectual disability affects 1—3% of the population in Western countries.[3] Since 1980 with the promulgation of the Disabled Welfare Act in Taiwan, the government began to certify and register residents with various disabilities. Based on data from 2000 to 2011 in the registration system, the prevalence of all disabilities in children 3—17 years old increased from 9.98/1000 to 15.41/1000. Intellectual disability was the leading category during this 11-year period in which the prevalence increased from 3.60/1000 to 5.91/1000.[4] The reasons were largely attributable to decreased discrimination, improved detection and referral services, and increased willingness of guardians to register.[5]

3. Screening and evaluation system for developmental delay in Taiwan

Since establishing the Child Welfare Law amendment in 1993, early intervention for children with DD has become a major focus of child health and welfare services in Taiwan.[6] This interdisciplinary service is composed of four steps: (1) screening and detection, (2) report and referral, (3) team evaluation, and (4) intervention service.[7,8] All cities and counties in Taiwan have established an Early Intervention Notification and Referral Center, a Center of Team Evaluation for Children's Development, and Early Intervention Case Management Centers to provide services from the medical, educational, and social welfare sectors.[7] For early detection, several screening strategies exist. National Health Insurance provides children 0—6 years old with preventive health care services. Evaluation of developmental milestones by pediatricians is a major item of this preventive service. The public health nurses of the health station in every village, township, or city have been requested to strengthen the screening for DD when they provide health services for children or during a home visit. The Ministry of Education also implemented on-the-job training for preschool teachers and child care workers to improve their capability in detecting children with DD.

If a child is suspected to have DD based on initial screening, the child is referred to the Center of Team Evaluation for Children's Development for a complete evaluation. The processes of the evaluation and the operative models of the evaluation centers follow government guidelines, but they may vary in different hospitals. Joint outpatient clinics are usually evaluated by interdisciplinary team members, which are composed of pediatric neurologists, physiatrists, therapists, psychologists, and pediatric psychiatrists. Referrals are made to other specialists, when necessary. The core framework for detecting and intervention for DD has been established, although shortages in funding and professional manpower remain.[9]

4. Clinical evaluation of developmental delay

Clinical evaluation should be comprehensive when applied to a young child with DD. The purposes of the evaluation are as follows: (1) to confirm and classify the severity of DD; (2) to search for a possible underlying etiology; (3) to refer the child to an appropriate rehabilitation unit; (4) to provide family counseling; and (5) to manage associated medical and behavioral problems.

Assessment begins with a detailed history-taking. Careful family history should be obtained and include consanguinity, presence of early postnatal death, and other affected family members with similar or relevant neurologic impairments. Maternal history and birth history are important clues for risk of neonatal encephalopathy. Developmental milestones should be reviewed and the age at the time the problem emerged should be documented. Clinicians should be alert to the loss or regression of previously acquired developmental skills, which suggests other possible etiologies such as inborn error of metabolism (IEM) or neurodegenerative disease.

General physical examination emphasizes possible dysmorphology, hepatosplenomegaly, and cutaneous markers. Growth curve, weight, and head circumference should be documented. Focal or asymmetric neurologic findings and visual and auditory impairments should be carefully examined. Developmental assessment includes gross motor, fine motor, language and cognition, activities of daily living and social interaction. Abnormal behaviors such as avoiding eye contact, repetitive or restricted behavior, and communication impairment may suggest an autism spectrum disorder.

According to the American Academy of Neurology and Child Neurology Society guidelines,[10] neuroimaging is strongly recommended as part of the diagnostic evaluation for children with GDD. Magnetic resonance imaging (MRI) is preferable to computed tomography, especially in children who have microcephaly, seizures, or focal neurologic signs. If the history suggests seizure or epilepsy, an electroencephalogram (EEG) should be obtained. Children with IEMs may present with failure to thrive, unusual odors, episodic symptoms such as seizures or