Detection of 1(p36) deletion in patients with developmental delay and facial dysmorphism

Thesis Submitted for Partial Fulfillment of M.Sc. Degree
In Clinical and Chemical Pathology

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2010

ABSTRACT

1p36 deletion syndrome is considered to be one of the commonest chromosome deletion syndromes. It results in a clinically recognizable phenotype including dysmorphic features, mental retardation, developmental delay and others e.g. hearing abnormalities, visual abnormalities and cardiovascular manifestations. The diagnosis of 1p36 deletion syndrome is suggested by clinical findings and confirmed by detection of a deletion of the most distal band of the short arm of chromosome 1 (1p36). Conventional G-banded cytogenetic analysis, FISH, or array CGH can all be used to detect deletions; however, the complexity of some deletions may only be revealed by array CGH.

Key words: Developmental delay; mental retardation; 1p36 deletion; FISH; Facial dysmorphism.

ACKNOWLEDGEMENT

Before all and after all thanks to GOD

I would like to express my deepest gratitude to ***Prof. Samia Ali Temtamy***, Professor of Human Genetics, National Research Center for her sincere guidance, Kind supervision, continuous encouragement and valuable instructions throughout the whole work.

I am very grateful to ***Prof. Hoda Mohamed Abd El-Ghani,*** professor of Clinical and Chemical pathology, Faculty of medicine, Cairo University for her constant assistance, valuable instructions, generous guidance and precious time she offered me throughout this work to make it complete.

Many thanks for ***Dr. Rania Mohammed Samy,*** Lecturer of Clinical and Chemical pathology, Faculty of medicine, Cairo University for her beneficial help throughout the course of my thesis.

I am deeply indebted to ***Dr. Marwa Ibrahim Shihab,*** Assistant professor of Human cytogenetics, National Research Center for her kind assistance, constant support, and valuable supervision.

Special respects to ***Dr. Moustapha Ahmed Abd El- Rahmen,*** Lecturer of Orodental genetics, National Research Center for his Kind help.

My sincere gratitude to ***Prof. Mona Sabry Aglan***, Professor of Clinical Genetics, National Research Center for her help and advice to me during this work.

Lastly, I wish to thank all my professors, staff members and my colleagues for their kind help and support.

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1p	Short arm of chromosome 1
1pter	1p terminal
1qter	1q terminal
AAP	American Academy of Pediatric
aCGH	Array-Based Comparative Genomic Hybridization
BACs	Bacterial artificial chromosomes
BFB	Breakage-fusion-bridge
C.T.	Computerized tomography
CCA	Conventional cytogenetic analysis
EEG	Electroencephalogram
FISH	Fluorescence In Situ Hybridization
HC	Head circumference
I. FISH	Interphase FISH
ISCN	International System For Cytogenetic Nomenclature
Kb	Kilobase
KCNAB2	Voltage-gated K+ channel β-subunit gene
LCRs	Low copy repeats
M. FISH	Metaphase FISH
Mb	Megabase
MLPA	Multiplex Ligation- Dependent Probe Amplification
MQ	Motor quotient
MRI	Magnetic resonance imaging
NB	Neuroblastoma
NF1	Neurofibromatosis type-1
PCR	Polymerase chain reaction
YACS	Yeast artificial chromosomes

Introduction

Developmental delay/mental retardation affects one to three percent of all children under age 5 **(Paul,2003)** and affects about 1 - 3% of the general population, There are many causes of mental retardation, but a specific reason is detected in only 25% of cases (**Galasso et al ,2010).**

Genetic conditions are considered the most common causes of mental retardation one of them is a common newly delineated syndrome in which there is submicroscopic deletion of the short arm of chromosome 1 from 1pter-1p36.23. It is the most common telomeric deletion with an incidence of 1:5000 newborn **(Shaffer and Lupski, 2000)**. These deletions vary in size from 1 to 10 Mb and appear to have no common sequence homology at the breakpoints. However, patients carrying these deletions tend to have similar phenotypes, including characteristic facies (large anterior fontanel, deep-set eyes, straight eyebrows, flat nasal bridge, asymmetric ears, and pointed chin), mental retardation and developmental delay, as well as sensorineural hearing loss, eye/vision problems, seizures, and cardiovascular malformations may be present. These features possibly depending on the size of the deletion **(Redon et al, 2005)** suggesting that haploinsufficiency of contiguous genes in this region is responsible for the observed phenotype **(Kang et al, 2007).**

