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ORIGINAL COMMUNICATION

Cerebellar ataxia and congenital disorder of glycosylation Ia (CDG-Ia) with normal routine CDG screening

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Abstract Cerebellar ataxia can have many genetic causes among which are the congenital disorders of glycosylation type I (CDG-I). In this group of disorders, a multi-system phenotype is generally observed including the involvement of many organs, the endocrine, hematologic and central nervous systems. A few cases of CDG-Ia have been reported with a milder presentation, namely cerebellar hypoplasia as an isolated abnormality. To identify patients with a glycosylation disorder, isofocusing of plasma transferrin is routinely performed. Here, we describe two CDG-Ia patients, who presented with mainly ataxia and cerebellar hypoplasia and with a normal or only slightly abnormal transferrin isofocusing result. Surprisingly, the activity of the corresponding enzyme phosphomannomutase was clearly deficient in both leucocytes and fibroblasts. Therefore, in patients presenting with apparently recessive inherited ataxia caused by cerebellar hypoplasia and an unknown genetic aetiology after proper diagnostic work-up, we recommend the measurement of phosphomannomutase activity when transferrin isofocusing is normal or inconclusive.

Key words cerebellar ataxia · transferrin isofocusing · CDG-Ia · phosphomannomutase

Introduction

Congenital disorders of glycosylation (CDG) are autosomal recessive metabolic disorders characterized by defects in the glycosylation of proteins. CDG type Ia (MIM 212065) is the most frequent CDG and is caused by mutations in the phosphomannomutase (*PMM2*) gene located on chromosome 16p13 [8, 9]. Clinically, CDG-Ia patients present with a multi-system phenotype that may involve many organs. Neurological signs in CDG-Ia can include psychomotor retardation, epilepsy, peripheral neuropathy, hypotonia, and ataxia due to cerebellar hypoplasia. Just a few cases have been reported with isolated ataxia caused by cerebellar hypoplasia without the typical multi-system presentation [1, 2, 7]. In these cases, an abnormal isofocusing profile of plasma transferrin pointed to the diagnosis of CDG-Ia. In this report, we present two similar cases with cerebellar ataxia and normal or only slightly abnormal transferrin profiles.

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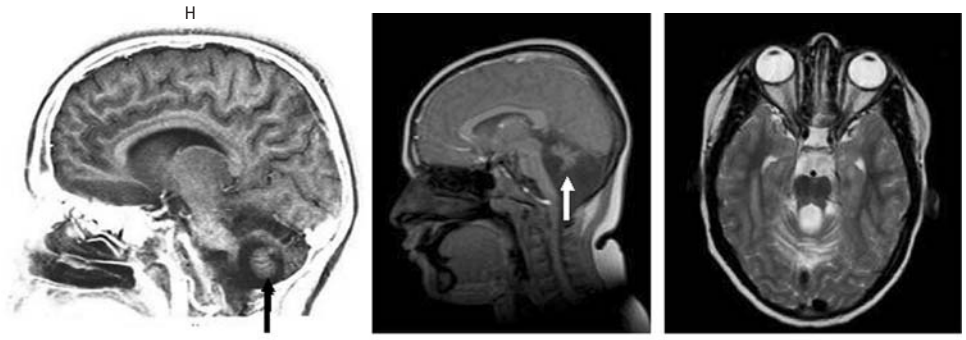
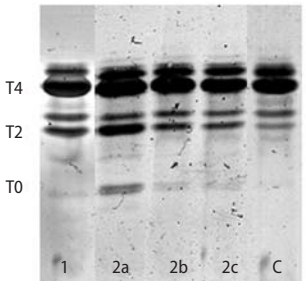
Fig. 1





	1	2a	2b	2c	Reference
T4	51.1	48	62.5	65.9	43.7–68.1
T2	13.8	22	9.5	7.5	2.5–9.8
T0	1.1	4.5	-	-	0–3

Case reports

Case 1

A female patient is the second child of consanguineous parents. Both siblings are healthy. She was born with a tetraloy of Fallot, for which she had surgery. At 5 years of age, she developed coordination problems resulting in a disturbed motor development. At 14 years of age, growth delay was noticed with a bone age of 11 years. Additional investigation revealed absent ovaries. At that time no clinical diagnosis could be made. At the age of 24 years she was referred to a neurologist because of increasing coordination problems. A cerebral MRI displayed severe hypoplasia of the cerebellum and hemispheres (Fig. 1). Seven years later she was re-evaluated in our hospital. At neurological examination a young woman of normal intelligence was seen with gaze evoked as well as spontaneous nystagmus, mild dysarthria, both mild gait and limb ataxia and generalized hypotonia. Routine metabolic screening for CDG showed a slightly abnormal transferrin profile (Fig. 1, lane 1) on subsequent tests. Further CDG diagnostics identified deficient PMM enzyme activity in leucocytes (0.09 mU/mg protein, reference: 0.41–1.81, CDG-Ia range: 0.0–0.17) and fibroblasts (0.07, reference: 1.30–4.58, CDG-Ia range: 0.04–0.59). Mutation analysis of the *PMM2* gene revealed a homozygous missense mutation (c.152A > G; p.Lys51Arg) in exon 2.

