Review



# Does Fetal Malignant Hyperthermia-Related Intrauterine Thermal Stress Contribute to Cerebral Palsy Risk?

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Posted Date: 10 April 2025

doi: 10.20944/preprints202504.0875.v1

Keywords: Cerebral palsy (CP); Hypoxic ischemic injury (HII); Malignant hyperthermia (MH); Malignant hyperthermia susceptible (MHS); Fetal hypoxia; Heat stress

 doi:10.20944/preprints202504.0875.v1



*Review*

# Does Fetal Malignant Hyperthermia-Related Intrauterine Thermal Stress Contribute to Cerebral Palsy Risk?

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**Abstract:** Fetal hyperthermia has been documented to lower the threshold for minor intrapartum hypoxic-ischemic events to cause significant brain injury. Excess heat production during the "human stress syndrome," malignant hyperthermia (MH), is still an unproven phenomenon in the fetus. This paper discusses the possibility that such reactions can be induced in susceptible fetuses by fetal hypoxia, reactive oxygen species and heat itself. An indicated prevalence in the Genome Aggregation Database (gnomAD) of 1/300-1075 individuals carrying RYR1 MH alleles, raises valid concerns over the possible overlooked importance of such heat stress reactions. The identification of pathogenic MH gene variants in several children with severe, non-progressive cerebral palsy (CP) referred to a South African clinic from diverse sources, may indicate a need to further investigate a possible relationship between antenatal/intrapartum MH and cerebral palsy (CP). Some of the birth defects and comorbid neurodevelopmental disorders described in CP clinical surveys may represent remnants of intrauterine heat stress in susceptible fetuses. Climatic heat, Infections and fetal hyperthermia due to compromise of the fetomaternal heat gradient caused by placental pathology can be expected to variably interact with Intrinsic fetal hyperthermia when studying the effects of heat stress in pregnancy.

Keywords: Cerebral palsy (CP); Hypoxic ischemic injury (HII); Malignant hyperthermia (MH); Malignant hyperthermia susceptible (MHS); Fetal hypoxia; Heat stress

## INTRODUCTION

A mild 37.5 - 37.9°C temperature increase during labor, bearing down, and/or epidural analgesia is a normal phenomenon. Intrapartum fever, defined as 38.0°C or higher, is generally associated with fetal brain temperatures of 39.5°C or higher [1], [2] which has been associated with a neonatal encephalopathy and cerebral palsy (CP) outcome [3].

In fetuses exposed to an acute hypoxic-ischemic event, even a mild fever lowers the threshold for brain damage. Addition of mild hyperthermia to underlying inflammation and hypoxia in a rat model resulted in damage when these two factors in themselves showed no adverse sequelae. [4] while maternal hyperthermia was shown to increase fetal cytokines without any evidence of chorioamnionitis [5]. Hyperthermia therefore is not only a risk factor acting on its own, but can also facilitate the induction of damage by other risks for hypoxic ischemic injury (HII).

While severe hypoxia-ischemia at birth is generally regarded a less common cause of CP in First World settings, a different situation prevails in low-middle-income (LMIC) countries. A large segment of the South African obstetric patient population is subjected to LMIC intrapartum health risk scenarios and non-genetic HIE-CP represents the most frequent observation in these CP children [6].

It nevertheless remains intriguing why CP only manifests in a minority of newborns born in large maternity units in South Africa, where the same labor management practices had likely been present during the births of scores of babies discharged without adverse neurological outcomes.

 doi:10.20944/preprints202504.0875.v1



HYPOTHESIS – CAN MALIGNANT HYPERTHERMIA SUSCEPTIBILITY BE THE HIDDEN FACTOR BEHIND THE DIFFICULTIES TO LOWER THE PREVALENCE OF NEW CP CASES?

Malignant hyperthermia (MH) is a genetic hypermetabolic reaction characterized by a massive sarcoplasmic reticulum release of intracellular calcium accompanied by a rapid buildup of heat and excess lactate. Triggers other than inhalational anesthetics and atypical MH clinical presentations have been recorded [7]. Apart from technical limitations and ethical considerations, It may be difficult to recognize in fetuses because of the large number of MH pathogenic variants with different functional effects under stress and likely atypical reactions of immature fetal muscle.

At the Brain Function Research Unit at the University of the Witwatersrand, we previously demonstrated abnormal in vitro caffeine- and halothane-induced muscle contractions suggestive of malignant hyperthermia susceptibility (MHS) in several children who had to undergo elective surgery for skeletal defects that were comparable to heat stress-induced defects in experimental animals [8–10]. At the time we proposed a model whereby intrauterine fetal hyperthermia arising through an antenatal malignant hyperthermia-like reaction could have caused these defects [11].