For deletion to be suspected detailed information of the clinical phenotype must be supplied to the cytogeneticists and appropriate clinical genetic consultation is required **(Battaglia et al, 2003).**

With the recognition that 1p36 is potentially the most common of the terminal deletion syndromes there is a need to improve diagnosis of this condition. FISH analysis is an important diagnostic adjunct in cases where the diagnosis is suspected following classical GTG banding techniques **(Lissauer et al, 2007)**. Recently array-based comparative genomic hybridization (array CGH) has emerged as the most efficient and comprehensive detection method for these aberrations **(D'Angelo et al, 2010).**

Aim of work

This study aims to:

1. Detection of 1p36 deletion in patients with developmental delay, and phenotypic features of the 1p36 deletion syndrome, using fluorescence in situ hybridization (FISH) technique to reach accurate diagnosis for proper genetic counseling and further management of those cases.

2. Detection of any other chromosomal abnormality among these patients.

Developmental delay

Definition

Growth and development are the increase in the size of the body as a whole or the increase in its separate parts and changes in function including those influenced by the emotional and social environments.

Deviations in growth patterns are non specific but very important indicators of serious medical disorders **(Foye and Sulkes, 1994).**

Children with developmental delays are those who present with delays in the attainment of developmental milestones at the expected age **(Moeschler and Shevell, 2006).**

Developmental delays are a group of related, etiologically heterogeneous, chronic disorders that share as an essential feature a documented disturbance in one or more of the recognized developmental domains: motor (gross or fine),speech/language,cognitive,social,and activities of daily living. Usually, the disturbance needs to be significant, that is, a performance of ≥2 standard deviations below the mean on an age-appropriate,norm-referenced,standardized developmental assessment. When more than one domain is affected, a global developmental delay exists. When a single domain (motor or speech) is affected, a gross motor or developmental language disorder (developmental dysphasia, specific language impairment) exists **(Shevell, 2005**).

Incidence

Developmental milestones are determined by the average age at which children attain each skill, therefore, statistically, about 3% of children will not meet them on time, but only about 15-20% of these children will actually have abnormal development. The rest will

eventually develop normally over time, although a little later than expected.

Developmental disabilities affect between 1 and 2% of the population in most western countries, although many government sources acknowledge that statistics are flawed in this area. The worldwide proportion of people with developmental disabilities is believed to be approximately 1.4%. It is twice as common in males as in females; some researchers have found that the prevalence of mild developmental disabilities is likely to be higher in areas of poverty and deprivation, and among people of certain ethnicities **(Armbrester and Margaret, 1992).**

Global developmental delay is common and affects 1% to 3% of children **(Shevell, 2003).**

At least 8 percent of all children from birth to six years have developmental problems and delays in one or more areas of development. Some have global delays, which mean they lag in all developmental areas **(Tervo, 2003**).

Etiology

There are many social, environmental and physical causes of developmental disabilities, although for some a definitive cause may never be determined. Common factors causing developmental disabilities include:

- Brain injury or infection before, during or after birth.
- Growth or nutrition problems.
- Abnormalities of chromosomes and genes.
- Babies born long before the expected birth date - also called extreme prematurity .

- Poor diet and health care .
- Drug misuse during pregnancy, including alcohol intake and smoking.
- Child abuse can also have a severe effect on the development of a child, specifically the socio-emotional development.
- Diagnosis of an autism spectrum disorder **(Emerson, 1995)**.

Management of a case of developmental delay

Clinical history and physical examination are the most important instruments to reach a diagnosis of developmental delay.

One third of the diagnosis is established based on clinical history and physical examination only; for another third clinical history and physical examination provided essential clues for additional investigations and a third were established by additional investigations **(Clara et al, 2005).**

The American Academy of Pediatrics (AAP) Committee on Genetics, 2001 favors an approach that emphasizes the importance of the clinical history, family history, and diagnostic skill of the clinical geneticist for diagnosis of a case of developmental delay; this is presented in figure (1).

