Iron deficiency is a common cause of anemia (IDA) in infancy and can be associated with neurocognitive impairments. Iron-refractory IDA (IRIDA) has recently been described as an inherited cause of IDA due to loss-of-function mutations in the TMPRSS6 gene. IRIDA is characterized by a lack of response to iron replacement. Here we report a new case of IRIDA with its biological parameters and its functional consequences, including neuropsychological impact. The latter was evaluated by the Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition and subtests. We report a 5-year-old French Canadian boy who was incidentally diagnosed with a severe microcytic anemia at 2 years of age (hemoglobin 52 g/L, mean corpuscular volume 50 fL). Except mild pallor, he was asymptomatic of his anemia. Although he had a slight response to intravenous iron therapy, his hemoglobin remained <92 g/L, with persistent microcytosis, low serum iron, but normal ferritin levels. Blood hepcidin level was higher than those of his parents and control (patient 11.2 nM, father 9.06 nM, mother 4.07 nM). Compound heterozygosity for TMPRSS6 paternally inherited c.1324G>A and maternally inherited c.1807G>C mutations were eventually identified. The patient had normal development and growth. Neuropsychological evaluation revealed excellent performance, with high Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition scores (ie, 82nd percentile for both global intelligence and general ability index). In conclusion, TMPRSS6 c.1807G>C in conjunction with c.1324G>A results in IRIDA. In contrast to the usual form of IDA, IRIDA may not be associated with neuropsychological deficits.
degradation of ferroportin, an iron channel localized at the surface of enterocytes, hepatocytes, and macrophages. Consequently, hepcidin limits intestinal iron absorption, recycling, and mobilization from body stores. In the case of deficient matriptase-2 activity, the resulting absence of negative regulation of hepcidin leads to decreased iron bioavailability and an iron deficiency state.3–6 In this article, we report a new case of IRIDA for which we explore the functional consequences, including neurocognitive impact.

MATERIALS AND METHODS

Complete blood cell counts and biological parameters, including serum iron, transferrin saturation, and ferritin levels, were measured on several occasions. Serum hepcidin level was measured with DRG Hepcidin 25 (Bioactive) enzyme-linked immunosorbent assay (DRG International Inc, Springfield, NJ). TMPRSS6 DNA sequencing analysis for IRIDA was performed on peripheral blood from the patient and his parents by the Duke University Health System Clinical Molecular Diagnostics Laboratory. Complete neuropsychological testing included the Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition (WPPSI-IV) and subtests and Conners’ Kiddie Continuous Performance Test and subtests. The study was exempted from our institutional ethics review board because it was a single case review.

RESULTS

A 5-year-old French Canadian boy was referred to our pediatric hematology service because of severe microcytic anemia incidentally found at 2 years of age. His past medical, personal, and family history was irrelevant from a hematologic point of view. At presentation, he had a hemoglobin of 52 g/L and a mean corpuscular volume (MCV) of 50 fL. Serum iron and transferrin saturation levels were 1 μmol/L and 1%, respectively, with a normal serum ferritin at 40 μg/L. He had a normal development, growth pattern, and physical examination except for mild pallor. He partially responded to adequate oral iron therapy with a hemoglobin increase to 78 g/L but remained with unchanged MCV and iron parameters. Multiple investigations were performed, including several negative guaiac stool tests and normal antitransglutaminase antibodies, along with normal IgA level, negative specific milk and soya radioallergosorbent tests, and normal esophagogastroduodenoscopy and rectoscopy (including biopsies). He also had normal blood lead level, sedimentation rate, and C-reactive protein, negative thalassemia testing, and a normal hemoglobin high-performance liquid chromatography. Bone marrow aspirate and biopsy revealed absence of ring sideroblasts, normal erythropoiesis, and iron-depleted Prussian blue staining (1/6). After partial response to oral iron therapy, he received 4 courses of intravenous iron–sucrose infusions (Venofer), which resulted in a mild increase in his hemoglobin level to 92 g/L, with an MCV of 60 fL, but he remained with low serum iron and normal ferritin levels. His blood hepcidin level was measured and found to be higher than that of his parents and control samples (patient 11.2 nM, father 9.06 nM, mother 4.07 nM) despite the microcytic anemia with low serum iron and transferrin saturation levels (Fig 1). TMPRSS6 DNA sequencing for IRIDA was undertaken on the patient and parents. We demonstrated a compound heterozygous state for 2 TMPRSS6 mutations in this patient, a paternally inherited c.1324G>A (exon 11) and a maternally inherited c.1807G>C (exon 15) (Fig 2).

