Journal of Case Reports in Medicine

Case Report ISSN: 2090-5351

Pregnancy Associated with Neurofibromatosis Type I and Becker Nevus Syndrome - Case Report

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Abstract

Neurofibromatosis type I and Becker nevus syndrome are very rare disorders as an entity, but co-occurrence of Neurofibromatosis type I and Becker nevus syndrome in a pregnant woman is exceptional and a real monitoring and management challenge. We report a case of Neurofibromatosis type I and Becker nevus syndrome with severe scoliosis in a 24 year primiparous gravida, 25 weeks of gestation. This case was marked by the severe spine deformity, in "C" shape associated with café-au-lait skin spots and two larger skin lesions, one of them hypertrichotic and with multiple papillomas. Also, the patient presented a restrictive respiratory dysfunction, worsened during pregnancy and decompensated on labor onset. This case is particular not only by its rarity but especially by the amplitude of the symptomatology. In our opinion, the overlap of Neurofibromatosis type I and Becker nevus syndrome, which individually involve changes in the spine, had an augmentative role in the severe deformity that was reached in this case. In the era of modern medicine, we faced a feminine, 2022 version of "The Hunch-back of Notre Dame" due to the absence of an early diagnosis.

Introduction

Neurofibromatosis type I (NF1) or Von Recklinghausen disease is a genetic condition charachterized by the presence of NF1 gene on chromosome 17. The presence of this gene leads to the loss of neurofibromin syntesis and uncontrolled cell growing implying mainly the neural cells [1]. As it is an autosomal dominant disorder with a 50% chance of inheritance, about half of NF1 cases are inherited, the other half of NF-1 gene mutations are de novo [2]. The diagnosis is guided by the specific signs developed in childhood, usually by age 10. The presence of integumentary neurofibromas, plexiform neurofibromas and café-au-lait spots, that tend to increase in number and size over time, are pathognomonic. Additional features described in patients with NF1 are macrocephaly, learning and attention disabilities present in about 50% of cases and skeletal malformations, respectively progressive scoliosis and pseudoarthrosis [3]. Two forms of scoliosis may develop in NF1 patients, dystrophic or non-dystrophic. Dystrophic scoliosis is the most severe type and includes kyphosis, abnormal thin ribs and abnormal vertebral bones [3]. In 8-13% of cases, plexiform neurofibromas progress to malignant peripheral nerve sheath tumors, which is the main cause of death in patients with NF1 (2). According to McLaughlin et al, neurofibromas posed progesterone receptors and there is associated a high risk of volume growth during pregnancy period [4]. As regards the pregnancy outcome in patients with NF1, complications such as preterm birth, intrauterine growth restriction, pregnancy induced hypertension and preeclampsia had an increased incidence among these cases [5].

Becker nevus syndrome (BNS) is included in epidermal nevus syndrome and is characterized by the presence of Becher nevus, an irregular, unilateral, circumscribed and hyperpigmented macule with or without associated hypertrichosis and ipsilateral breast hypoplasia or cutaneous, skeletal and muscular defects [6]. Other conditions found in BNS patients are ipsilateral foot

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Keywords: *neurofibromatosis type I, becker nevus, pregnancy*

Abbreviations: *NF1- Neurofibromatosis type I; BNS- Becker nevus syndrome; MRI- Magnetic resonance imaging*

Received: 12 July 2022; **Accepted:** 27 July 2022; **Published:** 5 August 2022

enlargement, spina bifida, scoliosis, and pectus carinatum [7].

NF1 and BNS are very rare disorders as an entity, the association of these disorders is exceptional but co-occurrence NF1 and BNS in a pregnant woman is a unique case and a real monitoring and management challenge.

We report a case of NF1 and BNS with severe dystrophic scoliosis in a 24 year primiparous gravida 25 weeks of gestation. Written patient consent was obtained for this case report.

Case report

A 24 year primiparous gravida 25 weeks of gestation, from rural area, presents for orthopedic clinical and paraclinical evaluation in the context of a severe deformation of the cervical-thoracic-lumbar spine, in "C" shape associated with multiple café-au-lait spots different in size and shape and generalized disseminated (Figure 1).

