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Epilepsy and Pregnancy: Problem of Diagnosis and Management (Case Report and Literature Review)

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Abstract: *Epilepsy is a chronic disease characterized by severe personal and social consequences. Because of its prevalence and socio-cultural consequences, it is a real public health problem. It can occur at any age. Epilepsy is one of the most frequent chronic pathologies affecting women of childbearing age. Pregnancies in epileptic patients are said to be at risk because of the risk of fetomaternal complications (FMC). Pregnancy in women with epilepsy requires preventive care before conception. This is not feasible in case of inaugural epilepsy during pregnancy, hence the difficulty of diagnosis and management. A good coordination between the obstetrician, the neurologist and the couple is necessary. We report the case of a young 23 year old primigravida patient admitted for the management of a seizure disorder in an 8 month old pregnancy without follow-up, with normal tantional figures, a biological check-up without any particularity and a negative proteinuria, a caesarean section for maternal and fetal rescue was performed with the birth of a premature newborn Abgar of 9/10 at the 5th minute; The gestational age was estimated by the neonatologist at 34 weeks of amenorrhea, the cerebral scanner was without anomaly. The patient was put under anticonvulsant and antiepileptic drugs with the occurrence of convulsive seizures in the post partum period. The realization of the electric exploration was in favor of the diagnosis of epilepsy*

Keywords: epilepsy, pregnancy, maternal and fetal risks

Epilepsie et grossesse : problème de diagnostic et prise en charge (case report et revue de la littérature)

Résumé

L'épilepsie est une atteinte chronique caractérisée par de lourdes conséquences personnelles et sociales. Par sa prévalence et ses conséquences socioculturelles, elle pose un véritable problème de sante´ publique. Elle peut survenir à` tout âge. L'épilepsie est l'une des pathologies chroniques les plus fréquentes touchant les femmes en âge de procréer. Chez les patientes épileptiques les grossesses sont dites à risque vu le risque des complications fœto-maternelles (CFM). La grossesse de la femme épileptique nécessite une prise en charge préventives en pré conceptionnele. Chose qui est non faisable en cas d'épilepsie inaugurale au cours de grossesse d'où la difficulté de diagnostic et prise en charge. Une bonne coordination entre l'obstétricien, le neurologue et le couple s'impose. Nous rapportons le cas d'une jeune patiente de 23 ans primigeste admise pour la prise en charge d'état de mal convulsif sur une grossesse de 8 mois non suivie avec des chiffres tantionnels normaux, bilan biologique sans particularité et une protéinurie négatives, une césarienne pour sauvetage maternelle et fœtale a été réalisé avec la naissance d'un nouveau né prématuré Abgar de 9/10 à la 5ieme minute ; l' âge gestationnel estimé par le neonatologue à 34 semaines d'aménorrhée , le scanner cérébrale était sans anomalie patiente mise sous anticonvulsivant et antiépileptiques avec la survenues des crise convulsive en post partum. La réalisation de l'exploration électrique était en faveur du diagnostic d'épilepsie puis la patiente est mise sous traitement anti-epileptique

Mots clés : épilepsie, grossesse, risques maternels et fœtaux,

INTRODUCTION

Epilepsy is among the most frequent chronic pathologies affecting women of reproductive age (1)¸ the number of epileptic women of reproductive age is difficult to estimate but it is increasing. Pregnancy in these women with epilepsy was for a long time not recommended, but the evolution of knowledge concerning the teratogenicity of the different antiepileptic drugs (AE) has fortunately allowed a softening of the medical discourse. (2) These pregnancies are said to be at risk because they are always associated with a risk of fetomaternal complications (FMC), even if 92 to 96% of them go ahead without problems. [3- 04, 05, 06].

