

Reproductive Issues in Neurofibromatosis Type 1: An Update

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Abstract

Neurofibromatosis type 1 (NF1) is a complex, multisystem, autosomal dominant disease that has widespread effects on ectodermal and mesodermal tissues. The progress in genetic studies and in cosmetics and aesthetic and reconstructive surgery have ameliorated the quality of life in women with NF1. In this review we update the most relevant data on gynecological life and reproductive issues in women with NF1.

Keywords: Neurofibromatosis type 1, Pregnancy, Rare disease, Neurofibroma degeneration

RASopathies are a clinical spectrum of diseases due to germline mutation in components or regulators of the RAS-MEK-ERK pathways. They include neurofibromatosis type 1 (NF1), Costello syndrome, Noonan syndrome, Noonan syndrome with multiple lentigines, Legis syndrome, cardio faciocutaneous syndrome, capillary malformation-arteriovenous syndrome, gingival fibromatosis and autoimmune lymphoproliferative syndrome [1]. Altogether these syndrome affects 1:1,000 newborns [2]. Each syndrome has distinct clinical aspects, although some characteristics are overlapping needing molecular diagnosis.

NF1 (Online Mendelian Inheritance in Man (OMIM), #162200), is an autosomal dominant multi-system disorder occurring worldwide in approximately 1/3,000-4,000 individuals [3]. The disease was described for the first time by Friedrich Daniel Von Recklinghausen in 1882 and for long time it has been confused non only by media but also by physicians with PROTEUS syndrome or “elephant man’s” disease, a distinct nosologically entity as discussed by Legendre et al. [4].

NF1 is due to gene mutation of proximal long arm of chromosome 17 that encodes neurofibromin, a ubiquitously expressed protein, which functions as a RAS-GTPase Activating Protein (RAS-GAP), a negative regulator of RAS activity [3]. Neurofibromin deficiency leads to increased RAS signaling which is believed to cause NF1. Mutation in neurofibromin gene is also detected in about 30% of all

cancers [5]. The disease may affect cellular proliferation, differentiation and survival rate. Issues of relevant interest concern the association with developmental anomalies, tumors development both benign and malignant, specific complications due to the disease and the possible effects on senescence [6]. NF1 is usually fully penetrant by age 5 and most adults with NF1 have been clinically diagnosed in childhood by NIH consensus criteria but in some cases molecular study may be necessary [7]. There is a high variability in clinical expressions and the outcome of the disease is unpredictability, even within family members, because phenotype-genotype correlation is possible only in a small percentage of cases.

Many factors have ameliorated prognosis for individual with NF1: higher knowledges and awareness on the disease, early diagnosis, better clinical counseling in reference centers, appropriate surveillance of symptoms, early surgical therapy in growing neurofibromas and better cosmetic treatment [3].

There is an 8-15 years reduction in average life expectancy and malignancies and cardiovascular disease are the most frequent causes of death [8,9]. On 2,467 Danish patients with NF1 diagnosis, nerve and peripheral ganglia disease, pneumonia, epilepsy, bone and joint disorders, and intestinal infections were major contributors to the excess disease burden due to the disease [10]. Non-tumor symptoms contribute significantly to morbidity especially in relation to size, location of tumor/s and growth velocity

that is unpredictable with possible compression on adjacent tissues. Many different tumors, both benign and more rarely malignant, have been described in patients with NF1 [3]. Neurofibromas arise due to bi-allelic inactivation of the NF1 gene in a subpopulation of Schwann cells and may be cutaneous, subcutaneous, nodular or diffuse plexiform, spinal and atypical neurofibromatosis neoplasms of uncertain biologic potential [11]. Cutaneous neurofibromas represent the hallmark of the disease evident in almost all adult patients and are associated with single nerve endings [11]. Neurofibromas continues to increase in number with advancing age with period of rapid growth during puberty and pregnancy. Cutaneous neurofibromas may cause tenderness, bleeding, itching, and severe negative effects on Quality of Life (QoL), although they do not appear to undergo malignant degeneration [12]. Subcutaneous neurofibromas are diagnosed on palpation. Mostly diffuse plexiform neurofibromas are congenital, arise and grow along length multiple fascicles of the nerve in the first ten years of life and then become relatively stable [13]. They are bigger than cutaneous neurofibromas, may cause compression or be very debilitating if their overgrowth involves significantly limbs or body segments because major disfigurement. Furthermore, neural involvement may be painful. Early surgery and complex treatments may be requested when growing neurofibromas becomes destructive or they are associated with major disfigurement.

