Middle interhemispheric variant of holoprosencephaly: A distinct cliniconeuroradiologic subtype

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CME

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A distinct cliniconeuroradiologic subtype

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Abstract—*Background:* The middle interhemispheric variant (MIH) is a subtype of holoprosencephaly (HPE) in which the posterior frontal and parietal areas lack midline separation, whereas more polar areas of the cerebrum are fully cleaved. While the neuroradiologic features of this subtype have been recently detailed, the clinical features are largely unknown. *Objective:* To present the clinical manifestations of MIH and to compare them with classic subtypes (alobar, semilobar, and lobar) of HPE. *Methods:* The authors evaluated 15 patients with MIH in a multicenter study. Neuroimaging and clinical data were collected and correlated. They compared the data with those of 68 patients who had classic HPE. *Results:* The frequency of endocrinopathy in MIH (0%) was lower compared with the classic subtypes (72%) ($p < 0.0001$). This correlated with the lack of hypothalamic abnormalities. The percentage of patients with seizures (40%) did not significantly differ from classic HPE. Spasticity was the most common motor abnormality, seen in 86% of MIH patients, similar to other subtypes. The frequency of choreoathetosis in MIH (0%) was lower than that for semilobar HPE (41%) ($p < 0.0039$). This correlated with the lack of caudate and lentiform nuclei abnormalities. Developmental functions, including mobility, upper-extremity function, and language, of the MIH group were similar to the least severe classic type, lobar HPE. *Conclusion:* MIH is a recognizable variant of HPE with differing clinical prognosis. Similar to the lobar subtype by functional measures, MIH differs from classic HPE by the absence of endocrine dysfunction and choreoathetosis.

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Classic holoprosencephaly (HPE) is a brain malformation that results from a primary defect in basal forebrain patterning during the first 4 weeks of embryogenesis.[1] This defect results in incomplete separation of the cerebral hemispheres. Based on the degree of hemispheric nonseparation, HPE has traditionally been classified into three "classic" types: alobar, semilobar, and lobar.[2] A fourth subtype, called the middle interhemispheric variant (MIH) of holoprosencephaly or syntelencephaly, was first identified in 1993.[3] MIH consists of an abnormal midline continuity of the posterior frontal and parietal regions of the cerebral hemispheres, with separation of the basal forebrain, anterior frontal lobes, and occipital regions (figure 1).[4]

Detailed neuroimaging analysis in 21 patients with MIH compared with those observed in classic HPE has been recently reported.[5] In addition to the topographic distribution difference of hemispheric nonseparation, deep gray nuclei differences were also noted. All MIH patients had normal separation of the lentiform nuclei and hypothalamus, unlike the ubiquitous nonseparation of various severities seen in classic HPE. The most commonly affected deep gray nucleus in MIH was the thalamus (nonseparated in 33% of the cases). The topographic distribution of the structures most commonly involved suggested that MIH was caused by a defect in dorsal patterning early in embryogenesis.[5,6]

In the current study, we detail the clinical characteristics of a cohort of MIH patients evaluated through a nationwide clinical research consortium.

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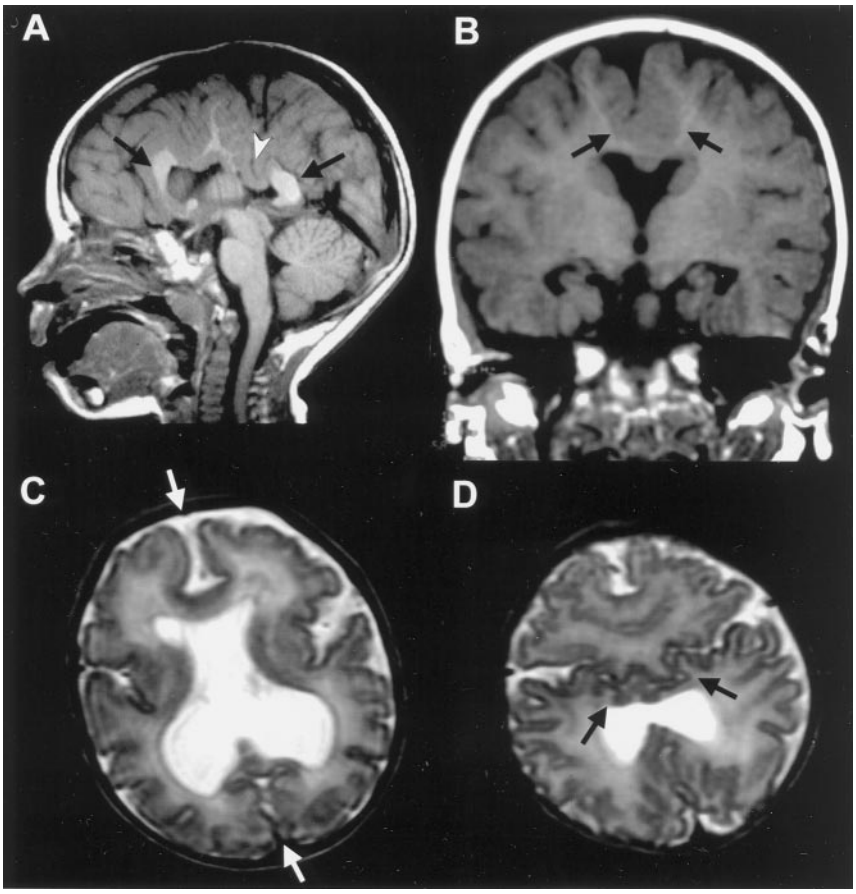


