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# Perinatal Distress in 1p36 Deletion Syndrome can Mimic Hypoxic Ischemic Encephalopathy

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## Abstract

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

None.

1p36 deletion syndrome is a well-described condition with a recognizable phenotype, including cognitive impairment, seizures and structural brain anomalies such as periventricular leukomalacia (PVL). In a large series of these individuals by Battaglia et al., “birth history was notable in 50% of the cases for varying degrees of perinatal distress”. Given the potential for perinatal distress, seizures and PVL, we questioned if this disorder has clinical overlap with hypoxic ischemic encephalopathy (HIE). We reviewed the medical records of 69 individuals with 1p36 deletion to clarify the perinatal phenotype of this disorder and determine if there is evidence of perinatal distress and/or hypoxic injury. Our data provides evidence that these babies have signs of perinatal distress. The majority (59% term; 75% preterm) needed resuscitation and approximately 18% had cardiac arrest. Most had abnormal brain imaging (84% term; 73% preterm) with abnormal white matter findings in over half of patients. PVL or suggestion of “hypoxic insult” was present in 18% of term and 45% of preterm patients. In conclusion, individuals with 1p36 deletion have evidence of perinatal distress, white matter changes, and seizures, which can mimic HIE but are likely related to their underlying chromosome disorder.

**Keywords**

1p36; hypoxic ischemic encephalopathy; distress

## Introduction

1p36 deletion syndrome is a well-described, common terminal microdeletion syndrome with a recognizable phenotype in part due to characteristic facies. This condition affects neurologic development with intellectual disability and/or developmental delay and poor/absent expressive language being common features. Other findings include hypotonia (95%), structural brain abnormalities (88%) including white matter anomalies such as periventricular leukomalacia, and seizures (44–58%) (Battaglia, 2013). There can be multiple organ system involvement such as congenital heart defects, genitourinary and renal abnormalities, and skeletal anomalies.

A study of 60 term patients documented that, “birth history was notable in 50% of the cases for varying degrees of perinatal distress” (Battaglia et al., 2008). However, specifics were not given.

Brain imaging of patients with 1p36 deletion shows variable white matter abnormalities including myelination delays, multifocal hyperintensities in the white matter, and periventricular leukomalacia (PVL) (Battaglia et al., 2008). PVL is characterized by focal necrotic lesions in the periventricular white matter and/or more diffuse white matter damage and has an association with motor abnormalities such as cerebral palsy given that corticospinal tracts run through the periventricular white matter (Carlo & Ambalavanan, 2016). PVL is one type of sequelae of neonatal brain injury associated with hypoxic ischemic encephalopathy (HIE) (Kinney & Volpe, 2018).

HIE is a clinical syndrome in term infants that results from a severe or prolonged hypoxic-ischemic episode before or during birth (Gopagondanahalli et al., 2016). Anecdotally, our genetics group was aware of a patient with 1p36 deletion syndrome who had previously

been diagnosed with HIE. Given the potential for perinatal distress, seizures and white matter abnormalities such as PVL, we questioned if this chromosomal disorder has clinical overlap with an HIE phenotype.

The purpose of this study is to review the medical records of individuals with 1p36 deletion to clarify the perinatal phenotype of this common disorder and to examine whether there is evidence of perinatal distress or suggestion of a hypoxic type of injury.

## Methods

### Editorial Policies and Ethical Considerations

This study was approved by the Stanford IRB.

Chart review was performed on a total of 72 cases of 1p36 deletion. Parameters reviewed included: gestational age; mode of resuscitation (if needed); Apgar scores at 1, 5 and 10 minutes; brain abnormalities on imaging including age at time of imaging; age at discharge from the hospital; and presence or absence of seizures including age of onset. Deletion sizes were not evaluated as part of this study. Patients were divided into term and preterm groups for analysis, with term defined as 37-weeks of gestation or more completed. Two patients had brain images available within the Stanford system that were interpreted by a single reviewer, a pediatric neurologist/geneticist. In cases where imaging was not available, the same reviewer examined information provided in the radiology reports to classify whether findings could be suggestive of PVL or some type of hypoxic injury or perinatal insult.

## Results

Data were reviewed for 72 patients identified with 1p36 deletion syndrome. Three patients were excluded from review due to not having information listed for multiple parameters, most notably gestational age, leaving 69 patients for final analysis. As referenced in Table 1, 81% (56/69) of patients were delivered at term and 19% (13/69) were preterm patients.