Overall neurofibromas are present in 30-50% of NF1 patients on clinical examination, but the incidence is higher on MRI in young NF1 adults [14]. 4-15% of NF1 patients develops malignant degeneration during their life, with a latency of 10-20 years, 80% arising from plexiform neurofibromas (MPNST), mostly before 39 years of age [15,16]. Growth of plexiform neurofibromas especially after the first decade of life may be malignant, but magnetic resonance imaging cannot always distinguish benign from malignant tumor [17]. It is necessary to take multiple biopsies to increase the probability of detecting a MPNST. The malignancies carry a poor prognosis with five-year survival rates around 16%.

Pheochromocytoma, neuroblastoma and melanoma arise from neural crests and may affect NF1 patients. Also, Wilms tumor, malignant nodular hidradenoma, leukemia, rhabdomyosarcoma, T-cell-lymphoma are described in the literature [18]. Causes of high prevalence of neoplasm in NF1 patients, both benign and malignant, are not completely known, and genetic, hormonal and environmental factors may be implicated. It is well known the sensibility of hormones of pregnancy on neurofibromas because up to 80% of skin tumors increases in dimensions in pregnancy [19]. Pheochromocytoma is diagnosed in 3.3-13% of autopsies, but many are clinically asymptomatic, 22% in one series [20]. Usually, the median age of presentation is 43 years with a wide range (14-61 years)

and are almost benign. Twenty per cent are multifocal [21]. Their relevance during pregnancy is linked to the high risk of perinatal and maternal death if undiagnosed and incorrectly treated.

Emotional, psychological and social issues are evident on Quality of life in NF1 patients especially in transitional phases, such as puberty, transition to full adulthood and during pregnancy. Anatomical lesions, especially visible, and symptoms can be particularly stressful as they can be painful and disfiguring since puberty, disrupt proper fit to clothing with severe aesthetic concerns [22]. NF1 individuals may suffer fatigue and lack of energy that reduce engagement in social activities [23,24]. The experience of poor social relationships experienced during childhood may continue into adulthood that later may be further aggravated by difficulties in obtaining employment [7]. Almost 1/3 do not recognize themselves as good life partner [25,26]. They are more likely to report less self-confidence, reduced self-esteem and symptoms of depression and anxiety [27]. In those cases, screening for psychiatric disorders is appropriate [28]. Individuals with NF1 were significantly delayed in graduating mandatory school education compared to persons without NF1 and when 90% of persons have graduated, individuals with NF1 were 1.2 times older than the NF1-free persons. Delays in mandatory school may negatively affect further educational achievements and employment [29]. Another effect are difficulties in communication to maintain interpersonal relationships [30] and difficulties in social communication may be attributable to reduced ability to engage in prosocial behavior [7] and reduced opportunities to meet others if education and work life are limited [31]. It has been also supposed a reduction in social cognition which may limit the understanding of social context and the skills necessary to build relationships [32]. Intriguingly experimental study in *Drosophila* with loss of neurofibromin 1 results in social deficits due to sensory information primary disruption of a group of peripheral sensory neurons. The data suggest that there is a specific circuit mechanism in *Drosophila* through which Nf1 regulates social behavior [33]. In NF1 individuals the reduced ability to initiate and maintain sexual relationships or have a long-term union or starting a family may affect well-being and long-term health [34]. NF1 patients hospitalized are older when they have their first relationship, are less likely to engage in marital or cohabiting relationships but, when it has been established, those couples are not at greater risk of ending the relationship [35]. The unpredictable course of the disease with uncertainty about prognosis and severity and the high risk of transmitting NF1 to offspring may influence the decision not to have children as well partnering and planning of family life [30].

Gynecologists should increase the awareness on NF1 disease because the diagnosis may be underestimated

in the general population and NF1 may be diagnosed for the first time during gynecological examination or during pregnancy [36,37]. They should consider many issues concerning anatomical development, cancer risk and complexities of reproductive choices. Neurofibromas, especially disfiguring are the most relevant concern for affected individuals because they have relevant effects on perception of their own body image as woman and as intimate partner. Specific attention should be dedicated to transitional phases such as puberty and pregnancy planning, psychological and social support. Pregnancy should be planned. Hormonal contraception is not contraindicated [38]. Individual with NF1 should be counseled in a multidisciplinary team in a center for rare disease or dedicated to NF1.