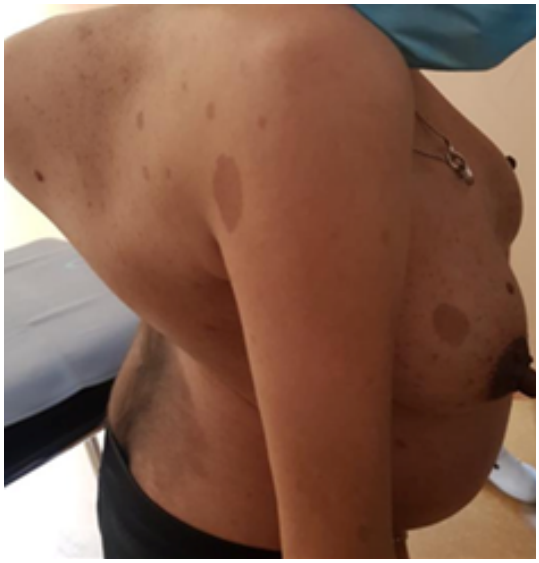

Figure 1: Severe scoliosis, in "C" associated with diseminated café-au-lait spots, different in size and shape, 25 weekes of gestation.

According to her medical history the beginning of the disease was insidious at the age of seven accompanied by walking difficulties. The patient has no information regarding the existence of any sibling with a genetic disorder but affirms that her mother and her sister presents skin spots of the same aspect.

The patient states multiple presentations to the family doctor in the context of obvious skeletal deformities but without additional investigations that would have outlined a diagnosis.

From the gynecological point of view, anamnestic, are worth mentioning the late menarche, at 18 years old, regular menstrual cycles starting with the age of 20, without abortions, without births and the current pregnancy obtained spontaneously. Additionally, the physical clinical exam highlights a cachectic state (27 kg), restrictive respiratory dysfunction (Total Lung Capacity decreased with 60%) and a slight restrictive cardiac insufficiency. Two larger skin lesions, at the sacral region (hypertrichotic, with multiple papillomas, approximatively 28/25 cm) and left ankle level, accompanied by the left foot enlargement, suggestive for Becker nevus, were noted (Figure 2).

Given the complexity of this case, a multidisciplinary team, involving specialists in orthopaedics, ophthalmology, dermatology, radiology, medical genetics, pathological anatomy, anaesthesia and intensive care along with obstetricians, was formed.

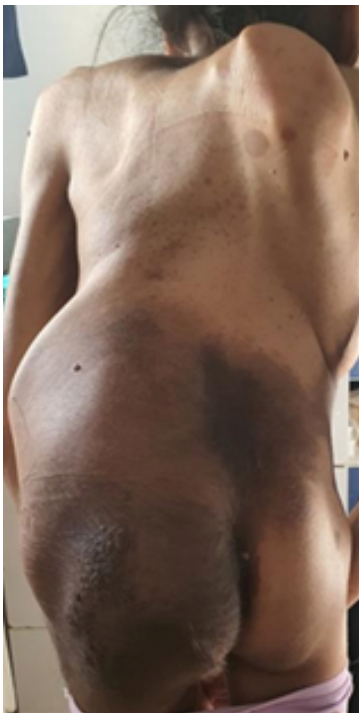

Figure 2: Large skin lesion including lumbar, sacral and left gluteal regions, hyperpig-mented, with local hypertrichosis and multiple papilomas suggestive for plexiform neu-rofibromas, predominant on the left side.

No Lisch nodules were find on ophthalmological examination and a difference in length of the superior limbs with severe deformation of the thorax with kyphoscoliosis in right angle and the limitation of the movements of the spine in all planes was described by the orthopedic team (Figure 3).

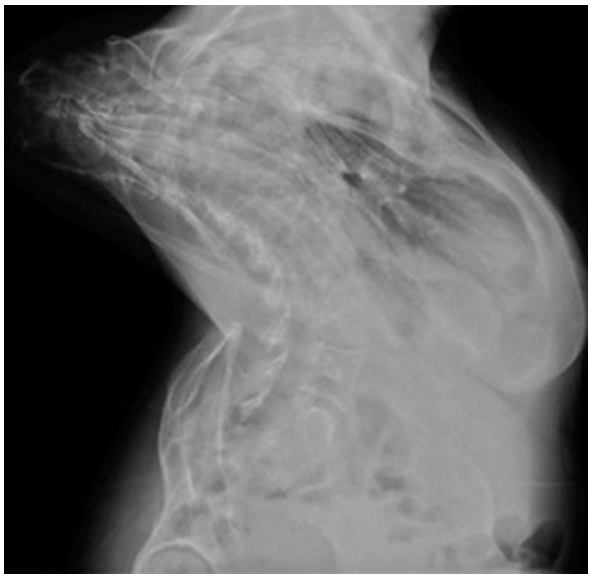

Figure 3: Postpartum. Profile view of the spine, extreme cervicothoracic kyphosis.