An average of 67% (term and preterm) patients needed resuscitation. Patients were not counted as needing resuscitation if only warming and/or stimulation was reported. Resuscitation methods included oxygen support through blow-by oxygen and positive pressure ventilation, intubation, and chest compressions. One patient received an opioid antagonist during resuscitation, otherwise, medication information was not provided. Some form of resuscitation was required in 59% (17/29) of the term patients and 75% (6/8) of the preterm patients. For babies that required resuscitation after delivery, use of chest compressions or report of “cardiac arrest” occurred in 18% (3/17) of the term patients and 17% (1/6) of the preterm patients. There was an additional patient reported as needing “vigorous resuscitation”; however, this was not included in the cardiac arrest category, given ambiguity of response.

The average one-minute Apgar score was 6.6 for term patients and 5.1 for preterm patients. The average five-minute Apgar score was 8.4 for term patients and 6.4 for preterm patients. Standard deviations for Apgar scores are provided in Table 1. There were few patients with 10-minute Apgar scores and therefore this parameter was not included for final analysis.

Abnormal brain imaging was present in 84% (42/50) of the term patients and 73% (8/11) of the preterm patients. Abnormal white matter findings occurred in 27/50 (54%) of term patients and 55% (6/11) of the preterm patients. Periventricular leukomalacia, suspected evidence of hypoxic injury and/or perinatal insult were noted in 9/50 (18%) of term patients and 45% (5/11) of preterm patients.

The average age of discharge was 10 days for term patients excluding an outlier of 210 days for one of the term patients and 9 days for preterm patients. Standard deviations are provided in Table 1. Most patients went home at four days or less [61% (17/28) of term patients and 58% (7/12) of preterm patients]. The median age of discharge for term patients was three days.

Seizures were a common feature in our cohort, occurring in 72% (34/47) of term patients and 55% (6/11) of preterm patients. Most seizures were diagnosed in infancy.

## Discussion

1p36 deletion syndrome is a well-described condition (Battaglia et al., 2008), but the perinatal phenotype of affected individuals has not been described in detail. Based on previous reports of perinatal distress in patients with 1p36 deletion syndrome (Battaglia et al., 2008), we analyzed the perinatal findings of a large cohort of affected individuals to better delineate their phenotype.

In this cohort of 69 patients with 1p36 deletion, most were born at term and would be predicted not to need resuscitation. Guidelines report that 5–10% of newborns need active resuscitation including stimulation to breathe and only 1–10% of babies born in the hospital are expected to need assisted ventilation (Niermeyer et al., 2000). However, in our cohort, 59% of term patients and 75% of preterm patients required resuscitation beyond just warming and stimulation. Both patient groups underwent cardiac arrest at a similar rate (17–18%), which was surprising because needing this level of resuscitation is predicted to occur in 0.1% of term infants (Perlman et al., 2015) and because one would have anticipated that preterm patients would have a higher likelihood of experiencing cardiac arrest versus their term peers.

The average 1-minute Apgar score for term patients was 6.6 compared to 5.1 in preterm patients and both scores were lower than the national average of > 7 (American Academy of Pediatrics, 2015). Both term and preterm patients had an increase in their 5-minute Apgar scores to 8.4 and 6.4, respectively, showing a response to resuscitation. One would anticipate lower Apgar scores if these babies had a true hypoxic-ischemic event, as a large study of HIE patients showed a 1-minute Apgar score of 0–2 and many criteria for cooling therapy for HIE require an Apgar score of 5 or less at 10 minutes (Laptook et al., 2009; Papile et al., 2014). We did not include 10-minute Apgar scores for analysis as it was a parameter not available for most, likely because it was not necessary to obtain given improvement in 5-minute Apgar score. Nevertheless, one would expect that given that the average Apgar scores at 5 minutes is above cooling threshold of 5, they would not have met cooling criteria even if a 10-minute Apgar score was available.

The average age at discharge was 10 days for term patients and 9 days for preterm patients. Most patients went home at ≤ 4 days (61% term; 58% preterm). The median length of hospital stay was three days for our term patient cohort compared to a HIE patient study which reported median length of stay of 13 days with an in interquartile range of 9–22 (Massaro et al., 2016). The Apgar scores being close to the national average of 7 or greater and the fact that there was not a prolonged hospitalization course suggests that the perinatal difficulties detected in the 1p36 deletion patients were not indicative of significant hypoxic events.