Although limiting antenatal scenarios to anesthetic risk, the European MH Group states that "It is important to remember that there are two different situations in which MH-susceptibility is of major importance in a pregnant patient:

1. The mother is known or suspected to be MH-susceptible (in this case even the fetus may be MH-susceptible)
2. The fetus may be MH-susceptible but not the mother (because the father of the child is known or suspected to be MH-susceptible)" [12].

The fact that heat itself can produce MH reactions potentially links various causes of external heat stress with a fetal genetic hypermetabolic reaction [13].

It is postulated here that a) stress-triggered MH in a fetus could represent a potentially common, actionable and largely overlooked genetic factor increasing their vulnerability to intrapartum hypoxic-ischemic injury (HII) and b) the reported increased prevalence of birth defects in CP children may reflect earlier antenatal heat stress influences in these babies.

## EVALUATION OF THE THEORY

Is a supposedly rare disorder such as MH relevant as a potentially important cause of fetal hyperthermic events? Traditional perceptions concerning the prevalence of MHS are based on the confirmed number of MH reactions during anesthetic procedures. Based on analysis of data from gnomAD, the Genome Aggregation Database set up for large-scale sequencing projects, RYR1 pathogenic variants were found in 1/300 and 1/1075 individuals. "*A prevalence of 1:300 is approximately ten times higher than prior prevalence figures for MH pathogenic variants in the population and up to 833 times the clinically recognized incidence of MH during surgery*" [14]. However, there is not a 1:1 relationship between MHS and MH expression; overall penetrance for RYR1-related MH is considered to be 40.6%. Among individuals with an RYR1 pathogenic variant, the probability of developing MH on exposure to appropriate triggers is 0.25 [15].

**'Stress' plays an important role.** "There is indisputable evidence that humans susceptible to MH have stress-related abnormal responses in the absence of exposure to triggering anesthetic agents" [16], Susceptible humans display signs of MH in stressful situations (the 'human stress syndrome') [17], similar to 'capture stress myopathy' (exertional rhabdomyolysis). In such a situation, body temperature increases rapidly above 42°C together with muscle spasms, stiffness, and paralysis [18]. A similar genetic predisposition background is found in individuals at risk for MH, exertional heat illness (EHI) and recurrent rhabdomyolysis [19].

***Fetal stress associated with normal labor and birth.*** Catecholamine concentrations in fetal scalp samples at the beginning of normal labor are about five times higher than the concentrations in a resting adult and spikes a hundredfold when the mother bears down [20]. While fetal distress during

 doi:10.20944/preprints202504.0875.v1



difficult labor or delivery is not necessarily associated with neonatal complications, the situation may be different in a fetus genetically sensitive to stress.

***Intrapartum hypoxic stress and MH***. Raised intracellular Ca is found in resting MHS muscle cells and RyR1-mediated calcium release occurs at lower levels of stimulation in the presence of MH-associated mutations [21]. An increase in intracellular Ca2+ is a constant early responses in the presence of hypoxia [22].

In a MHS fetus with an increased basal intracellular calcium aggravated by stressful labor, associated with excessively raised catecholamine production, hypoxia causes raised intracellular Ca2+ and reactive oxygen species (ROS). The latter occurs as a result of decreased electron-transport rate and reduced aerobic oxidative respiration in the mitochondria [23]. Excessive ROS appears to trigger MH crises by itself. Oxidative stress during an MH process causes an enhanced sarcoplasmic reticulum Ca2+ leak [24]. This combination of events could set the stage for a runaway fetal MH reaction.

Shared pathophysiological features between HIE and perinatal heat stress sequelae.

