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REVIEW ARTICLE

Counseling for Fetal Central Nervous System Defects

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Abstract Fetal central nervous system defects are one of the commonest antenatally detected abnormalities. They consist of a wide array of lesions with heterogeneous etiologies and outcomes. Counselling of the family in such cases forms an integral part of management. However, this can be challenging due to diagnostic and prognostic uncertainties for many defects. Some lesions like anencephaly, holoprosencephaly, and lissencephaly, have an invariably poor outcome, and decision regarding pregnancy termination is straightforward. On the other hand, lesions like mild ventriculomegaly, isolated corpus callosum agenesis and posterior fossa lesions have a highly variable outcome, ranging from normal to severe handicaps, hence counseling for these is difficult. Detailed sonography by an expert sonologist and fetal MRI can help in detection of additional cerebral or extracerebral abnormalities, which being associated with a poor prognosis, can help in accurate counseling. An often-neglected aspect of counseling is the possibility of recurrence in subsequent pregnancies, due to an underlying genetic etiology in many of these defects. This can be assessed by pedigree information, suitable genetic testing and postmortem examination in case of pregnancy termination. Diagnosis of the genetic abnormality helps in accurate recurrence-risk prediction as well as early and timely prenatal diagnosis in at-risk pregnancies.

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Introduction

Abnormalities of the central nervous system (CNS) are one of the commonest birth defects, found in 1–10 per 1000 live births and comprise of at least one third of prenatally detected fetal malformations [1–5]. These defects have direct implications for subsequent neurodevelopmental outcome and are important to diagnose in a timely fashion using appropriate imaging modalities. They may occur in isolation or be associated with other anatomical abnormalities [6]. An important aspect of management of a pregnancy complicated by a fetal CNS abnormality is counseling of the family for facilitating informed decision making [7]. The counseling in turn involves various aspects related to diagnostic pitfalls, prognosis, available therapies, and recurrence risks for subsequent conceptions. The diverse types of lesions, heterogenous etiologies, diagnostic, and prognostic uncertainties for many conditions and association with genetic syndromes which may not be apparent on imaging, make counseling challenging [8]. This review attempts to cover counseling aspects for some common CNS lesions.

Counseling as Relevant to Individual Conditions

Neural Tube Defects

(a) Prognosis of the lesion per se: Anencephaly and large encephaloceles are invariably associated with extremely poor prognosis and postnatal lethality.

Prognosis for spina bifida aperta is also guarded, with mortality due to posterior fossa syndrome (15–30%), hydrocephalous requiring shunt placement (80%), motor and bowel/bladder disabilities (50–70%) and intellectual disability (IQ < 80 in 30%) being associated [9]. Outcome for occult spinal defects is favourable in absence of associated abnormalities. Rarer defects like craniorachishis and iniencephaly are invariably associated with poor outcome.

(b) Therapies available: Postnatal therapies are available for spinal defects, involving operative closure of the defect, placement of ventriculoperitoneal shunt in case of hydrocephalous and supportive therapies. However, residual morbidities remain and complications of operative procedures are common [9]. Prenatal surgical repair of the spinal defects have recently gained prominence, with the MOMS trial reporting significant benefit in terms of motor abilities and reduction in shunt requirement for cases undergoing prenatal repair. This option is however available in limited centers across the world and is feasible for few select cases [10].

(c) Association with genetic syndromes and recurrence risks: Majority of neural tube defects are sporadic and multifactorial in etiology with empirical recurrence risk of 5%. Spinal defects may rarely occur as part of spondylocostal dysostoses, which are autosomal recessive conditions. Encephaloceles are associated with a large number of genetic syndromes, primarily the ciliopathies and the dystroglycanopathies, with recurrence risk of 25%; hence, careful search for additional findings is important. Some rare families with monogenic inheritance of neural tube defects consequent to VANGL1 & 2, SHROOM3, CELSR1 mutations are also known. 1–6% cases may have a chromosomal abnormality indicating the need for fetal karytotyping [9–13].

