INTRODUCTION

Global developmental delay is described as significant delay in two or more developmental domains (gross motor, fine motor, cognition, speech/language, and personal/social). And defined as performance at least two standard deviations below the mean of age appropriate. ***(Ballaglia et al., 2003)***

Global developmental delay is a common problem in pediatric age group and may become evident during infancy or early childhood. It becomes more apparent & therefore more often diagnosed in early school years. ***(Walters, 2010; Mcdonald et al., 2011)***

Development is a continuous process which begins from conception and continues up till maturity. However, during this process several factors like genetic, metabolic, endocrine, vascular, malformation syndromes, traumatic, infections, toxins & environmental causes can have adverse effects of delay in milestone which can be evaluated using four domains of gross motor, fine motor and social and language skills. ***(Momen et al., 2011)***

Imaging plays a central role in the evaluation of the global developmental delay. Magnetic Resonance Imaging (MRI) is the best modality to evaluate children with global developmental delay. It gives the important information about

the patient and type of brain abnormalities. MRI helps identify these diseases and their prognosis and also helpful for parental counseling regarding the outcome of their child and to identify any possible risk of recurrence in the siblings. ***(Althaf et al., 2015)***

Aim of the Work

The aim of this study is to identify the proportion of normal MRI and the prevalence of brain abnormalities in children with global developmental delay referred to our institution.

Chapter 1

GLOBAL DEVELOPMENTAL DELAY

Developmental delay is a common problem in pediatric age group, affecting 1-3% of the population. It may become evident during infancy or early childhood. It becomes more apparent & therefore more often diagnosed in early school years. ***(Walters, 2010; McDonald et al., 2011)***

Developmental delay is a descriptive term used for children whose difficulties are apparent earlier in childhood where a cause is not yet established. It does not imply a particular organic or syndromic cause. ***(Williams, 2010)***

Developmental delay is defined as significant delay (more than two standard deviations below the mean) in one or more of the following developmental domains: ***(McDonald et al., 2011)***

- Gross motor
- Vision & Fine motor
- Hearing, Speech & Language
- Social, Emotional & Behavioural

Identifying the aetiology of a child's delayed and disordered development is important to establish causation, predict functional impact and prognosis, alter management,

influence prevention strategies, identify rare conditions that are imminently treatable, not miss conditions that may exacerbate a developmental delay and provide accurate genetic counselling for the family. ***(McDonald et al., 2011)***

Etiology of Global Developmental Delay

Global developmental delay can be the presenting feature of a huge number of neurodevelopmental disorders (from learning disability to neuromuscular disorders).

The etiology of GDD had wide range of the causes includes hypoxic ischemic encephalopathy, neurometabolic disorders, congenital malformation and infection may lead to GDD. It can be categorised into exogenous, genetic (non-metabolic) and genetic (metabolic). The diagnosis of exogenous causes includes teratogenic agents (alcohol and drugs); prenatal, perinatal causes (prematurity, infections); and social causes often best assessed by history but must not be assumed. ***(Engbers et al., 2008)***

Developmental surveillance requires monitoring of the child's developmental progress over a period of time, using opportune moments such as routine physical checks, visits for immunisations or other incidental acute medical issues. ***(Rydz et al., 2006)***

Formal developmental screening can be performed using parental reporting measures such as the Parents' Evaluation of

Developmental Status or the Ages and Stages Questionnaire. Interactional tools, such as the Brigance Screen or the Australian indeed Parental concerns regarding developmental delay are usually valid. ***(Rydz et al., 2006)***

The investigation of global developmental delay in preschool children varies between centres and between paediatricians. Following a literature search and review of the evidence based guidelines were developed to assist in the assessment and management of such children presenting to secondary level services. Evidence supporting the use of genetic and biochemical investigations on a screening basis was found, but there was no evidence to support the use of metabolic investigations or neuroimaging in the absence of other positive findings on history or examination. Detailed history and examination are paramount in the assessment of children with global developmental delay. Investigations can be a useful adjunct in determining aetiology. Evidence based guidelines have been developed to assist doctors in the selection of appropriate investigations for this group of children. ***(Gringras, 1998)***

Clinical Evaluation

History

History should be comprehensive, and must include a detailed prenatal, perinatal, and postnatal history. The mother

should be asked about drug ingestion during pregnancy and early threatened miscarriage. It is important to note that there must be clear evidence of neonatal encephalopathy and a significant motor disorder before problems are attributed to the perinatal period. It should be ascertained whether the child has developmental delay or regression, and a detailed family history should be sought. ***(MacLennan, 1999)***