OBSERVATION

The patient was F.B., 23 years old with no notable pathological history, admitted for the management of 2 generalized tonic-clonic convulsive seizures without regaining consciousness during a pregnancy that had not been followed up for 8 months, the diagnosis of eclampsia was strongly suspected, The examination on admission found an unconscious patient, GCS at 10, normal respiratory rate, blood pressure at 126/80 cmhz, the search for proteinuria with the strip is negative, the obstetrical examination had objectified a supple uterus, normal uterine height for the presumed gestational age, the fetal heart sounds are perceived and regular, the patient

is out of labor, the obstetrical ultrasound has objectified a monofetal pregnancy in cephalic presentation with homogeneous fundal placenta, fetal biometry corresponds to 33-34 weeks of amenorrhea, the amniotic fluid is in normal quantity, the index of resistance of the umbilical artery is normal. During the examination the patient presented a generalized tonic-clinical seizure. Biological analysis was in favor of a hemoglobin at 10 g/dl, microcytic hypochromia, normal platelet count, liver and renal functions are without particularity, capillary glycemia at 0.92g/l, ionogram is without particularity. A caesarean section for maternal and fetal rescue was performed under general anaesthesia with the birth of a premature newborn Abgar of 9/10 at the 5th minute; the gestational age estimated by the neonatologist at 34 weeks of amenorrhea, the cerebral scanner performed postoperatively was without anomalies. The patient was taken in charge in intensive care with the start of an anticonvulsant treatment. After the operation, a convulsive seizure occurred and was managed by the resuscitators. The electrical exploration was in favor of the diagnosis of epilepsy and an antiepileptic treatment was started.

DISCUSSION

Epilepsy is one of the most frequent chronic pathologies affecting women of reproductive age (1)¸ Epilepsy is a real public health problem characterized by its serious personal and social consequences. Currently, epilepsy is defined as "A brain pathology characterized by an enduring predisposition to generate seizures and by the cognitive, behavioral, psychological and social consequences of this condition. This definition requires only the occurrence of at least one seizure. " [7]. Pregnancy has long been discouraged in women with epilepsy because of the high rate of fetal malformations. (2), While epilepsy itself does not influence the course of pregnancy, antiepileptic medicaments are responsible for fetomaternal complications. The risk of these complications seems to be greater in the case of polytherapy with intake during the first trimester (4). The prevalence of this condition in women of childbearing age is increasing (6). The evolution of this pathology is influenced by the hormonal status of the patient [8]. Catamenial epilepsy is defined as the exacerbation of seizure frequency in a specific phase of the menstrual cycle [9]. For a long time, it was not recommended during pregnancy, because of the fear of fetal malformations induced by the use of antiepileptic drugs before and during pregnancy, as well as the risk of imbalance of the epileptic disease in pregnant women. Fortunately, the evolution of knowledge concerning the teratogenicity of the different antiepileptic drugs (AE) has allowed to optimize the management of these pregnancies. In all cases, a pregnancy project will require a concerted planning and information of the couple with a preconception consultation. During this consultation, adaptation of the antiepileptic treatment may be required before the pregnancy is initiated: stopping the treatment, reducing the number and dosage of drugs, replacing a very teratogenic antiepileptic drug (AED) with another. The real benefit of preconceptional folate prescription at a dose of 5 mg/d is currently very controversial (it is accepted at 0.4 mg/d once pregnancy is declared in the general population) [10]. Nevertheless, folates should be initiated 2 to 3 months before the onset of pregnancy and continued for at least the first 4 months of pregnancy, while making it clear to patients that this prescription does not cancel out the risk of malformations, in particular lack of neural tube closure (spina bifida).

