CASE REPORT

# The Role of the Primary Care Pediatrician in Fumarate Hydratase Deficiency

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## ABSTRACT

Fumarate hydratase deficiency, also known as fumarase deficiency or fumaric aciduria, is an exceptionally rare autosomal recessive condition with only 40 reported cases globally caused by a deficiency of the Krebs cycle enzyme fumarase. Affected children may present with an early infantile encephalopathy characterized by developmental delay, poor feeding, failure to thrive, lethargy, hypotonia, or seizures with associated dysmorphisms including frontal bossing, wide-spaced eyes, a depressed nasal bridge and microcephaly. Affected children typically do not survive infancy.

This case reports a female infant over her first year of life, starting from her first well child check since discharge from the neonatal intensive care unit (NICU). Her NICU course was significant subclinical seizures on electroencephalogram now managed with phenobarbital, gastrostomy tube placement, and genetic and metabolic evaluation significant for fumaric aciduria, diagnostic of fumarate hydratase deficiency.

In this case we discuss the critical position of her primary pediatrician in coordinating her care across multiple services including neurology, gastroenterology, medical genetics, high-risk neonatology and home care services in the outpatient setting. We will continue to optimize her daily well being based on family's goals and multidisciplinary team input all while taking into consideration her overall poor prognosis.

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## INTRODUCTION

Fumarate hydratase deficiency, also known as fumarase deficiency or fumaric aciduria, is an exceptionally rare condition with only 40 reported cases worldwide [1,2]. Fumarate hydratase deficiency is caused by an autosomal recessive lack of the Krebs Cycle enzyme fumarase [3]. Fumarase and succinate dehydrogenase are two critical enzymes in this cycle, with fumarase responsible for catalyzing the hydration of fumarate to L-malate [4]. Aside from this role in the Krebs Cycle cycle, fumarate hydratase also acts as a tumor suppressor, and mutations have been connected to predisposition to cutaneous and uterine leiomyomas and renal cancer [4].

Prenatal findings may include polyhydramnios, intrauterine growth restriction, ventriculomegaly or abnormalities of the corpus callosum [2]. Affected children may present with an early infantile encephalopathy characterized by developmental delay, poor feeding, failure to thrive, lethargy, hypotonia, or seizures accompanied by polycythemia, leukopenia or neutropenia [1,3]. On examination, these infants typically have dysmorphisms including frontal bossing, wide-spaced eyes, a depressed nasal bridge and microcephaly [1]. Imaging of the brain typically reveals polymicrogyria and ventriculomegaly [2].

Affected children typically do not survive infancy and those that are surviving beyond childhood typically have severe psychomotor retardation [3]. The degree of neurologic compromise is variable, and the disease may not progress for the first two years of life or may be fatal during this interval [2]. The level of activity of fumarate hydratase has not been connected to this clinical variation [2]. Given this diverse range of clinical manifestations, it has been suggested that even moderate increases in fumarate excretion should be evaluated for fumarate hydratase deficiency and consideration of tumor surveillance protocols [5].

The aim of this article is to discuss the challenges and opportunities associated with the care of a newborn with fumarate hydratase deficiency in a primary care setting.

## CASE REPORT

This is the report of a female infant from birth through the first year of life, born at 39.1 weeks by normal spontaneous vaginal delivery with a past medical history of

fumarate hydratase deficiency and gastrostomy tube dependence.

The patient was born at 39 and 1 weeks to a G1P0 mother with breech presentation. Her parents are first cousins of Uzbek descent. As the Mother had followed with in-system Obstetrics, her Labor and Delivery Team as well as the Neonatal ICU were alerted of her labor due to an abnormal magnetic resonance imaging (MRI) of the brain during the fetal period demonstrating absence of the corpus callosum and ventriculomegaly. The baby emerged crying, with APGARs of 7 and 9 at 1 and 5 minutes, respectively. After delivery, continuous positive airway pressure (CPAP) was initiated and she was unable to be weaned from CPAP and was admitted to the neonatal intensive care unit (NICU) for respiratory distress.

On admission, her physical exam was notable for prominent clitoral hood and edematous labia majora and minora concerning for ambiguity. Other findings included low-set ears and flexed posturing. She was noted to be hypotonic, with poor suck, minimal rooting, weak Moro, and hypotonic posturing.

Genetic evaluation revealed markedly elevated urine fumarate, confirming fumarate hydratase deficiency. Her ammonia was mildly elevated but decreased to a normal range on subsequent testing. Further, her acyl carnitine/free carnitine ratio was 1.6. Her genitalia were found to be slightly virilized, but she had normal cortisol levels and congenital adrenal hyperplasia profile.

An echocardiogram demonstrated a small patent foramen ovale versus a small secundum atrial septal defect with left to right flow across the interatrial septum as well as mild peripheral pulmonary stenosis.