Cerebral and spinal magnetic resonance imaging (MRI) describes abnormal T2 hyperintense foci adjacent to frontal horns of the lateral ventricles, in perivascular spaces. The spinal MRI was very difficult to interpret due to the position artefacts. What is to be highlighted are the severe axe abnormalities (dextroconvex scoliosis and angular kyphosis) but with an

inappreciable angle. Also, at the T8 level, paravertebral, a meningocele-like structure of about is observed 25/35 mm with no abnormal T1 and T2 signals of the spine. From the obstetrical point of view, the fetus of feminine sex was sonographically appreciated as normal. The patient was informed about the suspected diagnosis, the possibility of genetic transmission and the need for biopsy of skin lesions in order to certify the diagnosis. The patient agrees to perform the skin biopsy in the postpartum period.

The pregnancy evolved uneventfully until 32 weeks of gestation when the patient is admitted with restrictive respiratory failure with an oxygen saturation 90% on oxygen supplementation, labor onset and fetal tachycardia. Birth by emergency cesarean section is decided given the vicious maternal position in clinostatism and acute fetal distress. Under general anesthesia we used a classic Pfannenstiel approach with segmental-transverse uterotomy after clarifying the uterine position, which was modified by the severe scoliosis of the patient. The individualization of the round ligaments and having them as a bilateral landmark before choosing the section point was necessary and helpful. A healthy preterm, female newborn of 1890 grams is extracted with excellent neonatal evolution. The newborn was given to the mother for breastfeeding 4 days after birth and was discharged at 10 days when the evolution in terms of adaptability and weight gain provided security for further progress.

The size, shape and number of skin lesions and the intensity of hypertrichosis did not change during pregnancy.

Postpartum, the patient's respiratory function improved and the biopsy was performed from the papillary formations superimposed on the hyperpigmented area of the sacral region with the subsequent histopathological diagnosis of neurofibroma (Figure 4); clarifying this way the diagnosis of NF1.

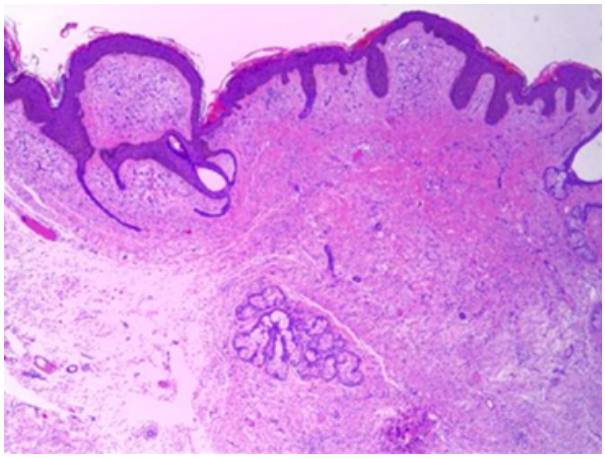

Figure 4: Neurofibroma- benign dermal proliferation of wavy Schwann like cells, col HE, ob. 4x.

In Romania, the national health system offers free genetic testing for a limited number of patients, thus leaving only the option of paid testing for many of the patients. By appealing to the collective support, the patient and her child were genetically tested. For the mother, the loss of 1235kb within the 17q11.2 chromosomal region was identified by NGS-CNV analysis and confirmed by array CGH, having this way the confirmation of the genetic diagnosis of Chromosome 17q11.2 deletion syndrome, including NF1.

The chromosomal microarray analysis of the newborn showed negative result for chromosome 17q11.2 deletion encompassing NF1 gene.

Discussions

This case is particular not only by its rarity but especially by the amplitude of the symptomatology.