The pelvic examination needs to evaluate the normal anatomy of internal and external genitalia diagnosing anomalies and tumors, especially growing lesions. Rarely neurofibromas may cause genital disfigurement such as clitori-domegalia with normal testosterone level [39], mass in external genitalia [40,41] or in single or both breasts [42]. More rarely the tumors may represent a mass in the vagina causing bleeding as reported in a postmenopausal woman [43]. In other cases, precocious puberty is due to optic pathway glioma, that can be detected in 15% of overall NF1 patients, mostly asymptomatic [44]. Only few cases of plexiform neurofibromas seriously infiltrating vagina, uterus, bladder and other pelvic tissues have been described in the literature [45,46]. In pregnant women huge tumors may cause obstructed pelvis [47-49]. Rarely NF1 may grow in the bladder or in the tube [50]. Early surgery is indicated when technically possible. The association of pelvic neurofibromatous masses with other type of tumors such as uterine fibromyoma should not overlooked [51].

Earlier breast cancer screening is indicated because the incidence of breast cancer is increased in NF1 women [18]. Furthermore, cluster of freckles may be present under the breast, helping diagnosis. NF1 individuals may show focal bone lesions, dystrophic and nondystrophic scoliosis with associated Dural ectasia, vertebral degenerative changes and spinal compression that may be relevant for a successful anesthesia [52,53]. Furthermore, bone mineral density is decreased and osteoporosis in adults with NF1 significantly progress over time [54]. NF1 women may undergo earlier osteopenia and/or osteoporosis and it is mandatory to have an adequate counseling.

In recent years, hundreds of pregnancies have been described in NF1 patients because of normal fertility, better psychological and social support, ameliorated quality of life and successful surgical and cosmetic treatment. Data from some national registries are available, as well as cohort

studies and many case reports published in the literature prevalently with complications. Recently Kenborg et al. [55] in their study on 1,006 Danish women reported that the cumulative incidence of first pregnancy at 50 years was slightly lower in those with NF1 than in control group. Two pregnancies were expected per woman at age of 50 years irrespective of a NF1 diagnosis. 63% of pregnancy ended in live births (783/1252) vs 68% in the control group.

Obstetricians have to discuss the complexity of genetic counseling, the possible effects of pregnancy on NF1, the specific complication due to NF1 arising during pregnancy, the association with common complications of pregnancy, mode of delivery, complexity of analgesia/anesthesia and the needs of a dedicated team. Pregnancy should be planned for a safe delivery with adequate counseling, and multidisciplinary medical team with genetics, obstetrician, cardiologist, neurologist, neurosurgeon in a tertiary level hospital. The team should be prepared for severe and unpredictable maternal and fetal complications. Miscarriage can occur frequently, and the ongoing pregnancy may be complicated [56].

Many reproductive options are available: no reproduction, gamete donation, adoption of a child, preimplantation genetic diagnosis, prenatal diagnosis and no diagnosis at all. Villocentesis or amniocentesis may be proposed for prenatal diagnosis. Furthermore, the diagnosis of NF1 has been performed by evidence of NF1 paternal mutation detected in free DNA in maternal blood [57]. Genetic counseling may be complex because of no phenotype-genotype correlation in NF1 patients. The mutation is dominant autosomic and between 50-75% of neurofibromatosis cases stems from *de novo* mutation [58]. NF1 is associated with advance paternal age, while no effects are evident for maternal age [59]. In an affected couple, preimplantation diagnosis is possible through planned pregnancy obtained by assisted reproduction but is costly and performed only in few centers [60]. However, request of prenatal diagnosis for NF1 seems correlated to many factors such as cultural background, familial and social support, psychological condition, educational level, previous child affected, longer follow-up, awareness on the natural history of NF1 with specific knowledges of the disease [61]. Many NF1 patients choose not to receive prenatal diagnosis [62]. Recently we have described a woman with NF1 and HIV infection with negative viral load after antiretroviral therapy; she had four pregnancies and delivered three babies without HIV infection, two with signs of NF1. No maternal huge transformation of neurofibromas or malignant degeneration was evident in a seven years follow-up and HIV infection remained stable. She denied prenatal diagnosis in all pregnancies because of no willingness to interrupt pregnancy in an affected fetus by NF1 [63].