Video electroencephalogram was obtained and demonstrated subclinical seizures. Phenobarbital was initiated on day of life 3 and continued through the day of presentation. An MRI of the brain on day of life 15 revealed an intact corpus callosum, ventriculomegaly and bilaterally hemispheric polymicrogyria, consistent with her diagnosis. Neurodevelopment was consulted in the NICU and recommended Early Intervention.

On day of life 15, a speech and swallow evaluation were completed and recommended against oral feeds. Given the absence of her suck reflex and to prevent risk of aspiration, a gastrostomy tube was placed.

Prior to discharge, the NICU coordinated several follow-up appointments, including Neurodevelopment and High Risk Neonatology. Further, inpatient Social Work connected the family with home nursing and physical therapy.

She was first seen by her pediatrician at 1 month of age. Since discharge, the patient had been well. Her mother had been providing a pacifier frequently to improve coordination, noting some improvement. She was tolerating her G-Tube feeds without reflux, vomiting or diarrhea. The baby was comfortable when swaddled but became fussy when hungry or gassy. Regarding her development, the patient did not smile spontaneously, regard face or regard her hand. She did not follow to midline. She was responsive to sound but did not vocalize. She had equal movements of the extremities but could not lift her head.

At the time of our initial visit, the baby had gained 500 grams since delivery. Her weight was at the thirtieth percentile. Her mother was advised that there is no need to medicate her for the gassiness and the normalcy of this symptom was discussed. This offered a critical moment to advise on the normalcy of fussiness in infants. Framing this as an expected, developmentally appropriate symptom offered this family a valuable moment of normalcy. We also discussed following the baby's weight and tolerance of feeds as we look to continue to advance.

Her mother confirmed that she has all supplies necessary for her feeds. She had seen Gastroenterology, who advised continuation of her inpatient feeding regimen. However, as the baby has grown her mother has worked with pacifier skills and is optimistic about the prospect of oral feeds. The mother had initiated small volume pleasure feeds of roughly 1 milliliter, despite her risk for aspiration. Though initiated without medical guidance, this has permitted the mother to feel more active in her daughter's feeding and assist in her development.

In addition, the baby was able to receive services including home nursing and physical therapy who were seeing the baby with regularity. The family was connected with a Care Coordinator through the pediatrician's office to assist in follow-up appointments and connection to Early Intervention. The providers involved in the visit reached out to the services that had not yet seen the baby, including neurology, gastroenterology and pediatric surgery to assure proper follow up.

Now, as she approaches her first birthday, she has continued to grow adequately on her current feeding regimen, as prescribed by gastroenterology. Fortunately, she has had no complications associated with her gastrostomy tube. She continues on phenobarbital and has not demonstrated overt seizure activity. Aside from a lone Emergency Department visit for fever, attributed to a viral infection, she has been free of health complications.

Primary care appointments during this time interval have given the opportunity to discuss a multitude of topics including feeding, weight gain, constipation, rashes of infancy including nevus simplex, and immunization. Discussing these routine topics alongside her more pressing medical issues provides both the family and providers with a semblance of routine well child care, with priorities and care that is not focused on her underlying diagnosis.

She has followed closely with Neurology, Genetics and Development and Behavior. All teams have had the opportunity to discuss the prognosis with the mother, while also focusing on the progress she has made, despite profound delays. Development and Behavior has assured access to Early Intervention and is working to maximize her PT, OT and Feeding Therapy. Currently, this team is working to engage Palliative Care to foster a more longitudinal relationship with this service. Given the natural history of this condition, this model of care would benefit the family to permit an evolving discussion of the goals of care. Genetics has worked closely with the family to perform proper screening to assess the risk in subsequent pregnancies.

However, her delays have become more pronounced in subsequent visits, and her mother is more aware of her failure to progress. She remains very hypotonic with significant head lag and failure to achieve motor milestones. Despite these challenges, we continue to celebrate moments of normalcy, including teething, routine vaccinations and sleep hygiene.

## DISCUSSION

Fumarate hydratase deficiency is diagnosed by increased fumaric acid and alpha-ketoglutarate on urine organic acid analysis alongside increased succinyl adenosine on urine purine and pyrimidine analysis [1]. Management of these patients includes antiepileptic therapy, gastrostomy tube, feeding therapy, and developmental therapies [1].