(d) Diagnostic pitfalls: Second trimester ultrasound in expert hands has high detection rate for neural tube defects (92–95% sensitivity and almost 100% specificity). Rarely, occult defects may pose a diagnostic dilemma, and fetal MRI may be considered [9].

Midline Defects

Holoprosencephaly

(a) Prognosis of the lesion per se: Alobar, semilobar, middle interhemispheric variants of holoprosencepahly are associated with poor postnatal outcomes with intellectual disability and seizures being seen in nearly all individuals. Additionally, there is 85% neonatal mortality in alobar type. Lobar holoprosencephaly has a variable phenotype and this uncertainty needs to be communicated to the family. In case of associated abnormalities, syndromic etiology and poor prognosis is likely [13–15].

(b) Therapies available: No corrective therapies are available for these defects.

(c) Association with genetic syndromes and recurrence risks: Holoprosencephaly is associated with chromosomal abnormalities in 25–45% cases, most commonly trisomy 13, submicroscopic copy number variants in 25% and single gene defects in 15–25% cases involving SHH, SIX3, ZIC2, TGIF, and few other genes with autosomal dominant inheritance. Recurrence risk in subsequent pregnancies can vary from 1% for chromosomal abnormalities to 50% for the single-gene defect if one of the parents is also carrying the same mutation. In view of incomplete penetrance and variable expressivity of these mutations, the parent may be clinically asymptomatic or have mild symptoms. It is essential to examine them for microforms of the disease, like presence of single centre incisor, hypotelorism; as this would help in providing accurate recurrence risk [13, 14].

(d) Diagnostic pitfalls: The milder variants of holoprosencephaly like the lobar and middle interhemispheric variant may be missed on antenatal ultrasonography or be mistaken for other entities with relatively better outcome like corpus callosum agenesis or absent septum pellucidum. It is essential to perform a detailed neurosonography for anatomic delineation and a fetal MRI in case of diagnostic dilemma [15].

Corpus Callosum Agenesis

(a) Prognosis of lesion per se: Corpus callosum agenesis may occur as an isolated defect or with cerebral and extracerebral abnormalities. Isolated agenesis is associated with normal neurodevelopmental outcome in 70–75% cases, whereas presence of associated findings indicates a poor prognosis [8, 16].

(b) Therapies available: None.

(c) Association with genetic syndromes and recurrence risks: Overall 12–33% cases of prenatally detected corpus callosum agenesis are of syndromic etiology, with 18% incidence of chromosomal abnormalities, 9% of submicroscopic copy number abnormalities and at least 160 single gene disorders reported to be associated. The recurrence risk may be up to 25% for the single gene defects as per the inheritance pattern [16–18].

(d) Diagnostic pitfalls: The most challenging aspect of diagnosis of corpus callosum agensis is to assess whether it is an isolated finding or associated with other abnormalities. Additional cerebral findings can be found on neurosonography in 46% cases, in an additional 22% on prenatal MRI and in a further 15% apparently isolated cases on postnatal MRI. A false positive diagnosis has been reported in 0–20% cases in various reports. Hence, fetal MRI forms an important modality for accurate diagnosis and counseling for this defect [8, 16].

Absent Septum Pellucidum

(a) Prognosis of the lesion perse: Isolated absence of septum pellucidum is associated with good outcome. However, in up to 18% cases it is associated with septo-optic dysplasia which has poor postnatal outcome, with visual deficits and hypopituitarism being present in varying degrees [8].
(b) Therapies available: None.
(c) Association with genetic syndromes and recurrence risks: Most cases are sporadic with low recurrence risk. However, septo-optic dysplasia can be associated with mutation in SHH, SIX3, and HESX genes, with recurrence risks up to 25% [8, 19].
(d) Diagnostic pitfalls: False negatives are high for septo-optic dysplasia as pituitary and optic tract abnormalities are difficult to diagnose by ultrasonography or MRI [8].