- Maternal history, for example recurrent spontaneous miscarriages suggesting chromosomal rearrangement/ unbalanced translocation;
- Previous stillbirths, neonatal deaths or sudden infant death may underlie an inborn error of metabolism;
- Exposure to potential teratogens, for example anti-epileptics, antidepressants, warfarin, roaccutane, alcohol (including binge drinking in the first trimester), nicotine and illicit drugs;
- Early neonatal events: complications of delivery, hypotonia, hypoglycaemia and/or seizures;
- Family history, for example parental consanguinity, history of neurological disorders, learning or developmental problems;
- Sleep disturbance and nocturnal snoring;
- Diet and pica; and General medical history.

Clinical examination and evaluation of important milestones:

A complete physical examination must be performed, including: ***(MacLennan, 1999)***

- Growth parameters (Table 1).
- Dysmorphic features
- Abdominal examination for visceromegaly
- Spine, reflexes, and gait
- Neurocutaneous stigmata, for example tuberous sclerosis or neurofibromatosis.
- Dysmorphism, congenital abnormalities and reduced family resemblance.
- Features of storage disorders, for example hepatosplenomegaly,
- Cardiomyopathy, for example mitochondrial respiratory chain disorders.
- Vision and hearing.
- Review the child with delayed development without a specific diagnosis over time to document progression and monitor for a possible emerging phenotype. Developmental regression in one or more domains requires urgent specialist referral and investigation.

Table (1): Important milestones.

Important Milestones

Domains		Development	
Receptive language	12 month	responding to their name	
	18 mth - 2 yrs	pointing to body parts, parents, pictures	
	12 - 18 mths 2 yrs	following instructions 1 step: throw in the bin 2 step put this ball in box and bring shoes	
Expressive language (verbal & non verbal)	12 month 2 yo 3yo 4yo 5yo	mama & papa, pointing to what they want linking words, naming 2 - cat, dog repeats 3 word phrases gives name & identifies colours name colours, self, fluent repeats 4 - 6 word phrases	
Social Emotional Self help (ASD)	3 - 6 mth 18 - 24 mth	eye contact reciprocal play pretend play joint referencing, share interest	
Gross motor - to test for GDD	12 - 18 mths 2 yr 3 yr 4 yr 5 yr	walk walk sideways 2 steps, kick a ball stand on 1 foot, tiptoe 3 steps stand on 1 foot for 1 secs, tiptoe 4 steps hop 2 hops on 1 foots stand on 1 foot for 5 secs	
Fine motor - to test for GDD	18 mths 2 yr 3 yr 4 yr 5 yr	scribbles / line line / circle circle / cross copies square copies triange	3 blocks 6 blocks 9 blocks
Offer to test hearing Ask for f/h of delayed speech: more common in children with +ve f/h			

Investigations

If the diagnosis is not apparent after a full history and physical examination, **first line laboratory investigations** should be performed as outlined (Fig. 1-1), included thyroid function tests for two reasons, despite the lack of evidence. Firstly, hypothyroidism is an easily treatable disorder, with significant implications if the diagnosis is missed. Secondly,

many chromosomal abnormalities are associated with an increased risk of hypothyroidism, for example trisomy 21, 45X, and 22q11 deletion. Urate is included as this is more stable than both ammonia and lactate, and is an easy way to diagnose purine disorders, which may present as isolated global delay. We also suggest testing for iron deficiency, as this can be associated with developmental delay and is easily measured and treated. ***(Yager & hartfield, 2005)***

Second line investigations should be selective, and guided by history and examination findings.