Brain abnormalities were found in 84% of term patients and 73% of preterm patients in our cohort which is expected as this is a well described feature of this disorder. Just over half of the term patients had white matter abnormalities (54%), 18% of which had PVL, compared to 55% of the preterm patients who had white matter abnormalities, most of which was attributed to PVL or suggestion of hypoxic injury (45%). It is interesting that suggestion of a perinatal insult based on imaging was higher in the preterm patient group given that HIE is not as well-defined in this population with variable clinical features and lack of clear definitions (Gopagondanahalli et al., 2016). This raises the question of whether preterm patients with 1p36 deletion syndrome may be more likely to present with an HIE-like phenotype than term patients.

These data also demonstrate that 1p36 deletion patients have a higher incidence of white matter abnormalities and PVL than was previously reported in a study of term individuals (Battaglia et al., 2008). In fact, 54% of term patients studied by us had abnormal white matter versus 16% in that cohort; 18% of our term patients had either frank PVL or suggestion of hypoxic injury/perinatal versus 6% in their cohort. This difference is intriguing given that we both had a similar number of patients (49 patients in their study compared to 50 in our study). Therefore, we question whether white matter abnormalities and a perinatal insult type of injury such as HIE may have been underestimated in the past.

The majority (72%) of term patients had seizures compared to 55% of preterm patients, which is slightly higher than previously reported (Battaglia, 2013). The fact that most seizures began in infancy also suggests early neurologic involvement which would be expected for an HIE patient as well.

Based on our findings, patients with 1p36 deletion have an increased rate of perinatal distress, including cardiac arrest and greater need for resuscitation, and have a high likelihood of white matter abnormalities similar to those seen with hypoxic injury. These findings may be interpreted as sequelae of HIE but given the absence of prolonged hospital stay and low Apgar scores, we favor the hypothesis that these features are part of the underlying chromosomal disorder.

The data from this cohort indicate that additional support at delivery is warranted for infants prenatally diagnosed with 1p36 deletion syndrome, given their high need for resuscitation and chance of cardiac arrest. A diagnosis of 1p36 deletion syndrome should be considered in those with an HIE-like presentation, particularly if the clinical scenario does not include

history of asphyxia and highlights the importance of investigating for a genetic etiology in such cases.

There are several limitations to this study, however. First, the data sets were not fully complete as many patients had parameters that were not provided. Table 1 lists the number of patients with information available for each category. Second, the study could be strengthened if we had brain images for all patients. Brain images were only available for two patients, therefore, we often had to rely on imaging reports for our pediatric neurologist to review.

## Conclusions

1p36 deletion syndrome is a well-described, common terminal microdeletion syndrome with a recognizable phenotype including seizures and white matter brain abnormalities. We describe the perinatal complications of this condition including high need for resuscitation with some babies undergoing cardiac arrest. We further emphasize the similarities and differences between 1p36 deletion and HIE, showing that 1p36 deletion patients can mimic an HIE phenotype. However, given that there was not prolonged hospitalization or low Apgar scores suggestive of HIE, we hypothesize that these features are related to their underlying chromosome disorder. Our cohort of 69 patients provide evidence that additional resuscitation support at delivery is warranted for babies prenatally diagnosed with 1p36 deletion. Lastly, a diagnosis of 1p36 deletion syndrome should be considered in patients with an HIE-like clinical picture.

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**Table 1.**

Features of 1p36 deletion syndrome patient cohort

| **PATIENTS *N* = 69** | **TERM *n* = 56** | **PRE-TERM *n* = 13** |
|---|---|---|
| **RESUSCITATION (%, *n*)** | 59% (17/29) | 75% (6/8) |
| **CARDIAC ARREST (%, *n*)** | 18% (3/17) | 17% (1/6) |
| **APGAR 1 MIN (*Mean, SD, n*)** | 6.6 (2.5) (40) | 5.1 (2.7) (7) |
| **APGAR 5 MIN (*Mean, SD, n*)** | 8.4 (1.4) (39) | 6.4 (2.9) (7) |
| **ABNORMAL BRAIN IMAGING (%, *n*)** | 84% (42/50) | 73% (8/11) |
| **ABNORMAL WHITE MATTER (%, *n*)** | 54% (27/50) | 55% (6/11) |
| **PVL/PERINATAL INSULT (%, *n*)** | 18% (9/50) | 45% (5/11) |
| **AGE AT DISCHARGE (*Mean, SD, n*)** | 10 days * (14.8 *) (28) | 9 days (9.5) (12) |
| **SEIZURES (%, *n*)** | 72% (34/47) | 55% (6/11) |

* Excluding outlier of 210 days