Disorders of Cortical Development

Lissencephaly

(a) Prognosis of the lesion per se: Lissencephaly is invariably associated with poor postnatal outcome, with severe intellectual disability and seizures in affected individuals [20–22].
(b) Therapies available: None.
(c) Association with genetic syndromes and recurrence risks: Classic or type I lissencephaly is most commonly caused by heterozygous LIS1 mutations or deletions of 17p13.3 region containing the LIS1 gene, the latter also known as Miller Dieker syndrome. These occur *de novo* in majority and recurrence risk in subsequent pregnancies is negligible. Other type 1 lissencephalies can be caused by mutations in ARX, DCX genes, both being X linked with up to 50% risk of recurrence in male offsprings; and in combination with ceberellar hypoplasia by TUBA1 and RELN mutations. Type II lissencephaly or Cobblestone lissencephaly belongs to the Dystroglycanopathy group of disorders, which are autosomal recessive with 25% recurrence risk in subsequent pregnancies [21, 22].
(d) Diagnostic pitfalls: The diagnostic findings of lissencephaly are not apparent early in gestation, as the cerebral sulcation gyration becomes apparent from 18 weeks onwards and continues till third trimester. Hence, an imaging based diagnosis of this defect is usually possible in only later half of pregnancy. This further reiterates the importance of a molecular diagnosis in the index case, as this enables first trimester prenatal diagnosis in subsequent pregnancies by invasive fetal sampling. Also, subtle migration abnormalities may not be apparent on ultrasonography and need an MRI based imaging at 28–30 weeks for detection [20, 23].

Microcephaly

(a) Prognosis of the lesion perse: the overall risk of abnormal neurodevelopmental outcome with head circumference (HC) between −2 and −3SD is 10%. If isolated microcephaly is confirmed, the outcome is reported to be similar to normal head sized fetuses, but behavioural problems may occur. With HC between −3 and −3.99SD, 51% have neurodevelopmental handicap, whereas 100% of fetuses with HC < −4SD have an abnormal outcome. If associated findings in the form of cerebral or extracerebral abnormalities exist, the prognosis is poor [24–26].
(b) Therapies available: None for established microcephaly. However preventive measures like control of maternal phenylketonuria, withholding teratogenic pharmacological agents and rubella vaccination can prevent recurrences in specific cases.
(c) Association with genetic syndromes and recurrence risks: Microcephaly is one of the presenting feature of many genetic syndromes, including chromosomal disorders, copy number abnormalities and single gene diseases, most of which present with additional anatomical findings. The recurrence risk can vary from 1 to 25% as per the underlying condition. Also, microcephaly is a common finding in presence of other CNS abnormalities like holoprosencephaly, lissencephaly and posterior fossa defects. In addition, at least 12 different genes can cause isolated microcephaly with mild to moderate intellectual disability postnatally and 25% recurrence risk in subsequent conceptions [26, 27].
(d) Diagnostic pitfalls: Microcephaly usually becomes apparent late in second trimester. In cases with HC

between −2 and −3SD, serial measurements may be necessary for the diagnosis. Subtle neuronal migrational abnormalities in an apparently isolated microcephaly, associated with worse postnatal prognosis, are not usually detected on ultrasonography and a fetal MRI is needed for the same. Hence, if an index case is available, genetic testing and identification of causative mutation is recommended to facilitate first trimester prenatal diagnosis in subsequent pregnancies by invasive fetal sampling [24, 25].

Megalencephaly

(a) Prognosis of the lesion per se: Most macrocephalies are benign, familial macrocephaly with autosomal dominant inheritance. Hence if a parent with macrocephaly is present, the prognosis is likely to be good. Isolated HC 2–3SD above mean is also likely benign with normal neuropsychological outcome except for behavioural problems. HC above 3SD usually indicates an underlying genetic syndrome and is associated with poor outcome. Presence of additional cerebral or extracerebral abnormalities invariably indicates poor prognosis [28, 29].
(b) Therapies available: None.
(c) Association with genetic syndromes and recurrence risks: Benign familial macrocephaly with an affected parent has 50% recurrence risk, but is of no clinical significance. Most genetic syndromes presenting with megalencephaly are due to *de novo* heterozygous mutations and have negligible recurrence risk [29].
(d) Diagnostic pitfalls: Migrational abnormalities which may coexist with an apparently isolated macrocephaly, and indicate a poor prognosis, are difficult to diagnose on ultrasonography and MRI findings may be apparent late in pregnancy [23].