Influence of pregnancy on epilepsy

Despite good compliance with treatment, a trend towards increased frequency of epileptic seizures (ES) during pregnancy has been observed in about 35% of women [04, 06]. Several factors may play a role in the increase of ES. These include hormonal changes, particularly hyperoestrogenism, metabolic changes, sleep disturbances, poor compliance with antiepileptic drugs (AEs) due to fear of teratogenicity, changes in plasma levels of AEs secondary to vomiting in pregnancy, drug interactions, expansion of plasma volume, and increased cardiac output with increased hepatic and renal blood flow, which accelerates the elimination of AEs [04, 08, 11]. It is important to minimize these factors to minimize the risk of ES during pregnancy. The AE treatment must therefore be adjusted if ECs appear. It is also necessary to avoid products that lower the epileptogenic threshold. These are H1 antihistamines (chronic exposure) [12], antidepressants (antidepressants with a dose-dependent effect: maprotiline, clomipramine; high-risk antidepressants: phenelzine, tranylcypromine, fluoxetine, paroxetine, sertraline, venlafaxine and trazodone) and antipsychotics (antipsychotics with a dose-dependent effect: chlorpromazine and clozodone): chlorpromazine and clozapine; high-risk antipsychotics: fluphenazine, haloperidol, pimozide, and isperidone) [13, 14], steroids, baclofen, opiates (morphine, tramadol) [15, 16]. Although the physiological changes in pregnancy are likely to give rise to ES, in about 55% of parturients the frequency of ES remains unchanged, and the frequency is decreased in 10% of cases [05,06]. In addition, women in remission, with no ES for about 9 months preconception, have an 84-92% chance of being without seizure throughout the pregnancy [17, 18].

Influence of epilepsy on pregnancy

Epilepsy itself has no adverse effects on the course of pregnancy. Comparison of women with epilepsy not treated with AE and women without epilepsy shows no significant difference in terms of risk of occurrence of fetal malformations [16]. It has also been shown that there is no relationship between the risk of occurrence of fetal malformations and the existence of untreated epilepsy [19 However, the occurrence of generalized ES during pregnancy causes lactic acidosis and a decrease in placental blood flow

responsible for fetal hypoxia with the consequences of fetal death in utero, fetal intracranial hemorrhage, and transient fetal bradycardia [20, 11]; therefore, it is important to avoid as much as possible the occurrence of ES during pregnancy by controlling and stabilizing the disease for about 9 months, before considering a pregnancy.

Influence of antiepileptic medicaments (aem) on pregnancy

Exposure to AEs is a risk factor for the occurrence of maternal-fetal complications (MFCs) in pregnant women with epilepsy [18]. The teratogenic malformative risk associated with the use of AEs is currently a hot topic with sodium valproate. This risk is real but depends on three parameters: the antiepileptic molecule itself, the dose, and the number of MAEs co-administered (8). A meta-analysis of 38 studies including 2837325 pregnancies showed a higher risk of FMCs (fetal malformations, miscarriage, pre-eclampsia, gestational diabetes, intrauterine growth retardation, fetal death in utero, preterm delivery, caesarean section, postpartum haemorrhage) in treated women with epilepsy than in untreated women [21]. The same meta-analysis shows that the risk of occurrence of FMCs is even higher in case of polytherapy.
In monotherapy: the major American [22], Anglo-Saxon [23-24] and European (EURAP) [25] pregnancy registries have so far collected more than 42,000 pregnant patients taking MAEs, and have shown that in monotherapy, not all MAEs have the same teratogenic potential.
Sodium valproate: has the highest teratogenic potential in monotherapy, all types of malformations combined, this teratogenic risk is dose-dependent: 24% of malformations at one year beyond a daily dose of 1500 mg/d and 5.6% at one year below 750 mg/d [25]. In view of the high teratogenic risk, restriction of sodium valproate use in girls and women of childbearing age is strongly recommended. The prescription of all valproate-containing drugs is now strictly regulated in patients with epilepsy
phenobarbital: proven teratogenicity, on 709 pregnancies listed in the Cochrane review (23 studies), we find a prevalence of major congenital malformations of 7.1% under phenobarbital. Again in EURAP, there is a clear dose dependence. Phenobarbital use is associated with a higher rate of heart defects
Carbamazepine also increases the rate of fetal malformations including neural tube defects,
cleft lip, heart disease and hypospadias, especially when taken in the first trimester of pregnancy [04, 26, 27].
Concerning the new antiepileptic drugs, exposure to lamotrigine during pregnancy increases the risk of pre-eclampsia (relative risk RR 7.5), fetal hypotrophy, metrorrhagia during pregnancy (RR 6.2) and postpartum hemorrhage [28, 29]. Fetal malformations related to lamotrigine exposure are rare. They are cleft lip and palate, hypospadias, esophageal or duodenal atresia [30, 31, 05].
The use of topiramate in the first trimester of pregnancy increases the risk of fetal complications such as microcephaly, intrauterine growth retardation, and cleft lip [32, 33,]. Compared to the general population, fetal malformations are rare with exposure to levetiracetam used as monotherapy [35, 36, 37]. The malformations reported are mainly skeletal anomalies [37].
Compared to the general population, there is no significant difference in the risk of occurrence of fetal malformations in women with epilepsy exposed to oxcarbazepine [38, 39]. The rate of fetal malformations related to exposure in the first trimester of pregnancy to gabapentin, vigabatrin, pregabalin is low and without significant difference compared to the general population [40].
Polytherapy significantly increases the risk of fetal malformations, especially when combined with sodium valproate. Even when combination therapy with sodium valproate is excluded, Vadja et al [41] showed that the rate of fetal malformations with combination therapy remained higher than with monotherapy (6.94% versus 3.64%), especially when the combination therapy included topiramate (14.94% rate of malformations)

