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Riluzole Use During Pregnancy in a Patient with Amyotrophic Lateral Sclerosis: a Case Report

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Pregnancy with amyotrophic lateral sclerosis (ALS) is rare and generally considered dangerous. Riluzole is the only drug approved for use in ALS, but the effect on maternal and fetal health is unknown. We describe the case of an ALS patient taking riluzole throughout pregnancy. A 34-year old Japanese woman, who had been diagnosed with probable ALS 4 years earlier, visited our hospital for abdominal distension, without knowing that she was pregnant. The patient had been taking riluzole for 2 years, inclusive of her gestational months, and we decided to continue administration of the medication. The patient delivered a normal female infant transvaginally at 38 weeks gestation. The patient's neurological status was stable 1 year after delivery and the baby had developed normally. We found that, in this case, riluzole did not cause any side-effects to the pregnant woman or her fetus.

KEY WORDS: Amyotrophic lateral sclerosis, Pregnancy, Riluzole

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disease of the upper and lower motor neurons, causing irreversible muscle weakness and atrophy. The illness is relentlessly progressive, leading to death from respiratory paralysis, with a median survival of 3 – 5 years. In the USA and Europe, males are somewhat more frequently affected than females, and the disease does not usually occur until after 50 years of age.[1] Some cases of ALS presented before or during pregnancy have been described.[2–11] The only drug that is licensed for the treatment of ALS is riluzole, which was approved in 1996 because it modestly lengthens survival, but there has been no report on its use during pregnancy. The present report describes a case of normal pregnancy and delivery in an ALS patient being treated with riluzole.

Case report

A 34-year old primigravida Japanese woman, visited Tokyo Women's Medical University Hospital with the chief complaint of abdominal distention, without realizing she was pregnant. She was diagnosed with probable ALS under El Escorial World Federation of Neurology criteria 4 years earlier.[12] Ultrasound examination revealed that the fetus had no anomalies and the estimated fetal body weight was 1647 g, leading to an estimation of 30 weeks gestation. Using transvaginal ultra-

sonography, the cervical length was found to be 9 mm, and cervical incompetence was diagnosed – a risk factor for pre-term labour.[13] The patient was, therefore, admitted to the hospital to try to prevent pre-term labour.

On neurological examination, the patient was found to have atrophy and fasciculation of the tongue and her four limbs, and bulbar palsy. She also had mild dysphonia and dysphagia but no sensory deficit. Her arterial blood gases while breathing room air showed a saturation of peripheral oxygen (SPO_2) of 96.2%, measured by pulse oximeter, pH of 7.501, partial pressure of carbon dioxide pressure (PCO_2) of 29.2 mmHg, partial pressure of oxygen (PO_2) of 74.1 mmHg, and bicarbonate (HCO_3^-) levels of 23 mmol/l. She did not need artificial respiratory support. There were no other abnormal physical or laboratory findings and no family history of ALS.

The patient had been taking riluzole (100 mg/day) for 2 years, inclusive of her gestational months, owing to the diagnosis of ALS. After discussion with the patient and a neurologist, it was decided to continue riluzole treatment. She was able to stand up and walk for a short time, with help, until near full-term but gradually could not balance herself while walking and began using a wheelchair. Her neurological status and breathing remained essentially unchanged throughout the remainder of her pregnancy. In weekly obstetric examinations, cervical incompetence did not progress, fetal growth was normal and biophysical profile (assessment of fetal health) was good.

At 38 weeks of gestation, the patient went into spontaneous labour, the first stage of which progressed smoothly. Due to malrotation of the baby and maternal fatigue, vacuum extraction was undertaken. The duration of labour was 7 h. The neonate was a normal female infant weighing 2280 g with Apgar scores of 8 at both 1 and 5 min. The Dubowitz score (assessment of the infant's apparent gestational age by considering both neurological and external signs of development)[14] confirmed the baby's gestational age as 38 weeks.

Uterine contraction was good and total blood loss was 174 ml. Maternal breathing was normal and pulse oximeter SPO_2 levels remained at 95 – 97% in room air throughout labour. Room air blood gases revealed a SPO_2 of 95.1%, pH of 7.478, PCO_2 of 39.1 mmHg, PO_2 of 76.5 mmHg, and HCO_3^- of 29.3 mmol/l just after labour. Pulmonary function tests showed a forced vital capacity of 1.46 l (46% of the predicted value) and a forced expiratory volume in 1 s of 1.3 l (47.7% of the predicted value) on the fifth post-partum day. The pulmonary function tests showed some restriction but the patient's general condition was stable and she did not need respiratory support. Her puerperium course was uneventful and both mother and baby were discharged on day 10 post-partum. At 1 year after delivery, the patient's neurological status had slightly declined but she did not need a respirator, and the baby was developing normally.