Other cortical development defects

Polymicrogyria: Usually not detected on ultrasonography and is diagnosed on MRI. Prognosis is likely to be poor, and recurrence risk up to 25% in some cases. Schizencephaly has a variable prognosis and low recurrence risks [23].

Posterior Fossa Defects

The major diagnostic challenge in this group of disorders is the difficulty in distinguishing the individual lesions, each of them being associated with different outcomes.

Dandy–Walker Malformation

(a) Prognosis of the lesion per se: Isolated Dandy–Walker malformation is associated with abnormal neurodevelopmental outcome in 50–60% cases. Associated findings indicate a poor prognosis [8, 30].
(b) Therapies: None available. Associated ventriculomegaly may be relieved partly by postnatal shunt placement if symptomatic.
(c) Association with genetic syndromes and recurrence risks: 16–50% cases show chromosomal abnormalities, approximately 30% copy number abnormalities and few cases may occur as part of single gene disorders like Walker–Warburg syndrome and Meckel–Gruber syndrome. Recurrence risks can vary from 1% for chromosomal etiologies to 25% for the single gene defects [8, 18, 30–32].

Inferior Vermis Hypoplasia

(a) Prognosis of the lesion per se: Isolated vermis hypoplasia has been reported to be associated with abnormal neurodevelopmental outcome in 0–30% cases as per different studies. Presence of associated findings indicate poor prognosis [30, 31].
(b) Association with genetic syndromes: Besides being associated with chromosomal disorders, vermis hypoplasia is a feature of Joubert syndrome, an autosomal recessive disorder with poor outcome. Recurrence risk in these cases is 25% [30, 31].

Blake's Pouch Cyst

(a) Prognosis of the lesion per se: This is a normal variant which usually regresses later in gestation and is associated with a good postnatal outcome [8, 30].

Mega Cisterna Magna

a) Prognosis of the lesion per se: If isolated, a normal neurodevelopmental outcome is expected in 90–100% cases. Presence of other abnormalities indicate poor prognosis [8, 30].
b) Association with genetic syndromes and recurrence risks: 0–62% cases of mega cistern magna are reported to be associated with chromosomal abnormalities or other malformations indicating a syndromic etiology [8, 31].

Diagnostic pitfalls for posterior fossa lesions: Antenatal sonography may not always delineate the exact lesion and fetal MRI is often needed for adjunct imaging [33].

However, MRI and USG findings may not always be concordant for these defects. Also, in many studies, post-mortem findings have often revealed normal morphology, these most likely representing a Blake's pouch cyst which is a normal variant or gestation dependent finding like vermis hypoplasia. These issues make counseling for these lesions challenging [8, 30].

Ventriculomegaly

(a) Prognosis of the lesion per se: Ventriculomegaly may be an isolated finding or associated with other cerebral or extracerebral abnormalities. The prognosis is poor in the latter situation. Prognosis for isolated ventriculomegaly depends on the degree primarily, although few studies have also reported difference in outcome depending upon unilateral vs bilateral lesion and underlying etiology. Severe ventriculomegaly (>15 mm lateral ventricle atrium diameter) has associated abnormalities in at least 46% cases, an additional 25% being detected on postnatal MRI. Abnormal neurodevelopmental outcome is likely in 70–90% cases if isolated and >90% cases with associated abnormalities. Majority progress in utero and a 20% neonatal mortality is likely. Mild ventriculomegaly (10–15 mm) is likely to resolve in 35% cases during pregnancy and 45% cases postnatally. It is associated with other findings in 13–30% cases, which indicate poor prognosis. Isolated mild ventriculomegaly is associated with abnormal neurodevelopmental outcome in 4–11% cases [34–38].

