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Two Pregnancies after Onset of Amyotrophic Lateral Sclerosis: Case Report and Review of the Literature

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Abstract

Pregnancy in patients complicated with amyotrophic lateral sclerosis (ALS) is an extremely rare in the clinical work. To date, only three cases have been reported that ALS patient became two consecutive pregnancies successfully. We described a case that became pregnancy twice during the slow progression of ALS. First pregnancy occurred one year after ALS onset; the patient was able to bear the discomfort of the whole pregnancy and delivered a healthy infant by cesarean section under total intravenous anesthesia without muscle relaxant at 36+5 weeks of pregnancy. The child was followed up to five years without abnormality. Three years later, she received a percutaneous endoscopic gastrostomy. Six years later, when she was already ben-ridden, she became pregnant again, at that time she was in a cachexia state with dyspnea and had to induce a labor in 16weeks of pregnancy. We summarize the 23 cases and a total 27 pregnancies and including this case, and analyzed the clinical characteristics of these cases and pregnancy outcomes to provide some reference experiences for clinicians.

Keywords: Amyotrophic lateral sclerosis; Pregnancy; Delivery; Anesthesia; Multidisciplinary cooperation

Abbreviations: ALS: Amyotrophic Lateral Sclerosis; CS: Cesarean Section; PEG: Percutaneous Endoscopic Gastrostomy; GA: Gestational Age; VEGF: Vascular Endothelial Growth Factor; SOD1: Super Oxide Dismutase

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects upper and lower motor neurons, resulting in relentlessly worsening paralysis of voluntary muscles until death ensues, with a fatal course within 3 to 5 years **[1].** The annual incidence is 2/100,000 in general population, the onset often occurs in the fifth to seventh decade, the ratio of men to women is 1.8:1 **[2,3].** Consequently, it is rare documented event in the obstetric population, about 2% of ALS patients was associated with pregnancy or delivery **[3].** Previous studies have confirmed that if pregnancy occurs in the early stages of ALS, both maternal and infants have good outcomes **[5-7].** When the disease progresses to the respiratory muscles, it can lead to maternal respiratory failure, fetal distress and other urgent requiring timely termination of pregnancy by surgery. To the data, only three ALS patients have delivered healthy babies successfully twice **[5,6,8].** We report the fourth case here. In our report, the patient became pregnant twice in the one year and six years after ALS onset. The first pregnancy she successful given birth a healthy baby girl by cesarean section at 36+5 weeks of gestation. But the second pregnancy, the disease involved respiratory system, dyspnea occurred and she was in a cachexia state, and had to induced labor to terminate her pregnancy at 16 weeks of gestation.

Case History

A 26-year-old female patient (G1P0), without similar family history, began to present with limited movement of her left lower limb in September 2014. Three months later, her symptoms of muscle weakness worsened: difficulty extending and bending the fingers of the left hand, unstable holding objects and stiffness of gait. The neurological examination showed hypertonia at left upper and double lower limbs, positive Chaddock sign, bilateral positive Hoffmann's sign, bilateral tendon hyperreflexia, atrophy of thenar and interphalangeal muscles of the left hand, and bilateral ankle clonus test was positive. The muscle strength of the left upper limb and both lower limbs increased. The muscle strength of the right limbs was grade 5, grade 5 in the left proximal upper and lower limbs, grade 5- in the left distal upper and lower limbs, grade 3 in the interphalangeal muscles. Bilateral ataxia was negative. Sensory system examination was normal. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) of the brain was moral. The diagnosis was probable ALS according to revised EI Escorial World Federation of Neurology criteria [9]. The patient began to take baclofen 5mg twice daily. One year later, she became pregnant and an Electromyography (EMG) test of the patient showed the presence of diffuse neurogenic damage of anterior horn cell consistent with ALS. The disease category was now classified as "definite ALS: UMN-D type and KCSS-2B stage". The disease progressed slowly during the whole pregnancy: in 16weeks of pregnancy, her right limbs muscles strength decreased; in 21 weeks of GA, muscle strength was further weakened and dysarthria occurred; in the third trimester, respiratory motility decreased. In the 36 weeks of GA, the patient was admitted to our hospital for waiting delivery. The pulmonary function test showed restrictive ventilation dysfunction, low vital capacity and total lung capacity, decreased ventilation function, and the ventilation reserve was 84%. After the comprehensive evaluation of multiple departments of respiratory, neurology, anesthesiology, maternal and fetal medicine, and obstetric, the patient underwent cesarean section under general anesthesia without muscle relaxants. The newborn weighted 2550 g and Apgar score was 10. They were discharged from the hospital five days after surgery. The patient continued to take baclofen 10 mg per day after one month of breastfeeding.