Metabolic investigations should be undertaken when history and examination findings increase clinical suspicion; findings that merit investigation include family history, parental consanguinity, developmental regression, congenital ataxia or dysequilibrium, epilepsy, organomegaly, and coarse facial features. If a metabolic disorder is suspected clinically, blood should be taken for lactate, amino acids, ammonia, very long chain fatty acids, carnitine, homocysteine, and disialotransferrins. Urine should also be tested for organic acids, orotate, glycosaminoglycans, and oligosaccharides. (Fig.1-1) ***(McDonald et al., 2006)***

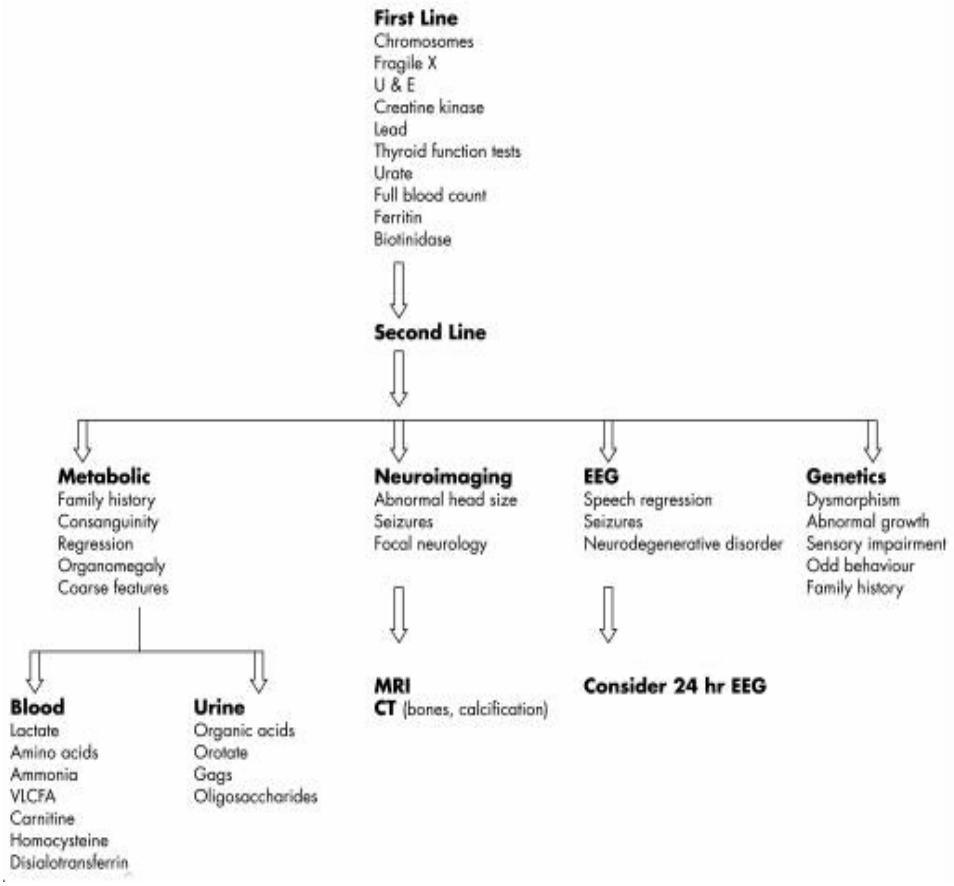

Figure (1-1): Guidelines for investigation of global developmental delay in preschool children, Department of Community Child Health, Royal Hospital for Sick Children, Glasgow. ***(McDonald et al., 2006)***

Neuroimaging is recommended if global delay is found in association with additional features, and MRI is the investigation of choice. CT is recommended for visualization of bony structures or calcification. ***(McDonald et al., 2006)***

EEG should be performed if there is a history of seizures or regression in speech. Twenty four hour EEG recording should be considered. ***(McDonald et al., 2006)***

Referral to the genetics department is particularly useful for the evaluation of dysmorphic features and syndrome diagnosis: clinical clues are abnormal growth (including head size), associated sensory impairment (vision or hearing), unusual behaviour patterns (for example, hyperphagia or onychotillomania), or a family history of a particular condition. Video or photographic documentation is essential. At the genetic clinic, additional genetic investigations may be ordered. For example, chromosome telomere studies may exclude submicroscopic or cryptic chromosome imbalance involving the chromosome ends or telomeres. A telomere abnormality is present in 5% of patients with previously undiagnosed learning difficulties, and such tiny imbalances are not detected by a conventionally stained cytogenetic study. ***(Devries et al., 2003)***

The development of new technologies to diagnose hereditary causes of learning difficulties underlines the value of referral to the genetic clinic. ***(Shevell et al., 2003)***