(b) Therapies: Postnatal shunt procedure for hydrocephalous is associated with favourable outcome in up to 40–60% individuals, though an overall mortality rate of 20–40% exists [39, 40]. Prenatal therapies like ventriculoamniotic shunting and cephalocentesis have been largely abandoned due to poor results, though recently there has been interest in revival of this approach for ventriculomegaly secondary to aqueductal stenosis [41].

(c) Association with genetic syndromes and recurrence risks: There are 3–10% cases of ventriculomegaly associated with chromosomal abnormalities and 12.5% cases have copy number abnormalities [32, 34, 35, 37]. Also, 107 OMIM genes are known to present with ventriculomegaly. Recurrence risks can range from 1% for chromosomal etiologies to 25% for recessive single gene defects.

(d) Diagnostic pitfalls: The presence of associated findings, which determine the prognosis, may not be detectable on ultrasonography and MRI findings may also become apparent late in pregnancy.

Miscellaneous

Various other CNS lesions may be seen occasionally like arachnoid cysts, vein of Galen aneurysm, disruptive lesions like hydranencephaly and others secondary to infections, hemorrhage. In most such cases, the prognosis depends on the extent of the lesion and the degree of parenchymal loss. Recurrence is unlikely due to primary acquired etiological bases [8].

Role of Pedigree Drawing

A three generation family history is important to look for segregation of a genetic disease in the family, which could explain the ultrasound findings. In a fetus with holoprosencephaly, one of the apparently healthy parent may have a milder manifestation or microform of the disease indicating autosomal dominant inheritance; in case of megalencephaly, a parent may have a large head indicating benign familial macrocephaly or a previous offspring may have similar or overlapping phenotype indicating autosomal recessive inheritance. These findings may help in arriving at a specific genetic diagnosis, which would facilitate more accurate prognostication as well as recurrence-risk estimation [7, 8].

Role of Genetic Testing and New Technologies

There is a significant contribution of genetic etiologies to CNS abnormalities, including chromosomal disorders (numerical and structural), submicroscopic copy number abnormalities (microdeletions and microduplications) and single gene defects (syndromic and nonsyndromic). The presence of an underlying genetic etiology is associated with a poor postnatal outcome, as most of these conditions present with intellectual handicap and various other co-morbidities which may not be detected on antenatal imaging. Hence, genetic testing of the fetus is an important modality which can help in predicting postnatal course and aid in accurate counseling of the family. Additionally, the testing helps in estimating exact recurrence risk for subsequent conceptions and enables early and definitive prenatal diagnosis by chorionic villus sampling at 11–12 weeks in at risk pregnancies [6, 7].

The testing traditionally involved fetal karyotyping, which detects numerical and structural abnormalities in chromosomes and has a yield varying from 1 to 6% for neural tube defects to up to 50% for defects like holoprosencephaly and Dandy–Walker malformation. However, karyotyping is limited in its resolution and cannot detect submicroscopic copy number abnormalities and single gene defects. Chromosomal microarray is a

Table 1 Genetic abnormalities and additional findings associated with specific CNS defects

	Chromosomal abnormalities on karyotype	Copy number abnormalities on CMA	Single gene defects*	Positive TORCH profile	Additional abnormalities on antenatal USG/MRI	Additional findings on Postnatal MRI
Ventriculomegaly	3–9%	12.5%	107 known	Yes- 8% one study	13–60% 10–20% on MRI	5–25%
Microcephaly	23% in one study	Isolated case reports	393 known 20% in one study	Yes	65–83%	NA
Megalencephaly	1% in one study	Isolated case reports	126 known	NR	16% in one study	NA
Holoprosencephaly	25–45%	25%	54 known 15–25%	NR	66–100%	NA
Lissencephaly	45–60% in MDS phenotype	100% in MDS	58 known	Yes	30–87%	NA
Dandy–Walker malformation	16–50%	30%	>1000 known	Yes	25–66% 14% on MRI	18%
Neural tube defect	1–6%	Nil in one study	100 known	NR	10–26%	NA
Corpus callosum agenesis	18%	9%	160 known	Yes	46–68% 22% on MRI	15%

