# Summary

The human brain develops in a series of critical steps, each of which must be correctly orchestrated to give rise to properly formed brain. Malformations of cortical development (MCD) include a wide range of developmental disorders that are common causes of neurodevelopmental delay and epilepsy. The rapid recent evolution of molecular biology, genetics and imaging has resulted in an explosive increase in the knowledge of cerebral cortex development. Prenatal 4D-ultrasound and fetal MRI can detect brain anomalies giving chance for early diagnosis of MCDs and subsequently, better management.

The study aimed to classify MCD according to brain MRI findings and to present the clinical spectrum, neurological manifestations, types of associated seizures and their response to antiepileptic drugs in relation to EEG and neuroimaging data. The study also aimed to determine the inheritance pattern of cases of MCD and their possible underlying etiologies.

The study was carried out in the Neuropediatric clinic in Abu-El Reish hospital and in Fayoum University hospital. Forty five cases; 31 males (68.9%) and 14 females (31.1%) were selected according to the presence of MRI findings suggestive of MCD. The brain MRI studies were performed in the course of a diagnostic work up for the undiagnosed neurological disorders such as psychomotor retardation, microcephaly and dysmorphic child with a global delay or epilepsy. Cases were subjected to history taking, clinical examination, ophthalmological examination, EEG and other imaging and laboratory investigations when indicated.

The ages of cases included in this study ranged from 14 days to 4 years with a mean age of 17.3 months. Regarding type of MCD, there were lissencephaly/pacchygyria spectrum in 26 cases (57.8%), schizencephaly in 8 cases

(17.8%), PMG in 6 cases (13.3%), TSC in 3 cases (6.7%), hemimegalencephaly in one case (2.2%) and holoprosencephaly in one case (2.2%). Twenty three cases (51%) had positive consanguinity, 6 cases (13.3%) had family history of similar condition, 4 cases (9%) had family history of neurological abnormalities, 2 cases (4.5%) had family history of non-neurological abnormalities, one case (2.2%) had family history of abortion, one case (2.2%) had family history of IUFD, 4 cases (9%) had family history of child death, 4 cases (9%) had family history of twin pregnancy and 2 cases (4.4%) had family history of prenatal insults. The study also revealed global delay in 42 cases (93.3%), seizures in 17 cases (37.8%), microcephaly in 35 cases (77.7%), macrocephaly in one case (2.2%), abnormal movements in 4 cases (8.9%), dysmorphic features in 6 cases (13.3%), cutaneous lesions in 4 cases (8.9%), congenital heart disease in 3 cases (6.7%), limb anomaly in one case (2.2%), cranial nerves dysfunction in 6 cases (13.3%) and abnormal gait in 17 cases (38%). Different types of seizures occurred in cases with MCD as GTC in 11 cases (24.4%), complex partial seizures in 2 cases (4.4%), myoclonic in 3 cases (6.7%) and infantile spasm in one case (2.2%). EEG showed abnormalities in 18 cases (40%) out of which 6 cases (33%) showed picture of low voltage hypoactive recordings (brain insult and slow waves), one case (5.56%) showed generalized epileptogenic dysfunctions, 10 cases (55.5%) showed focal epileptogenic dysfunctions and one case (5.56%) showed suppression burst. Regarding response to medical therapy, seizures were controlled on monotherapy in 6 cases (35%), polytherapy in 5 cases (29.4%) and were intractable in 6 cases (35%).

Different etiologies of MCD were suggested in this study as CMV infection in one case (2.2%), TSC in 3 cases (6.7%), prenatal insults in 2 cases (2.2%), Klipple Trenauny syndrome in one case (2.2%), muscle-eye-brain disease in one case (2.2%), pseudo-TORCH syndrome in one case (2.2%), autosomal recessive disorder

in 14 cases (31%) and XL disorder in one case (2.2%). The presence of high rate of consanguinity (in lissencephaly/pacchygyria and PMG), multiple affected family members (in lissencephaly/pacchygyria, PMG, schizencephaly and TSC) and significant male skewing (in lissencephaly, PMG and schizencephaly) strongly supports the genetic etiology of MCD with different pattern of inheritance (AR, AD, and XL).

Prenatal insults especially during the first trimester play an important role in pathogenesis of MCD. Regarding schizencephaly, there was correlation between clinical presentation and extent and laterality of schizencephaly but there was no correlation between the lesion and the presence or absence of epilepsy and EEG findings.

Statistical analysis done in this study showed insignificant correlation between type of MCD and ages at first presentation **(p value = 0.448)**; insignificant correlation between type of MCD and consanguinity **(p value = 0.085)**; insignificant correlation between type of MCD and prenatal insults **(p value = 0.168)**; insignificant correlation between type of MCD and global delay **(p value = 0.055)**; insignificant correlation between type of MCD and seizures **(p value=0.547)** and insignificant correlation between type of MCD and EEG findings **(p value = 0.526)**. However, correlation between type of MCD and microcephaly showed significant correlation between microcephaly and lissencephaly/pacchygyria spectrum **(p value = 0.026)** compared to microcephaly among cases with schizencephaly and PMG.

To conclude, MCD should be suspected in patients presenting with seizures, developmental delay, microcephaly or macrocephaly. Brain MRI allows accurate diagnosis of different types of MCD. Accurate diagnosis of MCD is essential for both clinical and genetic counseling. Prenatal diagnosis of MCD by either 3D ultrasound or fetal MRI should be taken in concern especially in pregnant women with positive consanguineous marriage, abortion, still birth, or history of similar

conditions. Molecular diagnosis of MCD is recommended for accurate diagnosis and hence future prenatal diagnosis by CVS and amniocentesis.