

Pregnancy with Global Developmental Delay (GDD) in previous child – A case series

Dr Tulika Joshi, Consultant Fetal Medicine, Tulip's Fetal care, Ranchi, Jharkhand, India



Introduction

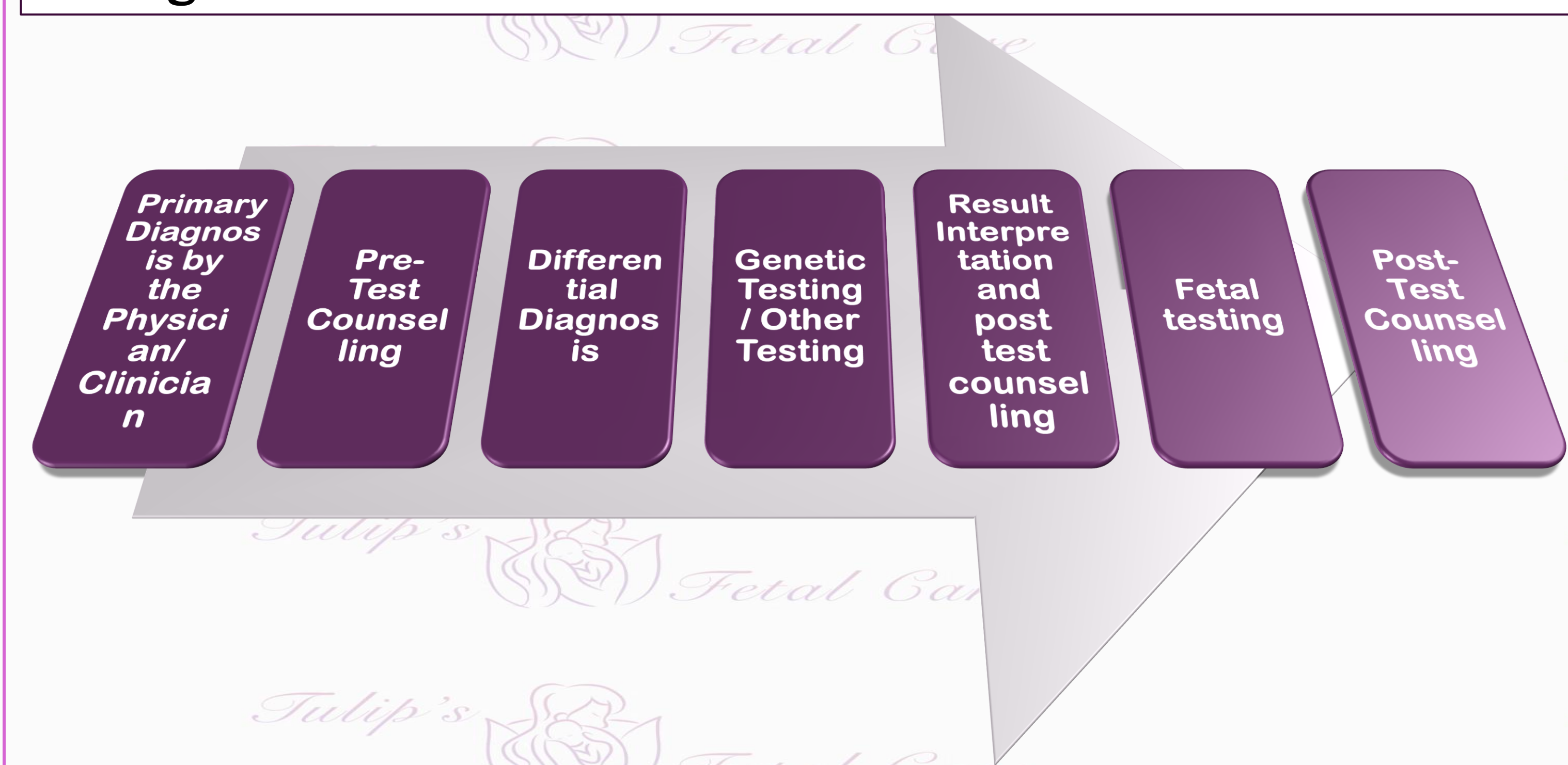
The global developmental delay/ Intellectual disability (GDD/ID) is characterized by significant functional mental impairment and adaptive functioning deficits in conceptual, social and practical domains. The genetic factors are responsible for around 40% of these cases. Often the couples who have one such previous child seeks counselling to get reassurance about the likelihood of recurrences their next pregnancy. I am sharing my experience of three such cases with variable outcomes.