CNS central nervous system; *CMA* chromosomal microarray; *TORCH profile* serum antibody profile for toxoplasma, others, rubella, cytomegalovirus, herpes; *MRI* magnetic resonance imaging; *NA* information not available; *NR* information not relevant; *MDS* Miller–Dieker syndrome

* For many of single gene defects, exact proportion of contribution towards the CNS defect is not known

technology which enables a genome wide detection of submicroscopic copy number abnormalities, which may involve deletion or duplication of small parts of a chromosome. Microarray in cases with CNS abnormalities has a diagnostic yield beyond karyotype of 4.2–8.2% with this being as high as 7.5–10% in case of multiple abnormalities. The ACOG recommends microarray to be used as the first tier test in case of fetal structural malformations, as this detects microscopic as well as submicroscopic chromosomal abnormalities [42].

Additionally, single-gene defects contribute to a significant proportion of CNS abnormalities, this being prominent for malformations like encephaloceles, holoprosencephaly, lissencephaly, and other cortical development defects. The detection of the causative mutation in this setting has important implications for subsequent pregnancies as recurrence risks can vary from 25 to 50%. A major limitation for this has been the genetic heterogeneity of these conditions, whereby multiple genes can lead to the same malformation, and the mutations within a single gene also differ between families. A novel technology, next generation sequencing has the potential to look at mutations in all the different genes in a single experiment, hence providing the molecular diagnosis in such cases. Recent case series have indicated that this approach can be used in pregnancies with fetal abnormalities, with a diagnostic yield of 20–30% [43]. Hence, a composite approach of chromosomal microarray followed by next generation sequencing based testing is likely to identify underlying genetic etiologies in fetuses with CNS defects, and help in subsequent informed management of index as well as subsequent pregnancies.

Role of Fetal MRI

Many CNS defects particularly the migrational abnormalities, midline defects and posterior fossa lesions are benefited by an MRI based imaging for identification and exact anatomic delineation. Literature review also indicates that MRI provides important additional information in 5–20% cases with CNS malformations, and can change management in up to 30%. Although, there are no recommendations regarding when to supplement neurosonography with MRI, it forms an important adjunct for accurate prognostication and management; and should be used if available [44, 45].

Role of Postnatal Evaluation

In the event of pregnancy termination, a postnatal evaluation is essential for identification of dysmorphic findings and other malformations which help in establishing