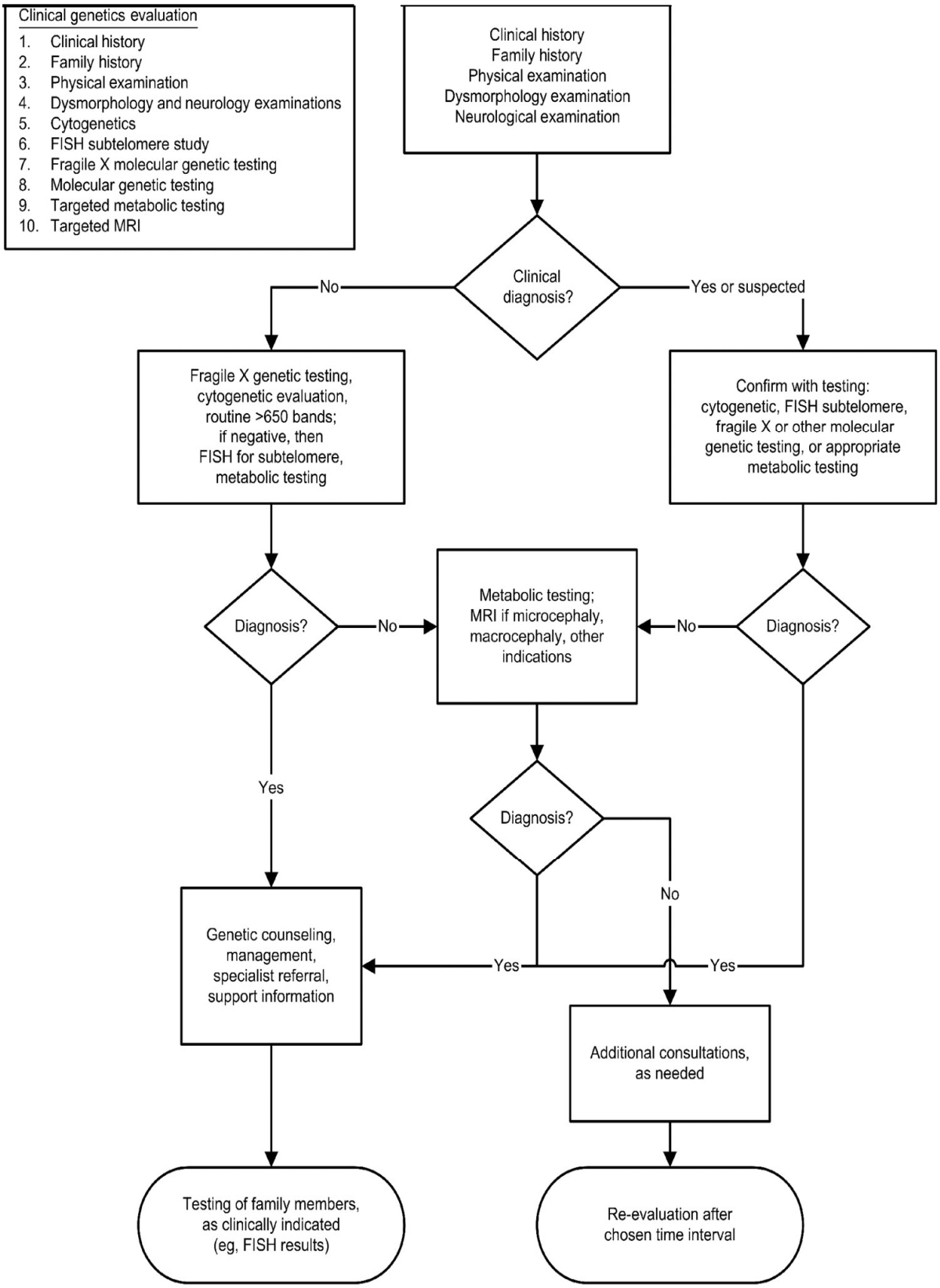

Figure (1): Schedule which have to be followed to reach diagnosis in a case of developmental delay (**American Academy of Pediatrics, 2001).**

History:

An optimal evaluation starts with a comprehensive history taking including a 3-generation family history with particular attention to family members with mental retardation, developmental delays, psychiatric diagnoses, congenital malformations, miscarriages, stillbirths, and early childhood deaths. The medical and family history allows suspecting an etiology and helps in guiding the diagnostic evaluation **(Moeschler and Shevell, 2006).**

Examination:

(1)General and physical examination:

The child height, weight, blood pressure and head circumference must always be measured and recorded **(Menkes and Sarnat, 2000**).

Serial measurements of height, weight and head circumference are much more useful than single measurements because deviation from a particular child growth pattern can be detected even if the value remains within arbitrarily defined normal limits (e.g., between the 3rd and the 97th percentiles) **(Foye and Sulkes, 1994).**

-Rules of Thumb for growth:

Weight

1. Weight loss in first few days: 5-10%of birth weight.

2. Return to birth weight: 7-10 days of age.

Double birth weight: 4-5 months

Triple birth weight: 1year

Quadruple birth weight: 2years