Objectives

To present approach to investigations in families with history of Global developmental delay.

Methods

All the families with one or more affected family member, who were willing for genetic counselling followed by genetic testing of the affected member and who were willing for the prenatal testing were included in the series. All the cases had pre test and post test counselling done by certified genetic counsellor and / or clinical geneticist. The invasive fetal testing was only done if a valid structural / genetic indication was present. Post test counselling was again done after the results of invasive fetal testing were available.



RESULTS

Case 1 G3P1L1A1 19w1D pregnancy with previous female child with global developmental delay, hypotonia, speech apraxia, mild ID, and on examination microcephaly and facial dysmorphism. Her MRI suggested dolichocephalic/scaphocephaly and thin white matter leukomalacia and karyotype reported normal female (46, XX). In 2nd pregnancy, antenatal scan reported microcephaly, with IUGR. After counselling, simultaneous testing of proband, fetus and the couple was performed by WES and CNVs. No significant pathogenic or likely pathogenic variant was detected in both samples. During the antenatal course the fetal head circumference continued to lag behind and measured at <1st centile at term. Although Exome Sequencing of the fetus haven't identified any significant variant, the male child at 4 months post birth was reported to have microcephaly, retrognathia, upslanting palpebral fissures and bilateral prominent antihelix (figure 1&2).

Case 2 a 3rd degree consanguineous couple with previous 6 years old male child affected with GDD, seizure disorder, intellectual disability and hyperactivity presented at 13weeks. Detailed maternal history revealed cases with similar features in first cousins, nephews, and nieces. WES of the proband was Homozygous for 1)- COX6A1, c.247-10_247-6delCACTC, Pathogenic (Charcot Marie Tooth disease 2)- COL1A2, c.2933G>A / p.Arg978His, VOUS 3)- EPRS1, c.131+5G>A, VOUS. Both parents were heterozygous for the same. The fetus was also found to be Homozygous for COX6A1, c.247-10_247-6delCACTC, Pathogenic (Charcot Marie Tooth disease). After counselling the couple chose to continue the pregnancy.

Case 3 A G2P1L1 with previous 7 years old child with broad spectrum GDD and seizure disorder presented at 18W5D. The patient herself had mild intellectual disability with inability to follow verbal instructions. A WES with CNVs of the previous child revealed hemizygous for 1220T>C p.Ile407Thr in GLRA2 (NM_002063.4 c) VOUS (an X-linked NOVEL variant) and heterozygous for COQ8A chr1:227170655 (C/T) AR likely pathogenic. On Sanger sequencing the patient was found to be heterozygous for the first variant and negative for the second. Further data search revealed similar mutations were reported in two male siblings (diagnosed with GDD and autistic spectrum disorder) of a consanguineous marriage. After further counselling the couple opted for prenatal testing which revealed the fetus to be hemizygous. After the post-test counselling the couple chose to terminate the pregnancy.

CONCLUSION

The approach to the pregnant couples with previous child / children / family members affected from GDD is difficult. The cases should be counselled by a multidisciplinary team of pediatrician, clinical geneticist, fetal medicine specialist and treating obstetrician. Adequate pre-test and post test counselling should be provided to help the couple to take informed decisions.

Image Gallery

Figure 1- Prenatal sloping forehead



Figure 2 - Postnatal