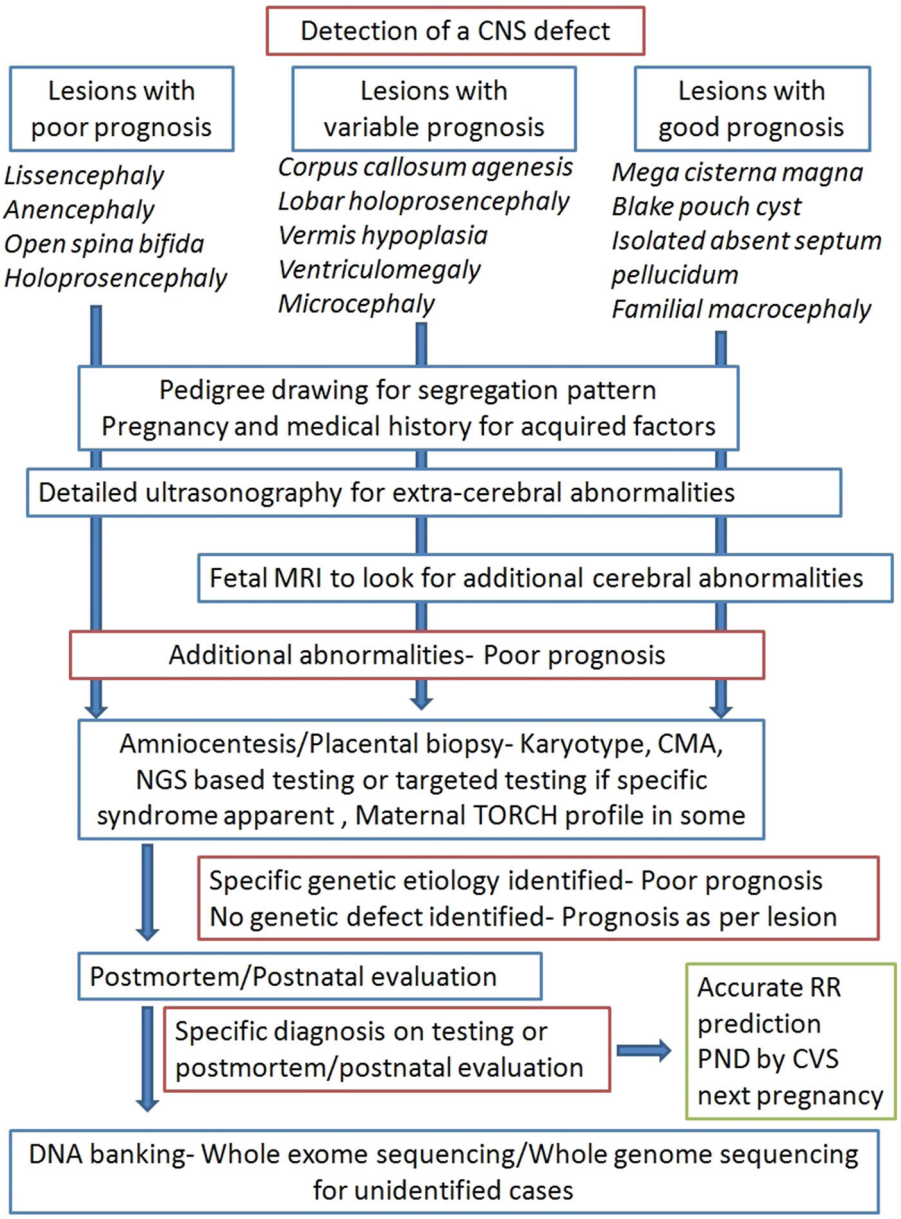

Fig. 1 An algorithm of approach towards workup and counseling for CNS defects. *CNS* central nervous system, *CMA* chromosomal microarray, *TORCH* toxoplasma, others, rubella, cytomegalovirus, and herpes, *RR* recurrence risk, *PND* prenatal diagnosis, *CVS* chorionic villus sampling

syndromic etiologies. Various studies have indicated that an autopsy helps in detecting additional findings and changes the antenatal diagnosis in 20–50% cases [46, 47]. A detailed gross and histopathologic evaluation of the brain helps in identification of the exact extent, type of lesion as well as provide clue to underlying etiology. An autopsy forms an integral component of arriving at the final diagnosis, and the family should be counselled and encouraged for the same in the antenatal period. For families deciding to continue pregnancy, postnatal assessment and serial follow up for neurodevelopmental outcome of the child also aids in arriving at the etiological diagnosis. This further facilitates recurrence risk prediction and prenatal diagnosis in subsequent pregnancies.

Summary and Conclusion

Antenatal detection of a fetal CNS defect is often followed by hasty decisions regarding pregnancy termination in view of an anticipated poor postnatal outcome. However, given the wide array of lesions with different prognosis, diagnostic pitfalls and uncertainties, counseling for these pregnancies is important for appropriate management and should precede decision making. In many cases, genetic defects are causative, and recurrence is likely. Table 1 provides a summary of additional findings and genetic defects in individual lesions. Counseling can be facilitated by providing estimates based on this information and relevant genetic testing can be offered to the family. An

algorithm is depicted in Fig. 1 outlining the diagnostic and counseling approach.

Counseling for fetal CNS defects can be complicated by various factors and remains challenging despite advances in imaging and genetic technologies. A comprehensive approach involving detailed neuroimaging, genetic testing, and consultation with a geneticist helps this process and allows for enhanced care of index as well as subsequent pregnancies.

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