One years after delivery, the physical examination of the patient showed dysarthria, uvula skewed to the left, weak upper force of soft palate, weak eye closure ability. Muscle strength was grade 4 in bilateral proximal upper and lower limbs, grade 2 in bilateral distal upper and lower limbs, grade 2 in the interphalangeal muscles, Clasp-knife reflex in limb muscles, a present Babinski and Chaddock reflex, positive Hoffmann's sign, Rossolimo's sign and Pussep's sign, atrophy on bilateral thenar and interphalangeal muscles, pectoralis major, supraspinatus and infraspinatus muscles. High cortical function is normal. The dose of baclofen was increased from 10 mg per day to 15mg. The patient received a percutaneous endoscopic gastrostomy because of dysphagia in 2017. In March 2021, this female patient was admitted to our hospital again due dyspnea and 16 weeks of menopause. Clinical examination showed severe malnutrition, salivating, long-term bedridden, no spontaneous activities, unable to open her mouth and extend her tongue, limb muscles atrophy, muscle strength was grade 0 in bilateral upper limbs, grade 0 in the left lower limb, grade 2 in the right lower limb, bilateral limb tendon reflex was not induced, high arch deformity of the foot, foot flexion, bilateral ankle clonus and patellar clonus were positive, bilateral Hoffmann sign was not induced, right Babinskin sign and Chaddock sign were positive, left pathological sign was not induced, sensory ataxia examination was not cooperative. Blood test showed that hemoglobin was 85 g/L and hematocrit was 28.3%. The patient was infused with 2 units of red blood cell suspension and blood recheck showed hemoglobin was 95 g/L. After the comprehensive discussion and evaluation by multiple departments experts, it was decided to induce a labor to the patient. In March 2021, the patient was treated with Mifepriston 100 mg and underwent Rivanol amniocentesis. The patient underwent intra-amniotic induction of Rivanol 80 mg, but induction of labor failed 72 hours postoperatively. 1 mg of Carboprost are given and administered once every 3 hours, and the fetus was excreted after the 2nd dose. Because the placenta was not stripped, curettage was performed. And 2 units of the erythrocyte suspension were given after surgery, and the retest hemoglobin was 90 g/L. The woman received anti-inflammatory treatment with ceftriaxone and metronidazole and was discharged from the hospital 4 days postoperatively. Until the time of writing the report, she has been suffering from ALS for 8 years and died.

Discussion

In clinical work, pregnancy in ALS patient is extremely rare. Except a report of pregnant cases complicated by ALS form Guam in 1956, other cases are sporadic **[10].** Literature of review was based on a search in PubMed from 1977 to 2021, with the key words "amyotrophic lateral sclerosis" and "pregnancy". A total of 19 literatures was retrieved. 23 pregnant patients and these cases experienced 27 pregnancies, of which 4 cases experienced 2 pregnancies (including this case), and 30 neonates (including 1 twin pregnancy) were delivered. Except for 1 newborn with congenital heart disease, the rest were healthy; Age ranges from 25 to 38 years; Only 2 cases had family history; A total of 11 cases were diagnosed during pregnancy, 12 cases were diagnosed before pregnancy; and the longest time from diagnosis was 6+ years, that is the second pregnancy of this case; The initial symptoms of 16 patients were limb weakness; The course of disease progressed slowly in 15 pregnancies and rapidly in 12 pregnancies. 12 cases were full term productions, 10 cases were preterm productions; deliveries time from 32+ weeks to 40 weeks of GA, 2 mid-term induced labor due to deterioration of condition, and 3 cases unreported; 13 vaginal deliveries (including 2 mid-term induced labor), 12 cesarean deliveries, 6 unreported; The birth weight of newborns ranged from 2000g to 3700g; in the literature, only 2 cases insisted on taking riluzole during pregnancy and delivered at full term, and both 2 cases had fetal growth restriction: one

newborn had congenital heart disease and the other had no malformation. 6 cases died from 6 weeks to 3 years after delivery. See **Table 1** for details.