- Sites of central nervous system pathology in heat-stressed animals share parallels with specific neuroimaging injury findings in term infants following neonatal HIE. Involvement of the basal ganglia and thalamus can occur under both circumstances [25]. Renal damage and acidosis is found in both HII and MH.
- In the absence of a so-called acute catastrophic (sentinel) event preceding HII, it has been suggested that testing for a RYR1 congenital myopathy should be considered [26].
- Activation of the thermosensitive cation channel TRPV4 after ischemia, was shown to induce damage to the blood-brain barrier in mice. This results in proteins and water leaking into the extracellular space, which causes brain swelling that peaks 3–5 days postdelivery [27]. This is the same time span for brain swelling in newborns after an asphyxic birth.
- Term infants who develop cerebral palsy after neonatal hypoxic-ischemic encephalopathy show early elevated cytokine expression. Inflammatory cytokines are released by heat stress, hypoxia, and the RYR1 Ca-release channel in MH individuals [28], [29].
- Encephalopathy has been described as an initial symptom of rhabdomyolysis in older individuals [30], where MH can be complicated by an encephalopathy. It needs to be investigated whether rhabdomyolysis following an intrapartum MH reaction could theoretically induce a neonatal encephalopathy.
- A link between CNS hemorrhage and RYR1 mutations has been reported [31]. It is suggested that an MH background has to be considered when investigating PAIS in newborns with HII-associated neonatal encephalopathy.
- Neuroradiological demonstration of hypoglycemic encephalopathy in CP newborns do not consistently correlate with available information about neonatal blood glucose levels (Personal observation). While this may be due to inadequate clinical record keeping, an association between blood glucose levels and MH/certain RYR1 mutations may add complexity to this scenario. Basal increased intracellular Ca2+ concentration in MH adversely affects glucose homeostasis. This results in an increased glucose-induced insulin response associated with MH [32]. Under such circumstances, glucose administration in the MHS neonate could more easily lead to a reactive hypoglycemia. Furthermore, a RYR-1 phenotype has been linked with ketotic hypoglycemia [33], also known as ‘accelerated starvation’. Although ketotic hypoglycemia is regarded as a post neonatal problem, there is no reason why this ‘starvation’ syndrome cannot occur in MH newborns with intrauterine growth retardation and reduced glycogen stores [34].

## EMPIRICAL DATA

***Hyperthermia and CP***: Marshall Edwards’ pioneering animal research demonstrated that the central nervous system bears the brunt of damage due to antenatal heat stress **[35] [36].** He first proposed that links between CP and antenatal hyperthermia in humans need to be investigated, albeit in the context of high environmental temperatures.

 doi:10.20944/preprints202504.0875.v1



Fifteen CP children with recurring febrile episodes were observed between 1956—1969 at the Uppsala CP clinic [37]. These especially occurred during emotional stress such as associated with hospitalization. Over a period spanning 10 years or more, five of eleven patients died, four of them in hyperpyrexia. Could these bouts of unexplained high fevers in CP children represent 'human stress syndrome'/non-anesthetic related "*Episodic RYR1-Related Crises*"?

A 2015 poster presentation at a European Paediatric Neurology conference described three individuals with CP and clinical MH manifestations and significant elevations of creatine kinase [38]. One child carried a RYR1 variant of uncertain significance. The possibility was raised of MH testing in CP cases as no other medical or infective causes could be determined despite detailed investigations. The question was asked *"whether genetic testing should be undertaken in CP looking for a predisposition to malignant hyperthermia?"*

***CP genetic clinic experience.*** Previous reports were retrieved of pathogenic MH gene variants in children who attended our Genetic Clinic with mixed spastic/dystonic CP over a four-year period. All had severe, mixed cerebral palsy with prototypical MRI findings of hypoxic ischemic injury (HII). These children tended to have narrow faces with long, slender limbs with narrow hands and feet. The most consistent finding was an increased arm span > height ratio. Due to the abnormal positioning of limbs with significant contractures or dystonia, the deviations in limb proportions were difficult to recognize. These features were not sufficient to label these phenotypes as 'marfanoid'.

***RYR1 pathogenic variants in four CP children (Table I)***. An obscure reference describing an association between MHS-associated ryanodine receptor (RYR1) genotypes and the described phenotype was found in the scientific literature [39]. "*Some individuals (with SELENON or RYR1 mutations) are slender and have a marfanoid habitus but no other features of Marfan syndrome"*. Other features of these cases were noted to include progressive scoliosis with progressive curtailment of respiratory function apart from which the clinical course is otherwise non-progressive. A comment was added to the site on 18 April 2019: "*Chapter retired: histologic diagnosis without strong genetic correlation*". This lack of associating muscle histology with genetic findings does however, not negate the observed relationship between a Marfanoid phenotype and RYR1 findings.

