Obstetrica şi Ginecologia LXV (2017) 147-151 **Review article**

ANOMALIES OF THE GANGLIONIC EMINENCES AND THEIR CLINICAL IMPLICATIONS

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Abstract

Ganglionic eminences are important temporary structures of the developing brain, as they produce interneurons that migrate and integrate into the nervous circuits. Whether their certain implication in congenital anomalies of the brain has a notable clinical importance or not is still a subject of debate, especially among physicians. Even if data concerning this subject are rare, our paper reviews the literature focusing on the anomalies of the ganglionic eminences that can be detected in clinical practice.

Rezumat: Anomaliile eminenţelor ganglionare şi implicaţiile lor clinice

Eminenţele ganglionare sunt structuri temporare importante ale encefalului în dezvoltare deoarece ele produc interneuroni care vor migra şi se vor integra în circuitele nervoase. Un subiect de dezbatere, în special printre clinicieni, este următorul : implicarea certă a acestor structuri în apariţia unor anomalii congenitale cerebrale are sau nu o importanţă clinică notabilă ? Chiar dacă studiile care se ocupă de acest subiect sunt rare, lucrarea noastră trece în revistă literatura privind anomaliile eminenţelor ganglionare care pot fi detectate în practica clinică.

Cuvinte cheie: eminenţe ganglionare, dezvoltare anormală a creierului

Introduction

Ganglionic eminences (GE) are transient subcortical structures which supply interneurons that migrate to different sites of the brain: basal ganglia, thalamus, olfactory system, hippocampus, globus pallidus and neocortex. GE contribute at least 35% to the population of interneurons that tangentially migrate toward to the cerebral cortex (1). The GE also represent an intermediate target for corticofugal and thalamocortical axons (2).

GE, as part of the germinal matrix pool, appear in the 5th week post-fertilization and reach their maximal development at about 18-22 GW (3). After that their volume decreases and they will disappear until the 35th week of gestation.

Müller and O'Rahilly (4) have shown that in humans the GE consist of two distinct parts with different origins: medial ventricular eminence (MVE) of diencephalic origin and lateral ventricular eminence

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(LVE) of telencephalic origin. From the undivided caudal portion of the ganglionic eminence (CVE) forms the amygdaloid nucleus (5, 6).

Recently we published a paper concerning the assessment of the GE within the early brain by 3D transvaginal ultrasound (7). Since then, we have presented the results of our work in a number of congresses and conferences. We noticed that the physicians are not used with the importance of these transitory structures of the developing brain, probably because of the fact that clinical data concerning this subject are very scarce.

The aim of this review is to deliberate on recent studies concerning the implications of the abnormal GE in clinical practice.

Disorders in proliferation and migration of interneurons

Cell migration is a key feature of mammalian brain development, with neurons arising in a number of progenitor regions and subsequently migrating via distinct pathways to take up their final positions in the mature brain (8). Cortical GABA-ergic interneurons, which are generated mainly from MGE and CGE cells, regulate neural networks by providing inhibitory inputs (9).

Disorders in neuronal excitation and inhibition occur in many neurological and psychiatric disorders (10). These mainly include epilepsy, schizophrenia, neuropathic pain, autism, Alzheimer's disease and Parkinson's disease (11, 12). In schizophrenia patients, post-mortem brain studies have consistently reported a reduction in cortical GABA-ergic interneurons (13). Furthermore, certain regions of post-stroke brain and brains exposed to alcohol during the prenatal period also display impaired inhibitory neurotransmission (14).

Abnormalities of the GE are associated with defective cellular proliferation and migration, which may cause complex brain anomalies such as microcephalies and lissencephalies. Lissencephaly, a rare but severe brain anomaly, is characterized by deranged cortical lamination and impaired gyration. Lissencephalies are primarily caused by abnormal neuronal migration (15). This condition is mainly caused by mutations in genes, many of which are involved in microtubule function (16). Severe micro-lissencephaly syndromes may associate marked brain derangement such as agenesis or extreme hypoplasia of corpus callosum, but all of them share the common feature of abnormal GE region (17).

Germinolysis

Destruction of the germinal matrix is predominantly associated with infections (18). Congenital infections such as CMV may produce a marked germinolysis as the GE are nervous structures characterized by a high rate of mitosis and a rich vascularization. On MR images, cysts or haemorrhages may be seen, and/or the region of the GE may appear inhomogeneous (19).

Other conditions related to the destruction of the GE are intrauterine growth restriction, circulatory deficits and malformations, which have been described as risk factors for germinolytic cysts (20). We suggest that a pathological process of uncontrolled apoptosis could be also implied in germinolysis.

Haemorrhage

Literature concerning the intraventricular haemorrhage is abundant. This condition often originate from the GE, the highly proliferative and metabolically very active part of the germinal zone, which has a rich blood supply between GW 24 and GW 32 (21). GW 26–28 has been suspected as the time period with the highest risk for a haemorrhage in the GE (22).

Considering the asymmetry of the hemorrhagic lesions, we can hypothesize that the ultrasound or MRI might show asymmetrical abnormal images of the GE. Hemorrhagic lesions within GE characteristically show an irregular shape and, most notably, abnormal T1-weighted hyperintense signal (23).

After birth, haemorrhage-associated suppression of cell proliferation in the GE could partially explain the reduced brain size and clinical effects in children who suffer germinal matrix haemorrhage after premature birth (3).