Table 1: Literature review of pregnant cases complicated with ALS.

Authors /Year	Age	Family history	pregnancy /delivery	Onset Time	Initial symptoms	Progress	GA of Delivery (weeks)	Delivery	Anesthesia	Infant status	Prognosis
Levine et al. [5]	36	Negative	2/2	6th month of pregnancy	Weakness of upper limb, dysarthria	Slow	38	Vaginal	Local	Healthy	Gradual Deterioration
	38	SP	3/3	2years before pregnancy	Weakness of all limbs, Bulbar palsy	Slow	40	Vaginal	Local pudendal	Healthy	Deterioration slightly, Alive at 3 years PP
Moret et al. [23]	27	Negative	1/1	Before pregnancy	Paralysis, dysarthria, dysphagia, dyspnea	Slow	39	CS	Spinal	NR	NR
Lupo et al. [16]	28	Positive	3/3	9th month of pregnancy	Weakness of lower limbs	Slow	Full term	Vaginal	NR	Healthy	Slow progression
	29	SP	4/4	1 year before pregnancy	N	Rapid deterioration	34	CS	Epidural	Twins Healthy	Death 6 weeks PP
	34	Negative	5/5	1 year before	Labored breathin	worsen	33	Vaginal	NR	Alive	Alive 18 months

				pregnancy	g						PP
Vincent et al. [17]	27	Negative	2/2	2 months before pregnancy	Weakness and tremor in right hand	Rapid deterioration	preterm	CS	General	Healthy	Stable condition within 4 months PP, with restrictive ventilatory distress
Jacka et al. [16]	33	Positive	1/1	8 weeks of gestation	Weakness of lower limbs	Rapid deterioration	preterm	CS	Epidural	Alive	Respiratory failure PP, underwent tracheotomy and PEG and long-term ventilation before discharged 8 weeks PP, Alive 18 months PP
Tyagi et al. [19]	29	Negative	1/1	6th month of pregnancy	Weakness of lower limbs, dysarthria	Slow progression	NR	Vaginal	NR	Alive	Slow progression, Alive 1 year after diagnosis
Chio et al. [7]	27	NR	1/1	6th month of pregn	Weakness and atrophy of hands	Slow progression	40	Vaginal	Epidural	Healthy	Developed severe dysarthria and

				ancy	with fasciculations and stiffness of gait						dysphagia 6 months PP
	29	NR	1/1	5th month of pregnancy	Weakness and atrophy of the right quadriceps	Slow progression	39	Vaginal	No	Healthy	Progression to atrophy of lower limbs with muscular spasm and clonus. Still able to walk with stick PP.
	33	NR	2/2	3th months of pregnancy	Weakness and atrophy of the shoulder gridle muscles	Rapid deterioration and respiratory failure	5 months	Induced labor	No	No survival	Death 3 months PP
	38	NR	3/3	1 year before pregnancy	Weakness and atrophy of right hand	Slow progression to dysphagia and spastic paralysis	34	CS	NR	Alive	Slow progression to dysarthria and weakness of upper limbs, and pyramidal signs at the lower limbs PP.

Sobrino-Bonilla et al. [24]	32	Negative	2/2	1 years before pregnancy	dysarthria	Rapid deterioration	38+	Vaginal (vacuum)	Epidural	Healthy	NR
Levecke et al. [21]	25	Negative	3/3	22 weeks of gestation	Weakness of left limbs, dysphagia, ptosis,	Rapid progression, involving respiratory system	34.5	Vaginal (vacuum)	NR	Healthy	Death 9 months PP
Sarafov et al. [8]	28	Negative	1/1	13 months before pregnancy	Weakness of right upper limb	Slow progression to weakness of both upper limbs and hyperreflexia of four limbs	40	Vaginal (midwifery forceps)	Epidural	Healthy	Progression to tetraplegia 1 year PP
	29	SP	2/2	28 months before pregnancy	Tetraplegia	Progression to dysphagia and cachexia, PEG performed	34	CS	NR	Healthy	Long-term mechanical ventilation performed 2months PP, and death 11 months PP
Kawamichi et al. [22]	34	Negative	1/1	4 years before pregnancy	NR	Progression to atrophy of the tongue and four	38	Vaginal (vacuum)	NR	Fetal growth restriction, but	Neurological status slightly declined 1 year PP