**Table 1.** Next generation sequencing findings of MH variants encountered in referred patients with CP.

| GENE | SITE/CHANGE | MH LINK | Increased arm span: height ratio; slender build |
|---|---|---|---|
| RYR1 | (NM_000540.3):c.7784_7791del, p.(Leu2595ArgfsTer4) | YES | YES |
| RYR1 | (NM_000540.3): c.10348-6C>G. p? | YES | YES |
| RYR1 | (NM_000540.3):c.14524G>A, p.(Val4842Met) | YES | YES |
| RYR1 | (NM_000540.3):c.14803G>A, p.(Gly4935Ser) | YES | YES |
| BChE | (NM_000055.4):c615G>A; p.(Trp205Ter) | YES | YES |
| BChE | (NM_000055.4):c.293A>G;p.(Asp98Gly) | YES | YES |
| STAC3 | (NM_145064.3):c.851G>C, p.(Trp284Ser) | POSSIBLE | Not present |

 doi:10.20944/preprints202504.0875.v1



| | | | |
|---|---|---|---|
| ATPAF2 | (NM_145691.3:c.794G>A; p.(Arg265His) | NO; VUS | YES |

*Two CP patients with BCHE mutations*

A similar phenotype was also observed in two children carrying pathogenic butiryl cholinesterase (BChE) mutations: (NM_000055.4):c615G>A; p.(Trp205Ter) and (NM_000055.4):c.293A>G;p.(Asp98Gly). BChE is a candidate for the study of loss-of-function mutations in humans. Case studies in older patients with BChE mutations described hyperthermia, rhabdomyolysis, and even MH in some patients [40]. Some CP children have been reported to display a discrepancy between ACh receptors and acetylcholinesterase available at the neuromuscular junction [41].

The **STAC3 c.851 G > C variant** which is due to a known ancient mutation in Africans, [42] was encountered in a CP patient without any clinical features similar to the other patients. Information on the European Malignant Hyperthermia Group website indicates that it would currently be premature to include STAC3 variants as diagnostic for MH-susceptibility [43].

A **homozygous ATPAF2 autosomal recessive missense variant of uncertain significance (VUS)** was found in a CP child with a slender appearance with a mitochondrial Complex V Deficiency nuclear type 1. This child showed a typical CP static encephalopathy with CP-typical hypoxic-ischemic encephalopathy MRI findings of the perirolandic-basal ganglia-thalamus (BGT) region. This child had central hypotonia, orofacial dyskinesis, joint contractures, small joint (finger) hypermobility, long slender limbs, narrow hands and feet, long myopathic face, high arched palate, low set ears, strabismus, and a severe kyphoscoliosis. The potential significance of this VUS remains unclear pending further functional gene studies. There is currently no link with malignant hyperthermia [44].

## CONSEQUENCES OF THE HYPOTHESIS

A 'perfect storm' could evolve during the management of the labour in a heat-stressed fetus, when introduced to a cascade of subsequent further heat-inducing events.

**A link between maternal RYR1 pathogenic variants and uterine "Ca2+-sensitization" hypercontractility?** RYR1 gene expression and Ca(2+) release in uterine muscle ryanodine-sensitive stores support uterine contractility during labor [45]. Can MH-associated RYR1 pathogenic variants be responsible for "*Ca2+-sensitization*", a process whereby a given increase in cytosolic Ca2+ leads to a greater contractile force? [46]. Uterine hypercontractility was found to be present in mothers of children who carried MHS pathogenic gene variants, although their own MHS status had not been determined [47].

**Epidural analgesia** The prevalence of epidural related maternal fever (ERMF) generally seems to occur in 15% to 25% of patients during epidural analgesia. In the absence of infection, epidural analgesia during labor has been shown to be associated with an increased risk of fever, defined as a maternal temperature ≥ 38°C [48]. Six cases were described who manifested MH during spinal or epidural anaesthesia [49]. Even if there is no link with MH, this febrile reaction during epidural analgesia may assume significance when superimposed on an underlying hypoxic-induced, fetal hyperthermia stress reaction for which the obstetric management requires operative delivery.

A systematic survey is required to determine the validity, clinical and genetic heterogeneity, and phenotype: genotype correlations of a MH-CP endophenotype. An encompassing gene screening panel needs to be developed to identify CP children and at-risk fetuses to study the questions raised in this article. Challenges which have to be met include a) the high number of variants of uncertain significance (VUS) and the size of the RYR1 gene and b) the possibility of combinations of calcium homeostasis genetic variants with genes not directly involved in Ca2+ regulation, such as those related to oxidative metabolism and membrane excitability [50].

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Should a link between malignant hyperthermia pathogenic gene variants and cerebral palsy be proven, identification of at-risk mothers and fetuses in early pregnancy needs to be pursued, followed by planned labor management and monitoring. This would optimally be done by means of non-invasive, intrapartum brain thermometry to identify fetuses requiring prompt pharmaceutic reversal of an identified MH reaction.

**Data availability:** No datasets were generated or analyzed during the current study.

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