Discussion

Amyotrophic lateral sclerosis is the most common form of progressive motor neuron disease. Although it may involve selective loss of function of only the upper or lower motor neurons at onset, it ultimately causes the progressive loss of both. While ALS is overwhelmingly a sporadic disorder, 5 – 10 % of cases are hereditary, caused by an autosomal dominant trait.[1] The cause of sporadic ALS is not well defined: some data have shown that excitotoxic neuro-transmitters, such as glutamate, might participate in the death of motor neurons in ALS.[1] In most societies, there is an incidence

of one to three per 100 000 and a prevalence of three to five per 100 000.[1]

A report published in 1956 detailed 21 pregnancies in 17 ALS women in Guam.[11] The disease is estimated to occur 100 times more frequently in Guam than in the continental USA and most cases are believed to be predominately familial.[11] Other than this report, pregnancy in ALS has rarely been described and the publication of similar cases is scant in the medical literature.[2 – 11]

Only 12 other cases of pregnancy with ALS have been reported in the English language literature since 1977 (Tables 1 and 2). Of these cases, five (including the present case) were diagnosed before pregnancy and eight were diagnosed during pregnancy. There were no deaths due to neurological complications, but some cases showed rapid worsening, respiratory failure, tracheostomy and gastrostomy during pregnancy, and death post-partum. One case resulted in therapeutic abortion because of severe dyspnoea,[4] and four others required delivery by caesarean section due to worsening of the maternal condition.[2 – 5] There were three cases of post-natal death[3,4,9] and five known pre-term deliveries (one due to premature rupturing of the membrane and the other four by worsening of the maternal condition).[2 – 4,9] Although the patient in the present study showed cervical incompetence, which is a risk factor for pre-term labour,[13] she delivered her baby at normal term. There have been no neonatal complications in any of the published reports. We therefore consider ALS and pre-term labour unrelated and conclude that pregnancy with ALS does not cause obstetric complications, but may limit maternal survival and reduce maternal quality of life.

The only drug approved for use in ALS cases is riluzole, which was licensed in 1996 having been shown possibly to lengthen survival. Lacomblez *et al.*,[7] in a double-blind, placebo-controlled, multicentre study, reported that riluzole was well tolerated and lengthened the survival of patients with ALS. The mechanism of this effect is not known, although it is postulated that the drug may reduce excitotoxicity by diminishing glutaminate release.[1] Pre-clinical studies have revealed evidence of embryotoxicity only at much higher doses than those used clinically.[15] The drug is categorized as class C in the Food and Drug Administration classification of fetal risks due to pharmaceuticals taken during pregnancy. This means that animal studies have shown an adverse effect on the fetus but there are no adequate well-controlled studies in humans and potential benefits may warrant use of the drug in pregnant women despite potential risks. We were reluctant to continue riluzole administration in the present case because of there being no reports on its effect on the human fetus. However, since the patient had already been taking riluzole throughout the pregnancy, we continued to administer the drug, making extension of life our priority, even if just for a few months. As a result, we found that the drug had no side-effects for mother and baby, and was able to keep the pregnancy stable.

The baby's weight was light-for-date, but it is not clear whether this was related to taking riluzole, since there could be other reasons for the low weight. For example, there may have been underestimation of gestational age since the expected date of confinement was uncertain, and there may have been effects due to the mother smoking cigarettes throughout the pregnancy.

Labour and delivery were not adversely affected by ALS. Uterine contractions were normal and uterine muscle is not involved in the ALS degenerative process, having only sympathetic and parasympathetic innervations. Paradoxically, the lack of tone of the pelvic floor muscle would facilitate

TABLE 1:
Literature review of patients with amyotrophic lateral sclerosis (ALS) diagnosed before pregnancy