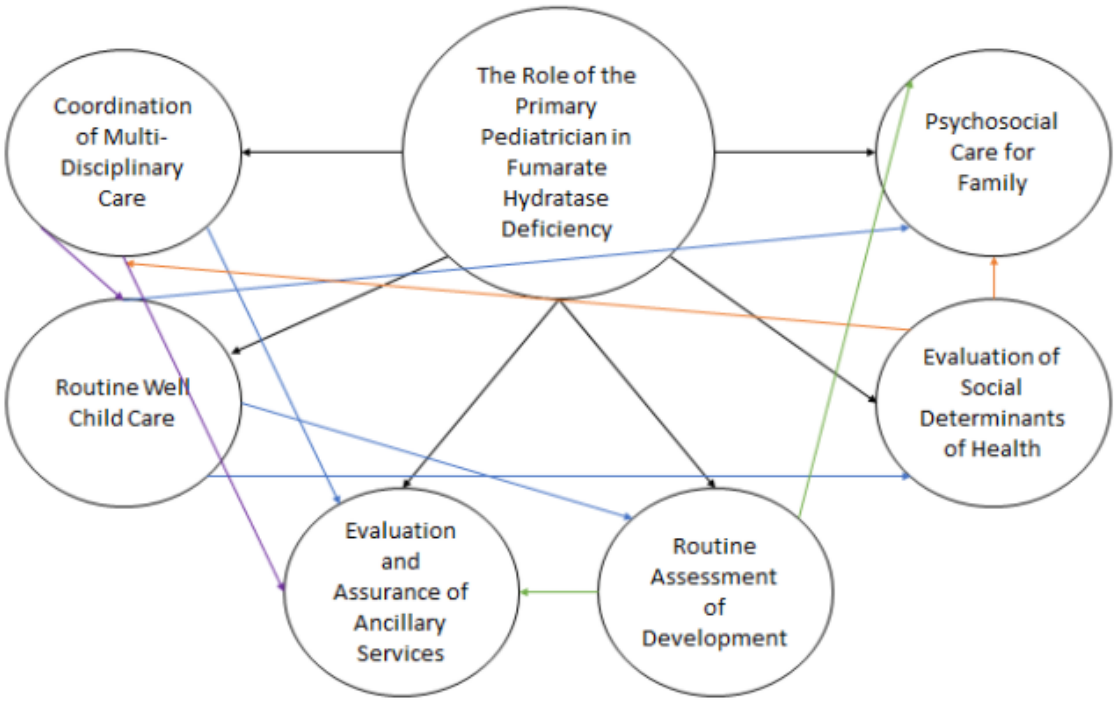
Patients that have heterozygous mutations in fumarate hydratase have been reported to have more mild clinical courses consisting of moderate cognitive impairment and long-term survival [3,6]. Though there is no treatment for this condition, a single report suggests a role of a high fat, low carbohydrate diet in older children with mild phenotypes though other cases do not report improvement with dietary modifications [6].

We have provided routine well child care at typical intervals alongside assessment of development and social determinants of health while providing psychosocial care and assistance for the family. However, these objectives cannot be considered in isolation, and it is imperative to consider their interplay on one another, as exemplified in Figure 1. Though the roles of the primary pediatrician in fumarate hydratase deficiency are numerous, when considering a biopsychosocial model of care, revisiting each of these roles during each visit permits for the most complete care of this complex patient.

*Routine Well Child Care*

In her infancy we will continue to optimize her feeds and monitor growth in coordination with her surgical, nutrition and

**Figure 1:** The Role of the Primary Pediatrician in Fumarate Hydratase Deficiency



gastroenterology teams. In addition to this coordination of subspecialty care, we have not advised against continuation of pleasure feeding, as this offers the mother an important sense of caring for the child without posing a significant risk of aspiration at the small volumes she is currently providing. She has since had to access Emergency Department-level care but regards our team as her primary source of care, calling the office before making trips to the hospital. From the Emergency Department, her Geneticist is contacted, but the robust outpatient notes have improved the understanding of her needs even in this care delivery milieu. In addition, the fundamentals of palliative care extend beyond hospital-level care into the primary care office. Focusing on comfort and goals of care have become routine conversations alongside assuring she has access to the care and services required to best support her development. Though prognostication is outside of the scope and comfort level of her primary team, maintaining transparent communication and opportunities to discuss these topics has been critical in building and maintaining rapport with this family.

*Routine Assessment of Development*

As our patient continues to grow, we will monitor closely for signs of developmental progression or regression as indications of her disease severity. Her mother is becoming more aware of her developmental delay with each visit. As she ages, the inevitable discussion about goals of care given the poor prognosis of this condition will become paramount. The inpatient palliative care team followed her throughout her NICU admission, and the family has been primed with an understanding of the expectations for their daughter regarding her development and life expectancy. The mother of the child has stated that she understands the poor prognosis but would like to have her child for as long as possible.

*Evaluation of Social Determinants of Health*

These challenges have been even more complicated as the father of the baby resides in Uzbekistan and visitation has been challenging in the time of COVID-19. Our team has been working closely with the mother to advocate for the father to be permitted to immigrate to the United States to assist in her care.