Pregnancy monitoring method

Management in pregnancy should be multidisciplinary. Data from the literature show that the risk of seizures is the same throughout the pregnancy and that having well-controlled epilepsy in the months preceding the pregnancy is a predictive factor for good control throughout the pregnancy. Another recent study from EURAP shows that stopping or replacing sodium valproate during pregnancy is associated with an increased risk of occurrence of tonic-clonic generalized seizures [42]. Changes in pharmacokinetic factors will require repeated and regular plasma determinations of antiepileptic drugs for possible dose adjustment. Close ultrasound monitoring in women with epilepsy under antiepileptic treatment is necessary to detect fetal malformations. In addition, the determination of alpha-fetoprotein in the maternal blood between the 14th and 18th week of amenorrhea allows the detection of neural tube closure anomalies [04].

Mode of delivery in the epileptic patient

There are no particular problems with vaginal delivery in women with
epileptic women. Delivery by the upper route should only be performed in case of obstetrical complications such as severe pre-eclampsia, metrorrhagia in the third trimester or in case of repeated generalized epileptic seizures with fetal distress.
In the postpartum period, vitamin K supplementation is necessary in newborns of women with epilepsy from epileptic women treated with enzyme-inducing AEs (carbamazepine, phenytoin, phenobarbital, etc.) [04]. The latter MAEs lead to depletion of vitamin K-dependent coagulation factors in the newborn and consequently to hemorrhagic disease of the newborn [11].

Is breastfeeding possible in the epileptic patient

All EAs are passed into breast milk but at varying concentrations depending on the molecule. The passage of AEs from maternal plasma to breast milk is based on the principles of passive diffusion, with low molecular weight, low protein binding and fat soluble AEs having a high rate of passage into breast milk [20]. Thus, exposure to AEs continues even after birth in children born to treated women with epilepsy. However, the serum concentration in the child of AEs depends on the absorption, catabolism and elimination of the drug by the child [26, 05]. Indeed, there is a risk of accumulation of these AEs in children with immature metabolic capacities with a major risk of toxicity [43].

The cognitive outcome of children born to mothers exposed to AEs

Concerning the cognitive outcome of children born to mothers exposed to AEs, the literature shows the occurrence of psychomotor retardation in children born to mothers who took valproate during their pregnancy [44]. Initially, this delay concerned mainly the verbal IQ, but since 2009, studies have shown that the delay was more global. Concerning the cognitive outcome of children born to mothers treated with carbamazepine, lamotrigine, topiramate or levetiracetam [45,46], the data, although reassuring, remain fragmentary, on small numbers, often with the bias of sodium valproate taken as a comparator. Larger prospective studies are required.

CONCLUSION

The diagnosis of epilepsy can be difficult and delayed if it is inaugural during pregnancy. In known epileptic patients of reproductive age, it is recommended that optimal antiepileptic therapy be instituted to prevent and/or minimize the risk of fetomaternal complications. Folic acid supplementation before conception appears to reduce this risk. Recent data from the literature encourage breastfeeding in women with epilepsy, regardless of the molecule used, but monitoring of the children is necessary because of the effects of certain molecules on the cognitive functions of children born to epileptic mothers treated during pregnancy.

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