Number and size of neurofibromas frequently increase in pregnancy especially in the second trimester and many new tumors may grow but in pregnant women the growth of cutaneous and plexiform neurofibromas is not significantly different in comparison to non-pregnant NF1 patients [64]. Up to 3% of NF1 patients are diagnosed during pregnancy due to the appearance of neurofibromas [65]. Furthermore, up to 22% of neurofibroma may regress during gestation [65]. Acute postpartum spinal compression due to neurofibroma has been described after uneventful pregnancy and delivery [66].

Concerns for the mother are related to stroke (mostly hemorrhagic), acute vascular rupture (overall incidence of vascular anomalies is estimated (0.49-6.4%), hypertension, preeclampsia, low platelet count, HELLP syndrome and eclampsia [56,67,68]. Particularly hypertension due to pheochromocytoma may change the prognosis for the mother and the fetus [69]. Possibly the association between hypertension preexisting to pregnancy and pregnancy induced hypertension. Pheochromocytoma should be considered in NF1 hypertensive patient over 30 years of age, or pregnant, or associated with hypertension-associated headache, palpitate, or sweating [70]. Plasma free metanephrine levels as single test is more sensitive and specific than other studies in NF1 clinically suspected to have the tumor [71]. It may be appropriate to screen pheochromocytoma prior to surgical procedures, pregnancy, labor and delivery because the tumor can trigger a severe cardiovascular crisis with increased fetal (up to 50%) and maternal death (up to 2-25%) [72,73]. Patients with symptoms due to pheochromocytoma need specific therapy according to endocrinologist before any surgery. However, overall maternal mortality in compliant patient with NF1 is rare.

Fetal pathologies such as Intrauterine Growth Retardation (IUGR), oligohydramnios, preterm delivery, sudden fetal death and emergency cesarean section have been described. Fetuses may be affected by NF1 and present higher incidence of malformations [74]. Stillborn incidence seems increased in women with NF1. Rarely the disease may manifest clinically during fetal life with developmental anomalies. Diffuse neurofibromatosis carries an unfavorable prognosis [75].

In the past obstructed labor due to pelvic neurofibromatosis masses has been reported [47,48], but today they are very rare due to earlier surgery. The incidence of cesarean section is higher than general population for elective psychological and social indications, and it should be remembered that macrocrania without hydrocephalus is present in up to 50% of fetuses [66].

General anesthesia should be avoided in pregnant women and especially in patients with NF1 because frequent

undiagnosed neurofibromas in oral cavity, esophagus and airways as well as cervical instability and neck mass that may cause difficult intubation. An expert anesthetist and fibroscope may be lifesaving. Any maneuver able to increase endocranial pressure should be avoided and arterial blood pressure accurately checked. In the past abnormal response to neuromuscular blocking agents has been described [76], but more recent studies have disproven this. Anyway, neuromuscular transmission should be monitored. Beta-blocker should be administered with caution due to possibility of an undiagnosed pheochromocytoma [77]. Neuraxial anesthesia in asymptomatic spinal neurofibroma may be cause of concern because single or multiple asymptomatic spinal neurofibromas are not rare [78]. Their puncture may cause sudden neurological symptoms due to spinal hemorrhagic compression. For this reason MRI of the spine may be appropriate to detect such tumor before neuraxial anesthesia and analgesia because they may contraindicate regional anesthesia [79]. Spinal compression may suddenly appear after normal pregnancy and delivery. Physicians should detect any new symptoms both typical and atypical and especially progressive.

In conclusion, in recent years, pregnancy is not rare in NF1 patients because they can plan pregnancy and deliver safely with adequate counseling and psychological and social support, but multidisciplinary medical team should be alerted for possible maternal and fetal complications. National or multinational registries are useful to better understand the natural history of the disease and the long-term effects of pregnancies on NF1 and vice-versa, especially in subgroup of patients with specific pathology. Although there is still no effective treatment [80], a multidisciplinary team in a tertiary level hospital may be successful in a lifelong approach starting from early diagnosis permitting successful reproduction. Society and especially workers in health system and social services need to improve the knowledge and awareness on the disease.

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