Pregnancy associated NF1 imply an increased risk of unfavorable prognosis with an increased incidence among these cases of gestational hypertension, preeclampsia, first trimester spontaneous abortion, intrauterine growth restriction, preterm labor, fetal demise and birth trough caesarean section [8,9]. Based on a small number of cases, it has been suggested that pregnancy leads to an increase in the number and volume of neurofibromas, is a risk factor for their malignant transformation or and presents recurrence at the next pregnancy [10].

As far as we know, no case of BNS and pregnancy has been published in the literature, our case becoming unique in this regard.

The diagnosis of BNS is mostly clinical. In our case the diagnosis was established based on the clinical manifestations, respectively the presence of Becker nevus associated with skeleton defects. Particularly, there was no breast asymmetry present in our patient, but the histopathological skin analysis from the area suspected for Becker nevus, described discrete papillomatosis, hairy follicles, with intensely hyperpigmented epidermal basal cells. In the area of the sacral Becker nevus a conglomeration of neurofibromas was present, absent in this form elsewhere in the body; only few small formations of this aspect, singular and sporadic throughout the body were observed. This aspect strengthens one of the proposed hypotheses to explain the association of Becker nevus and neurofibromatosis, two hormone-dependent disorders, respectively that the components of neurofibroma- fibrobalsts, secrete melanogenic cytokines that lead to epidermal pigmentation [11]. Both conditions associated in this patient have as additional feature skeletal deformities, mainly scoliosis. The incidence of scoliosis among NF1 patient range between 2 and 69%, with a colossal variation between reports [12]. In our case the dystrophic changes of the spine were clear, but the spinal cord was not compromised even during the pregnancy period in the context of a such dramatic alteration. Spinal tumors are found in more than 35% of NF1 patients [13], including those with no abnormal spinal curvature, in our case, even the MRI screening was difficult to be performed, nu aspects suggestive for tumors were identified but the regular MRI screening on an outpatient basis was strongly recommended. Our clinical argument remains that the overlap of these two conditions, which individually involve changes in the spine, had an augmentative role in the severe deformity that was reached.

During pregnancy there were no changes in size and shape of the neurofibromas and no aggravation of NF1 related clinical changes, which comply with the recent conclusion of a retrospective study on 13 mothers with NF1 [14]. The challenge was the severe dystrophic scoliosis and the consequences of it. We expected the worsening of the respiratory function with the increase in volume of the uterus and also the caesarean section had to be adapted to the vicious position of the patient.

Regarding the fact that the patient addressed the medical service in the context of obvious signs of illness and yet was not diagnosed and did not receive appropriate therapeutic conduct, forces us to mention some key features of the medical system in Romania. First, Romania ranks last in the European Health Consumer Index, with an underfunded and subsequently, inefficient medical system. The genetic testing it is not covered by health insurance and can be offered free of charge through various programs only for a limited number of patients, the rest

being forced to pay it from their own sources that exceed the financial possibilities of patients. Secondly, there is a severe lack of healthcare professionals with about 30% of positions unfilled in the country, most of this happening in rural areas [15].

Even though the identification of the NF1 gene mutation is not an indicator of the severity of the disease, in this case, considering the atypical severe manifestation we think that the genetic diagnosis was useful for targeted testing of the newborn, offering the chance for a more intensive monitoring and appropriate management in case of a positive result. Fortunately, in our case the genetic result provided mental comfort and peace to the mother.

Conclusion

Clearly, the combination of two rare diseases with pregnancy state can be named an explosive cocktail. The overlap of NF1 and BNS, which individually involve spine deformities, had an augmentative role in the severe kyphoscoliosis that was reached in this case. Also, considering the atypical severe clinical manifestation of the disease, we think that genetic testing of the newborn is useful for a more intensive monitoring and appropriate management. The position of the uterus is modified by the severe scoliosis, so, individualizing clear markings points before the incision is helpful. We consider this case an obstetrical success as two days after delivery the mother had the child in her arms. A multidisciplinary team in managing these kind of cases along with individualized and firm decisions are a must. However, this case is also a sign of awareness for the importance of early diagnosis considering that in the era of modern medicine we faced a feminine, 2021 version of 'The Hunchback of Notre Dame'.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest: none

Ethical approval: The written patient consent for publication has been obtained and this is available for verification if necessary

Data access statement: not applicable

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