How to Examine a Brain in Maldevelopment

Ferechte Encha-Razavi

Brain malformations are congenital deviations in anatomy and/or histology. They are related to a failure of the neurodevelopmental process with a primary event resulting in a pleiotropic cascade of secondary anomalies. A significant number of brain anomalies are malformative due to chromosomal and genetic abnormalities. Genetic factors interfere with the neurodevelopmental processes by disregulating specific signalling pathways. On the other hand, signalling pathways may be possible targets for exogenous disruptive factors, mimicking therefore similar pattern of malformations (phenocopy). By definition, secondary malformations cannot be inherited. However, inherited factors can predispose to secondary malformations.

The Checkup Procedure

To go further into the identification of neurodevelopmental disorders, a five-step checkup is necessary.

First, Describe

A detailed macroscopical and histological description of brain anomalies should be performed in details and the report should be understandable by a "nonspecialist." The macroscopical report must include information about (1) the growth of the CNS, (2) the external shape of the cerebral hemispheres, the brainstem, and the cerebellum, and (3) the internal configuration of the brain.

F. Encha-Razavi (✉)
Unité d'Embryofoetopathologie, Hôpital Universitaire Necker-Enfants malades, Paris, France
e-mail: ferechte.razavi@aphp.fr

J. Martinovic (ed.), *Practical Manual of Fetal Pathology*,
https://doi.org/10.1007/978-3-030-42492-3_12

The histological examination should focus at the level of cerebral walls (also called dorsal telencephalon, neopallium), the ventricular and subventricular zones (VZ, SVZ), the intermediate zone (IZ), and the cortical plate (CP). Examination should also describe midline structures, mainly the corpus callosum crossing tracts, the cavum, and the septal apparatus. At the level of the diencephalon (also called ventral telencephalon) the ganglionic eminences are described, as well as the basal nuclei and the anterior and posterior arms of the internal capsule. At the mesencephalic level, the colliculi (superior and inferior), the roof (called tectum) as well as the subcommissural organ just above the aqueduct of Sylvius are examined. An evaluation of the cranial nerve's nuclei (the III the oculomotor nerve and the IV the trochlear) should follow. The longitudinal cortico-spinal tracts (CST) are followed from the mesencephalic level to the medulla oblongata, where they form pyramids. Sagittal sections of the pons and the cerebellum allow to appreciate the pontine relief as well as the vermian foliation and lamination. On transversal sections of the hemi-pons, growth of tegmentum is compared to the basilar pons and pontic nuclei and projections are examined. At the level of the medulla, the superior olivary nuclei and the nuclei of XII cranial nerves (hypoglossal) have to be analyzed particularly in case of fetal akinesia and mandibular hypoplasia. At the level of the cervical spinal cord, the global architecture and the organization of the longitudinal tracts as well as the pyramids decussation are examined. In addition, the cellularity and integrity of the motoneurons is assessed. In the cerebellar hemispheres, lamination and deep nuclei (dentate and fastigial) are analyzed.

Two, Focus on the Primary Event

Brain malformations correspond to an arrest at a particular stage of the developmental process resulting in a failure of the following developmental stages. For instance, corpus callosum defects may result from an abnormal crossing or from a deficit in callosal fibers formation. In the first case identification of bundles of aberrant fibers (called Probst Bundles) confirms the axonal guidance defect and in the second a cortical malformation may explain the lack or reduction of callosal fibers resulting in agenesis or dysgenesis.

Three, Identify a Pathogenic Mechanism

For example, in the context of hydrocephalus, neuropathological evaluation may assign the malformation to the obliteration of the arachnoid space due to a neuroglial overmigration. Gaps in the glia limitans result in overmigration. The gaps may result from a damage to the brain or due to a developmental basement membrane defect.

Four, Recognize a Syndrome

For instance in fetuses, hydrocephalus due to overmigration when associated to cerebellar or ocular dysplasia and a meningoencephalocele is strongly suggestive of the Walker–Warburg syndrome part of the COMD (cerebro-oculo-muscular dysplasia) community, characteristic of alpha-dystroglycanopathies.

Five, Orient Genetic Studies

Neuropathological study by pointing out to a precise gene or a genetic cascade or to a community of pathogenetic events allows to save time and cost. For example, it could be conclusive when molecular investigations of a specific gene or a panel of genes are performed. In addition, neuropathological findings may facilitate the interpretation of pathogenic variations found by NGS.

Conclusion

Neurofetopathological examination requires a very good knowledge of the "origami" of neurodevelopmental process and its underlying molecular signalling pathways. Normal brain formation results from a cascade of biological and mechanical events driven by genetic and epigenetic factors. Genetic mutations disrupt these signalling pathways, which are also possible targets of exogenous factors such as virus, alcohol, hyperglycemia, and teratogens, thus mimicking similar phenotype (e.g., holoprosencephaly, microcephaly). For further identification of congenital neurodevelopmental defects, a five-step procedure is proposed:

First, describe
Two, focus on the primary event
Three, identify the underlying mechanism
Four, recognize a syndrome
Five, orient genetic studies

Acknowledgements My special thanks to Professor Michel VEKEMANS for his critical reading of this chapter and suggestions.