						limbs, bulbar palsy, dysphonia and dysphagia, use of riluzole during pregnancy				newborn was Healthy	
Scalco et al. [26]	38	NR	1/1	7 months before pregnancy	Weakness of four limbs, dysphagia, dysarthria	Slow progression and use of riluzole during pregnancy	37	CS	NR	Intrauterine growth restriction and born with congenital heart disease	NR
Martinez et al. [25]	37	Negative	1/1	9th week of gestation	Weakness of upper left limb	Stable condition	38	CS	NR	Healthy	Rapid deterioration Underwent an autologous intrathecal stem cell transplant 2 months PP, tracheoto

											my and PEG 2 years PP
Lunetta et al. [15]	32	NR	1/1	24th weeks of the 1st pregnancy	Weakness of upper limbs	Rapid worsening	NR	NR	NR	Healthy	Death 37 months after delivery
Kock-Cordeiro et al. [18]	25	NR	2/2	27 weeks of gestation	Weakness of lower limbs and Bulbar symptoms	Rapid deterioration to dyspnea and orthopnea	32+	CS	Spinal-epidural	Healthy	Long-term non-invasive ventilation
Porto et al. [11]	29	Negative	1/1	4.5 years before pregnancy	Twitching and numbness of the left hand and forearm	Rapid deterioration	37	CS	Epidural	Healthy	Remarkable weakness, selective dysphagia and new-onset dysarthria, changes to voice 6 weeks PP
Marsli et al. [4]	34	Negative	NR	1 year before pregnancy	Muscle spasm	Rapid progression to diffused fasciculations, weakness of four	NR	NR	NR	Healthy	Non-invasive ventilation was required every day, and Death 9

						limbs, transitory respiratory failure, dysarthria, dysphagia					months after ALS onset
Pathiraja et al. [12]	32	NR	5/4	2 years before pregnancy	Weakness of lower limbs and slurring of speech, quadriparesis	Slow progression to restricted mobility and shortness of breath	34	CS	NR	Healthy	NR
Xiao et al. [20]	27	Negative	2/1	1 year before pregnancy	Weakness of upper limbs	Slow progression to dysphagia	36+	CS	General anesthesia without muscle relaxant	Healthy	Slow progression, underwent PEG 2 years PP
Present case	33	SP	3/2	6 years before pregnancy	Weakness of upper limbs	Slow progression, laborious breathing	16	Induced labor	No	No survival	Long bed-ridden, restrictive ventilatory dysfunction

NR: not reported; ALS: amyotrophic lateral sclerosis; SP: same person who became different pregnancies; PEG: percutaneous endoscopic gastrostomy; CS: caesarean section; PP: postpartum; GA: gestational age

In this study, the patient first presented restricted left limb activity at the age of 26 and gradually developed symptoms of limb weakness, and was diagnosed as possible ALS. Generally speaking, the onset of ALS was limb weakness and atrophy, and the disease progress was relatively slow. The median survival time of ALS was 2-3 years. However, if the initial symptoms were related to bulbar damage, the progress was rapid, and the survival age was shorter, the median value was 27.5 months **[1].** Sporadic cases in ALS account for 90-95% **[1,11,12].** For this case, other family member had no disease and familial history, but whether there is chromosome mutation had not been checked. This case had been suffering 7 years and 8 months to date. Treatment of ALS in pregnancy was complicated. This patient could not take riluzole but received invasive treatments of PEG.