Cavitation and "cysts"

Cavitations are believed to be independent lesions, not related to hemorrhagic accidents or other conditions which could produce necrosis within the GE.

Bilateral and symmetric cavitations in the GE regions were reported in 5 cases (17). The authors hypothesize that these lesions had a malformative rather than necrotic-clastic origin, considering similar size of the lesions, with regular margins and no apparent signs of haemorrhage.

Cavitations within the GE could be assessed by ultrasound, as it is suggested by some experts, but objective data are missing for the moment.

The MRI in chronic fetal brain injury may show irregularities in or premature loss of the germinal zone (19). During the brain development, cavitations may change their dimensions. It was noticed a relatively decrease in their size with respect to the progressive growth of the whole brain (17).

After birth, microcystic changes in the basal ganglia were noticed in the brains of children with X-linked lissencephaly with abnormal genitalia, both at neuropathology (24) and by use of MR imaging scan (25).

Recently it was demonstrated that GE abnormalities may take place also in conditions with no micro-lissencephalies or even as isolated entities (23). Multiple small areas of abnormal signal intensity, possibly representing microcystic changes, were also observed in the basal ganglia of boys with ARX mutations and profound cognitive impairment but no lissencephaly (26). Whether these « cyst-like » lesions are correlated with the cavitations within the developing GE is still a matter of debate.

Enlarged GE region

GE of increased size were found in different circumstances and reported by some authors. A large GE in fetuses with TUBA1A gene mutation was observed, thus underlying the discrepancy between an abnormally large GE in an abnormally small (microencephalic) brain (27). In two studies on genetically modified murine models of lissencephaly, the *ARX* gene lissencephaly model (28) and the *DISC1* gene schizophrenia model (29), histology showed that GE size was clearly larger than the one of the wild rat type. It was speculated that this paradoxical transient enlargement of the GE within a relative small brain is due to the accumulation of an excessive number of neuroblasts, halted from their normal tangential migration process (23).

However, the objective criteria of an enlarged GE are missing and this observation is based only on the subjective impression of the examiner when compared with controls.

According to the experts who studied the problem by using fetal MRI, GE size enlargement may be associated or not with cavitations, and, conversely, cavitations may be accompanied or not with GE size increase (23).

Associated intracranial anomalies

Although the anomalies of GE may be isolated, usually they are associated with various brain anomalies such as corpus callosum dysgenesis, microcephaly, cerebellar hypoplasia, polymicrogyria, ventriculomegaly, enlarged subarachnoid spaces, and molar tooth malformation.

In a recent study (23) it was stated that ultrasound generally detect most of the associated intracranial anomalies, prompting the MR investigation; although, GE anomalies had not been detected by ultrasound in the cited study. Adversely, there are experts who advocate the role of ultrasound in the assessment of GE and even depict the cavitations within those structures, but published data are lacking for now.

Genetic correlations

The lissencephaly spectrum includes agyria, pachygyria, and subcortical band heterotopia. Abnormalities of the *LIS1, DCX, ARX, RELN, VLDLR, ACTB, ACTG1, TUBG1, KIF5C, KIF2A,* and *CDK5* genes have been associated with these malformations. Recent studies have established a relationship between lissencephaly, isolated or associated with other cerebral malformations, and

mutations of several genes (*TUBA1A , TUBA8 , TUBB , TUBB2B , TUBB3 ,* and *DYNC1H1*), regulating the synthesis and function of microtubule and centrosome key components and hence defined as tubulinopathies (30).

It is proved that reduced expression of *LIS1* gene causes the type 1 lissencephaly in humans by perturbing neuronal proliferation and migration (31). Also, gene mutation of tubulin alpha-1A (*TUBA1A*) impairs neural migration and causes lissencephaly (32). Tubulin alpha-1A is a critical component of microtubules of the cytoskeleton and is expressed transiently during neuronal development (33).

Abnormal proliferation of neuronal progenitors in the GE and subsequent abnormal migration of GABA-ergic interneurons has been demonstrated in the *ARX* knock out model (34). *ARX*-related lissencephaly is included among the so-called interneuronopathies, which are characterized by decreased number of cortical GABA-ergic interneurons. Evidence suggests that mutations in this gene cause an abnormal process primarily affecting GE development (17).

Perspectives

Applying the results of experimental research in the field of regenerative medicine is an attractive idea. The hypothesis that grafted cells should disperse, migrate and functionally integrate into the nervous circuits was promoted.

Experimental studies have shown the potential of GABA-ergic interneurons as sources for novel cellular therapies for epilepsy (35), Parkinson's disease (36), schizophrenia (37) and injury induced neuropathic pain (38), yet optimal cell sources for such therapies are limited (9).

A reliable source of GABA-ergic interneurons for transplantation is to be found. The use of MGE and/or LGE progenitors from the human fetal brain is not feasible because of both ethical concerns and unsuitability of such an approach to obtain the required amounts of cells needed for clinical application (39).

Conclusion

Considering the relative rarity of the anomalies of GE, studies on large number of cases are not available for the moment. Most of the papers concern isolated cases or small series of patients.

For now, the most used method for *in vivo* studies of GE is MRI, as it provides a high spatial resolution and an excellent tissue contrast. Novel possibilities emerge, like new ultrasound techniques such as HDlive, which contribute more and more to morphological assessment of the fetal brain.

Further studies are needed to clarify the clinical significance of the imaged anomalies of GE. It is also important to accurately establish their etiology, which is a difficult task to accomplish.

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