*Evaluation and Assurance of Ancillary Services*

The role of the primary pediatrician is critical in coordinating her care across multiple services. This family has already been connected with an in-office Care

Coordinator to assist in this process and to assure timely involvement of Early Intervention services including physical, occupational, speech, and feeding therapy. Fortunately, this was a quick process for our team and after our first visit, she had been connected with appropriate services in the two weeks until our subsequent appointment. This was an especially remarkable feat, as the child has received-home services since initiation of therapies. Similarly, her diligent inpatient Social Work team was able to establish home nursing services which she continues to receive.

*Psychosocial Care for Family*

The Care Coordinator has thus far been instrumental in successful scheduling and completion of appointments. Further, individual provider-to-provider conversations have ensured timely follow-up for this patient. Through close communication with both the primary care team and the family, we have been able to assure regular follow-up, access to medication and supplies and social support. This has also permitted providers and the family to focus on goals of care and shared decision making, including her current feeding plan, rather than on the logistics of office visits and scheduling.

The Care Coordinator in our office is a trained social worker with expertise in navigating the medical, insurance, and legal systems. She has been an asset for the family and for the baby's care. As the baby's lone caretaker, her Mother has relied on the Coordinator to schedule appointments and reminders while also sending requests for medication refills and supply requisitions. This has been instrumental in achieving optimal outcomes for the child as the mother of the child juggles caretaking responsibilities while navigating complex medical and immigration systems.

*Coordination of Multidisciplinary Care*

Thus far, her neurologic medication regimen has not changed and she continues to have no issues with her gastrostomy tube. Fortunately, communication has been clear and easy between services, via email, secure messaging and phone calls. A unified medical record throughout the system has also permitted quick access to all documentation. Aside from communicating medical recommendations, this has also proven fruitful in communicating the goals of her care and the social challenges facing this family.

Our team is eager to continue to care for this patient and her family as we seek to

better understand the progression and outcomes of fumarate hydratase deficiency as her primary pediatricians.

INFORMED CONSENT: Given by parent and article reviewed by parents per authors.

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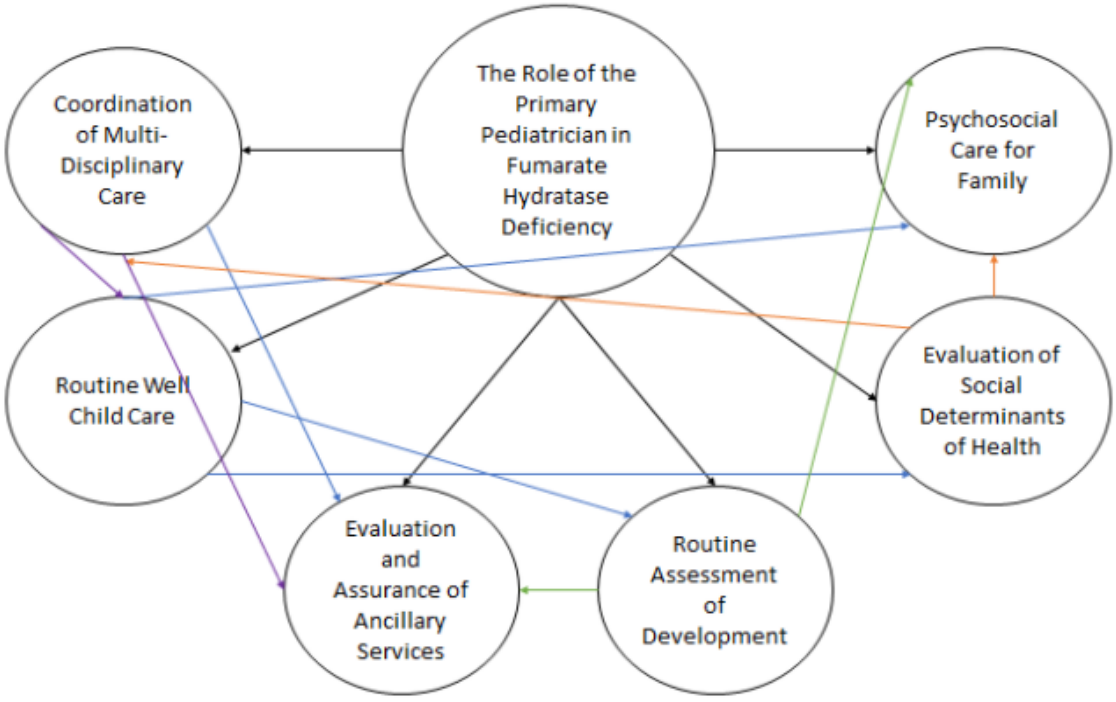
## FIGURES

**Figure 1:** The Role of the Primary Pediatrician in Fumarate Hydratase Deficiency



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