Although the aetiology for ALS is still unknown, some studies of genetic factors and pathogenetic mechanisms have been reported **[13-15],** such as VEGF gene polymorphisms and SOD1 gene mutation. A recent study supposed that pregnancy may unmasks an already present, but clinically silent ALS **[15].** The authors suggested that a drop in estrogen levels during pregnancy may trigger ALS symptoms in patients with SOD1 gene mutations because estrogen has a potential neuroprotective effect. In the literature, 4 cases had family history, but genetic information on these patients has not provided **[6,16].** So far, it is unclear whether pregnancy will accelerate the progression of the disease. Some cases reported rapid progression of ALS after pregnancy **[4,6,7,11,15-18].** Some cases progressed slowly during pregnancy and after delivery and this case **[19,20].** Our case progressed slowly for 6 years before 2nd pregnancy with dyspnea. One case showed slow progression during pregnancy and rapid development after pregnancy **[21].** The possible reason is that the disease continues to progress. In the late stage of the disease, the development of ALS is related to pregnancy or delivery complications, resulting in further deterioration of respiratory function, respiratory failure and even cachexia, which leads to the death of patients. Six patients died within 6 weeks to 3 years postpartum **[11].** The longest distance to diagnosis is 7 years and 8 months, which is our case, and who is still alive at present. Generally, pregnant women with ALS can tolerate vaginal delivery in the early stage of the disease. This is because the deterioration process of ALS does not involve uterine smooth muscle, and its contractility is normal, while the tension of pelvic floor muscle is weakened, which is facilitator to vaginal delivery. However, when both respiratory muscles and abdominal muscle are significant weaken in the late stage of ALS, vaginal midwifery **[8,22]** or CS **[11,20]** may be a good choice. In the literature, there were only 13 vaginal deliveries (including 2 mid-terms induced labors) in 31 deliveries, and 4 vaginal deliveries (3 aspiration and 1 forceps) in 11 late pregnancy deliveries; In the late stage of the disease or when there are obstetric indications, cesarean section is required to terminate pregnancy, a total of 12 cesarean deliveries. The first pregnancy of this case with ALS was evaluated in hospital twice, and multidisciplinary team discussions were carried out, including respiratory physicians, anesthesiologists, neurologists and maternal and fetal medical experts. Whether it can continue pregnancy, delivery methods and anesthesia methods were discussed in detail in the third trimester of pregnancy, and CS was finally selected to terminate pregnancy. On the other hand, neurologists believed that the patient's disease has been progressing. Although the respiratory system was not involved, the process and time of vaginal delivery were uncontrollable, and at the strong request of family members, so we finally had chosen cesarean section to terminate pregnancy.

When the patient became pregnancy again 6 years after the onset of the disease, multidisciplinary discussion was also held. At this time, the patient was in the late stage of the disease, with dyspnea and cachexia.

Considering that the pregnancy time (16 weeks GA) was still short at this time, the patient was treated with intensive surveillance and timely induction of labor to alleviate her clinical symptoms. With regard to the selection of anesthesia methods, both general anesthesia and regional neuraxial blockade were reported previously **[7,11].** Successful cases of CS combined with spinal epidural anesthesia and non-invasive ventilation have been reported **[9].** There also were cases of general anesthesia have been reported **[17,20]** and one case of subarachnoid anesthesia **[23].** However, for CS and delivery of this group of patients, epidural anesthesia is more popular **[6-8,11,16,24].** Epidural anesthesia can avoid intubation and has the least impact on the patient's respiratory system. During the first CS of our case, the patient delivered smoothly under general intravenous anesthesia without muscle relaxants **[20],** and the patient recovered to the preoperative state after operation; Anesthetics were not used at the second time of termination of pregnancy by induction of labor. It has been reported that autologous stem cell transplantation into the frontal motor cortex may alter the clinical course of ALS **[25].** It needs more research and clinical data to prove its effectiveness. For pharmacologic approaches, Riluzole is the only drug for the treatment of ALS **[1].** Whether riluzole can be used during pregnancy remains controversial. It has been reported that the use of riluzole during pregnancy may lead to fetal growth restriction **[22,26].** In the report, one of the new borns was found to have an atrial septal defect and patent ductus arteriosus after birth **[26].** Whether fetal growth restriction and neonatal malformation are caused by riluzole is unclear. Therefore, the safety of using riluzole during pregnancy for ALS patient needs to be further studied.

Conclusion

At a certain stage of ALS, it is unlikely that successful pregnancy will result in the birth of a healthy child and pregnancy is not recommended for ALS patients.

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