Neuropsychological evaluation including WPPSI-IV scale of intelligence revealed excellent neurocognitive impact.
performance in this child: 82nd percentile for both global intelligence and general ability index. The WPPSI-IV subscales showed excellent performance in most tests: 95th percentile for fluid reasoning, 84th percentile for visual spatial scale, 47th percentile for verbal comprehension, 97th percentile for working memory scale, 16th percentile for processing speed, and 97th percentile for memory scale.

DISCUSSION

The diagnosis of IRIDA has been clearly established in our patient. Findings were asymptomatic hypochromic microcytic anemia, very low serum iron and transferrin saturation levels, normal ferritin levels, inappropriately high hepcidin level compared with patient’s parents, and incomplete response to iron replacement therapy. As expected in this disorder, we documented an elevation of ferritin levels after iron replacement therapy without correction of the anemia, serum iron, and transferrin saturation levels. This finding is explained by the defective activity of TMPRSS6 preventing inhibition of hepcidin transcription, reducing the presence of ferroportin and therefore precluding intestinal iron absorption, recycling, and mobilization.

This patient was compound heterozygous for TMPRSS6 mutations: a paternally inherited c.1324G>A (exon 11) and a maternally inherited c.1807G>C (exon 15). The first mutation (c.1324G>A on exon 11, CUB domain) has been reported as a deleterious mutation causing IRIDA by Finberg et al. This mutation leads to a substitution of glycine to arginine at codon 442 (p.Gly442Arg). The second mutation (c.1807G>C on exon 15, serine protease domain) leads to a substitution of glycine at position 603 to an arginine (p.Gly603Arg). It has been reported once in a Korean female by Choi et al. However, in this particular study, data from biological parents and siblings were unavailable to confirm that both mutations were located on different chromosomes, proving the compound heterozygosity in this autosomal recessive disorder. Our case supports that c.1807G>C mutation in compound heterozygosity with another mutation on a different allele is probably a deleterious mutation responsible for IRIDA. Also, algorithms predicting the effect of amino acid changes on protein structure and function based on the alignment of similar protein motifs (Polyphen, SIFT, MutationTaster) consider this change as probably deleterious.

IDA is a common disorder in infancy. Chronic IDA may result in short- and long-term neurocognitive impairments such as poor language development, motor skills, environmental sound perception, cognitive processes related to visual attention and concept acquisition, and arithmetic school achievement. Some studies report that iron is important for appropriate neurogenesis, myelination, neurochemistry, and bioenergetics. Specifically, the neuropsychological consequences of IRIDA have not been evaluated to our knowledge. Growth and neuropsychological testing were considered normal in our patient. He had excellent performance scored at the time of intelligence evaluation by WPPSI-IV scale. Only selective visual attention was slightly below expected in relation to his overall capacities. Although it is possible that the young age of our patient at the time of the neuropsychological testing may have led to underestimation of potential deficits due to a lack of developmental maturity, our observation supports that IRIDA may not be associated with neuropsychological dysfunction, in contrast to the usual form of IDA. Considering that the environment plays an important role in neurodevelopment and that we have presented a unique case, we can only speculate on the potential role of TMPRSS6 in brain iron homeostasis. It is possible that inappropriately elevated hepcidin and normal to high ferritin levels compared with poor iron reserves may protect the brain in IRIDA. The mechanisms that regulate iron transport through the blood–brain barrier are not fully understood and could differ from those of other systemic organs. Additional studies are necessary to elucidate the role of hepcidin, ferritin, and ferroportin in cerebral iron regulation. In contrast, recent studies have suggested that neurodegenerative disorders can be related to iron accumulation and induced toxicity in neuronal cells. In the future, it would be interesting to explore the impact of TMPRSS6 mutations on neurodevelopment and evaluate the possibility of a protective role against neurodegenerative disorders.

CONCLUSIONS

In summary, we reported a 5-year-old French Canadian boy with IRIDA. We confirm that novel TMPRSS6 mutation c.1807G>C on exon 15 is deleterious in conjunction with another known mutation in the trans position. In contrast to the usual form of IDA, IRIDA may not be associated with neuropsychological impairments. Nevertheless, more studies are needed to explore the neuropsychological impacts of IRIDA.

ABBREVIATIONS

IDA: iron deficiency anemia  
IRIDA: iron-refractory iron deficiency anemia  
MCV: mean corpuscular volume  
WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition
REFERENCES


Iron-Refractory Iron Deficiency Anemia May Not Lead to Neurocognitive Dysfunction: A Case Report
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*Pediatrics* 2016;138;
DOI: 10.1542/peds.2015-3608 originally published online June 30, 2016;

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