The North American recommendations suggest that screening for lead toxicity should be targeted to those with risk factors for lead exposure, and that thyroid function tests should be performed only if there are systemic features which suggest thyroid dysfunction. Both of these investigations are performed as first line screening tests. Also routine measurement of creatine kinase and biotinidase to be considered, which are not mentioned in the North American guidelines. The North American guidelines contain recommendations in relation to cytogenetic testing, fragile X analysis, metabolic screening, EEG, and neuroimaging. ***(Shevell et al., 2003)***

So if there are no clinical features suggesting an etiology, a stepwise approach is recommended (Fig. 1-2), including initial neuroimaging (preferably MRI) and cytogenetic and fragile X screening. If these tests are negative, a metabolic evaluation, testing for subtelomeric rearrangements, and genetic consultation should be considered. ***(Shevell et al., 2003)***

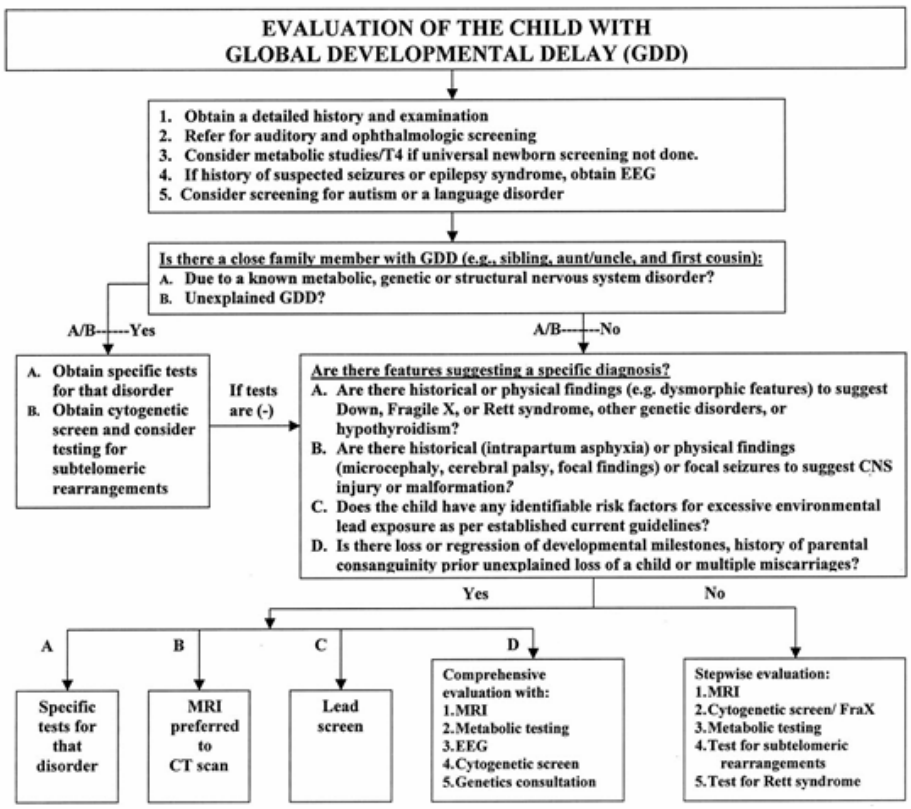

Figure (1-2): Algorithm for the evaluation of the child with developmental delay. Audiologic and ophthalmologic screening is recommended in all children with global developmental delay. Metabolic studies usually consist of obtaining a urine organic acid screen, quantitative serum amino acids, serum lactate and ammonia levels, capillary or arterial blood gas, and thyroid function studies. ***(Shevell et al., 2003)***

Chapter 2

MRI Brain in Global Developmental Delay

Imaging plays a central role in the evaluation of the global developmental delay. And can be performed to suggest any underlying abnormality. ***(Moeschler and Shevell, 2006)***

Brain MRI is the modality of choice to evaluate children with global developmental delay. MRI helps identify these diseases and their prognosis and helpful for parental counseling regarding the outcome of their child and to identify any possible risk of recurrence in the siblings. ***(Althaf et al., 2015)***

MRI provides great anatomical detail, high sensitivity and specificity in detecting brain abnormality, and also offers physiological and functional information of the brain. Therefore, it is the imaging modality of choice for the infant or child with GDD. ***(Althaf et al., 2015)***

MRI imaging protocol

Conventional MR Sequences

The MR sequences are recommended: sagittal T1-weighted images for the evaluation of the midline structures, frequently involved in congenital brain malformations and also useful for assessing the lateral aspects of the cerebral