Case 2

A male patient was born at term as the first child of healthy, non-consanguineous parents. His motor retardation became obvious from the age of 5 months onwards. On physical examination at 1 year of age he had normal growth parameters and slightly abnormal fat distribution in the sub-mamillar region without dysmorphic features. Neurological examination revealed minimal spasticity of the lower extremities, and both axial and peripheral ataxia. A cranial MRI showed severe cerebellar hypoplasia as well as slight cerebral atrophy without other structural brain anomalies (Fig. 1). Routine metabolic screening at 1 year showed a clearly abnormal transferrin profile (Fig. 1, lane 2a) and deficient PMM enzyme activity in both leucocytes (0.10 mU/mg protein, reference: 0.41–1.81, CDG-Ia range: 0.0–0.17) and fibroblasts (0.57, reference: 1.30–4.58, CDG-Ia range: 0.04–0.59). Mutation analysis of the *PMM2* gene revealed two compound heterozygous missense mutations (p.Arg123Gly/p.Arg162Trp) [10]. At 7 years, the transferrin profile was only borderline abnormal and had completely normalized by 8 years of age (Fig. 1, lane 2c). At his present age (10 years), the boy has a stable clinical syndrome with ataxic gait and a normal transferrin profile, while phosphomannomutase activity in leucocytes remains deficient (0.11, reference: 0.41–1.81, CDG-Ia range: 0.0–0.17).

Discussion

In this report, two patients are presented with cerebellar ataxia. In one patient, transferrin isofocusing was only slightly abnormal in the second decade, while in the second patient, who initially presented with an abnormal pattern, the isofocusing profile had completely normalized the second decade. The MRI in both patients clearly showed cerebellar hypoplasia. So far, two other cases have been described with a normal transferrin profile, one as a sibling from a CDG-Ia patient with an abnormal profile [3], the other because of a strong clinical suspicion of CDG-Ia [5]. Recently, normalization of the transferrin profile in a CDG-Ia case was reported in a child with multi-system presentation with prominent cerebellar ataxia [6]. So far, no reasonable explanation for these observations has been found. The relatively mild clinical presentation in case 1 suggests that the homozygous K51R mutation is a mild mutation, which contributes to the genotype-phenotype correlation in CDG-Ia. On the other hand, some mutations have been associated with a very severe presentation of hydrops fetalis [11]. In general, however, no clear genotype-phenotype correlation could be found [4]. In the diagnostic protocol of recessively inherited cerebellar ataxia, CDG screening by transferrin isofocusing is the standard method. Most patients with enzymatically confirmed CDG-Ia clearly show an abnormal transferrin isofocusing profile. However, our observations indicate that in rare cases a normal transferrin isofocusing profile does not definitely exclude the diagnosis CDG-Ia. Therefore, in patients presenting with a recessively inherited ataxia with cerebellar hypoplasia and an unknown genetic etiology after proper diagnostic work-up, we advise the measurement of phophomannomutase activity if transferrin isofocusing is normal.

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References

1. Bubel S, Peters V, Klein C, Hackler R, Schaefer JR, Hagenah J, Hoffmann GF, Vieregge P (2002) CDG (congenital disorders of glycosylation), Differential hereditary ataxia in adulthood diagnosis. Nervenarzt 73:754–760
2. Drouin-Garraud V, Belgrand M, Grunewald S, Seta N, Dacher JN, Henocq A, Matthijs G, Cormier-Daire V, Frebourg T, Saugier-Veber P (2001) Neurological presentation of a congenital disorder of glycosylation CDG-Ia: implications for diagnosis and genetic counseling. Am J Med Genet 101:46–49
3. Dupre T, Cuer M, Barrot S, Barnier A, Cormier-Daire V, Munnich A, Durand G, Seta N (2001) Congenital disorder of glycosylation Ia with deficient phosphomannomutase activity but normal plasma glycoprotein pattern. Clin Chem 47:132–134
4. Erlandson A, Bjursell C, Stibler H, Kristiansson B, Wahlstrom J, Martinsson T (2001) Scandinavian CDG-Ia patients: genotype/phenotype correlation and geographic origin of founder mutations. Hum Genet 108:359–367
5. Fletcher JM, Matthijs G, Jaeken J, van Schaftingen E, Nelson PV (2000) Carbohydrate-deficient glycoprotein syndrome: beyond the screen. J Inherit Metab Dis 23:396–398
6. Hahn SH, Minnich SJ, O'brien JF (2006) Stabilization of hypoglycosylation in a patient with congenital disorder of glycosylation type Ia. J Inherit Metab Dis 29:235–237
7. Mader I, Dobler-Neumann M, Kuker W, Stibler H, Krageloh-Mann I (2002) Congenital disorder of glycosylation type Ia: benign clinical course in a new genetic variant. Childs Nerv Syst 18:77–80
8. Matthijs G, Schollen E, Bjursell C, Erlandson A, Freeze H, Imtiaz F, Kjaergaard S, Martinsson T, Schwartz M, Seta N, Vuillaumier-Barrot S, Westphal V, Winchester B (2000) Mutations in PMM2 that cause congenital disorders of glycosylation, type Ia (CDG-Ia). Hum Mutat 16:386–394
9. Matthijs G, Schollen E, Pardon E, Veiga-Da-Cunha M, Jaeken J, Cassiman JJ, Van SE (1997) Mutations in PMM2, a phosphomannomutase gene on chromosome 16p13, in carbohydrate-deficient glycoprotein type I syndrome (Jaeken syndrome). Nat Genet 16:88–92
10. Matthijs G, Schollen E, Van SE, Cassiman JJ, Jaeken J (1998) Lack of homozygotes for the most frequent disease allele in carbohydrate-deficient glycoprotein syndrome type 1A. Am J Hum Genet 62:542–550
11. van de Kamp JM, Lefeber DJ, Ruijter GJG, Steggerda SJ, den Hollander NS, Willems SM, Matthijs G, Poorthuis BJHM, Wevers RA (2007) Congenital disorder of glycosylation type Ia presenting with hydrops fetalis. J Med Genet 44:277–280