Reference	Maternal age (years)	Parity	Family history and other complications	Onset of ALS	Clinical course of ALS during pregnancy	Mode of delivery	GA (weeks)	Neonatal outcome	Clinical course of ALS after delivery
Lupo *et al.*, 1993[3]	34	4	No	1.5 years before pregnancy	Full-time ventilator support. Premature rupturing of the membrane at 33 weeks	VD	33	Healthy 2330 g	No clinical worsening
Vincent and Rodríguez-Ithurralde, 1995[5]	27	1	No	2 months before pregnancy	Worsening Patient did not go to hospital until her condition deteriorated. C/S performed due to rapid deterioration	C/S	UN	Healthy 2800 g	3 months AD, restrictive ventilator insufficiency
Chiò *et al.*, 2003[4]	38	2	No	1 year before pregnancy	Rapid worsening. C/S performed due to rapid deterioration. Definite ALS	C/S	34	Healthy	Slow progression
Sobrino-Bonilla, 2004[10]	32	1	No	1 year before pregnancy	Rapid progression before 1 year	VE	38	Healthy	No clinical worsening
Present case	34	0	No	4 years before pregnancy	No clinical worsening Probable ALS	VE	38	Healthy 2280 g	Slow progression

GA, gestational age; VD, vaginal delivery; VE, vacuum extraction; C/S, caesarean section; UN, unknown; and AD, after delivery.

TABLE 2:
Literature review of patients with amyotrophic lateral sclerosis (ALS) diagnosed during pregnancy

Reference	Maternal age (years)	Parity	Family history and other complications	Onset of ALS	Clinical course of ALS during pregnancy	Mode of delivery	GA (weeks)	Neonatal outcome	Clinical course of ALS after delivery
Levine and Michels, 1977[6]	36	1	No	6 months gestation	Slow progression	VD	UN	Healthy	Slow deterioration
		2[a]			Severe bulbar palsy but uneventful	VD	38	Healthy 3700 g	Slow deterioration
Lupo *et al.*, 1993[3]	28	2	Yes	36 weeks gestation	Slow progression	VD	UN	Healthy	Slow deterioration
		3[b]	Yes		Rapid worsening by 34 weeks gestation. Induction of labour failed	C/S	34	Healthy 2270 g[c] 2270 g[c]	Patient died of respiratory failure 6 weeks later
Jacka and Sanderson, 1998[2]	31	0	Yes ITP	8 weeks gestation	Worsening. Dyspnoea by 32 weeks gestation. C/S performed due to respiratory insufficiency and risk of fetal thrombocytopenia	C/S	32	Healthy 2810 g	1 week AD, tracheostomy and gastrostomy
Tyagi *et al.*, 2001[8]	29	0	No	6 months gestation	Ataxia and dysarthria had onset during the pregnancy but had not been considered remarkable.	VD	UN	Healthy	Progression
Chiò *et al.*, 2003[4]	27	0	No	6 months gestation	Slight progression. Definite ALS	VD	40	Healthy 2280 g	6 months AD, gastrostomy
Chiò *et al.*, 2003[4]	29	0	No	5 months gestation	Slight progression. Definite ALS	VD	39	Healthy	Slight progression

TABLE 2 (continued):
Literature review of patients with amyotrophic lateral sclerosis (ALS) diagnosed during pregnancy

Reference	Maternal age (years)	Parity	Family history and other complications	Onset of ALS	Clinical course of ALS during pregnancy	Mode of delivery	GA (weeks)	Neonatal outcome	Clinical course of ALS after delivery
Chiò *et al.*, 2003[4]	35	1	No	3 months gestation	Rapid progression. The pregnancy was interrupted due to severe dyspnoea. Definite ALS	TA	UN	Dead	Patient died 3 months after termination
Leveck and Davies, 2005[9]	25	2	No	14 weeks gestation	Rapid progression. Intubated at 29 weeks gestation. Labour induced at 34 weeks gestation	VE	34	Healthy 2305 g	Patient died 9 months AD

GA, gestational age; VD, vaginal delivery; VE, vacuum extraction; C/S, caesarean section; TA, therapeutic abortion; UN, unknown; AD, after delivery, ITP, idiopathic thrombocytopenia purpura.
[a]Two years after previous pregnancy. [b]Eight months after previous pregnancy. [c]Two breech male twins.

vaginal delivery.[3,4] Labour progressed smoothly until cervical dilatation was complete, but the patient could not push down fully and became fatigued. Vacuum extraction was performed as there was malrotation of the fetus. Lupo *et al.*[3] reported that the management of labour and delivery in patients with ALS should include blood gas monitoring before labour to indicate whether the patient is retaining carbon dioxide or is in danger of having their respiratory drive shut off by oxygen therapy. Some recommend the use of a pulse oximeter during labour.[2,3] Our patient did not retain a high carbon dioxide level and was monitored by a pulse oximeter during labour, which revealed no change.

The ALS patient in the present study showed a smooth progress of labour, as has been previously described in other reports. This is, however, the first case that we know of an ALS patient taking riluzole throughout pregnancy and delivering a normal baby. Riluzole was not found in this case to cause any side-effects either to the mother or fetus.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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