Figure 1. MIH patients' MRIs. (A) Sagittal T1-weighted image through the midline shows the presence of genu and splenium of the corpus callosum (black arrows). The body of the corpus callosum is absent in the region of nonseparated hemispheres (white arrowhead). (B) Coronal T1-weighted image through incompletely separated hemispheres at the level of the body of the lateral ventricle shows continuity of the gray matter (black arrows). The septum pellucidum is absent. The deep gray nuclei are well separated. (C) Axial T2-weighted image shows presence of anterior and posterior interhemispheric fissures (white arrows), as well as, the presence of frontal and occipital horns of the lateral ventricles. (D) Posterior frontal and parietal region axial T2-weighted image shows the abnormally appearing sylvian fissures communicating across the midline over the vertex (black arrows).

The goals of this study were to compare the clinical problems and neurodevelopmental function of MIH with the classic forms of HPE.

Methods. *Patient selection.* Patients evaluated at one of three Carter Centers (a national consortium funded by a nonprofit private foundation) were prospectively enrolled between 1998 and 2001. Confirmation of diagnosis by review of imaging studies and formal evaluation at the Carter Centers were required for inclusion. Each Institution's Review Board approved the study before initiation. Informed consent was obtained from the parents before enrollment.

Neuroimaging assessment. Two pediatric neuroradiologists (E.M.S. and A.J.B.), who were unaware of the patients' clinical status, evaluated the neuroimaging studies. Available imaging included MRI or high-quality CT. To be included in the study, the CT had to have slice thickness of ≤5 mm and adequate image quality to allow for the assessment of key structures (basal ganglia, thalami, and interhemispheric fissure). The type of HPE (alobar, semilobar, lobar, or MIH) was determined by previously published criteria.[2,5,7] The neuroimaging features of subsets of these patients have been previously reported.[5,8,9]

Neuroradiologists graded the degree of caudate, lentiform, and thalamic nuclei nonseparation according to previously published criteria.[8] The portions of the corpus callosum present (determined by assuring that the commissure connected neocortical white matter of each hemisphere) were documented. When imaging allowed, the pituitary gland was subjectively graded as normal or abnormal in size and signal intensity for age. The interocular distance (IOD) was determined by correlating the interpupillary distance and bony interorbital distance with patient age, according to standard techniques.

Clinical assessment and scoring. All 15 patients whose scans were scored as described above received complete evaluations at one of the participating Carter Centers. The evaluations included obtaining medical history from direct questions and review of medical records, physical examination, and assessment of developmental achievements. For comparison, we used the 68 patients with classic HPE types (alobar, semilobar, and lobar) that were evaluated in a similar manner. The clinical characteristics of classic HPE patients have been described in a recent publication.[10]

Results. There were 15 patients (6 boys and 9 girls) identified with MIH who were evaluated at the Carter Centers. The detailed neuroimaging analyses of these patients were derived from MRI (12 cases) and CT (3 cases). The mean age at time of evaluation was 3.8 years (range 0.5 to 14 years). One patient was less than 1 year of age and was excluded from the analysis of motor and developmental functions. All patients had normal chromosomes. All patients had mutational analysis for Sonic Hedgehog and *ZIC2* gene. Only one patient had a documented mutation located in the *ZIC2*.

The clinical and neurologic problems in MIH patients are detailed in the following sections. The comparison of MIH patients with the classic HPE cohort is provided in the Discussion section.

Endocrinopathy and temperature dysregulation. None of the 15 patients with MIH had any type of endocrinopa-

Table *Motor dysfunction*

	No. of patients (%)			
	None	Mild	Moderate*	Severe
Hypotonia	6 (43)	6 (43)		2 (14)
Dystonia	7 (50)	6 (43)		1 (7)
Spasticity	2 (14)	7 (50)	5 (36)	0 (0)
Choreoathetosis	14 (100)	0 (0)		0 (0)
Feeding difficulty	8 (57)	4 (29)		2 (14)

* Only spasticity included a moderate category in the grading scheme.

thy (including diabetes insipidus). None required treatment with replacement hormones. No patient had temperature dysregulation.

Seizures and epilepsy. Six of 15 patients (40%) had a history of at least one seizure. Of these six, only one (17%) had difficult-to-control seizures. Despite being treated with two antiseizure medications, the patient continues to have several seizures each year.

Dorsal cyst, hydrocephalus, and CSF shunting. Four of the six patients (67%) with a dorsal cyst on neuroimaging studies required CSF shunting because of the accompanying hydrocephalus. No patient without a dorsal cyst required shunting. The degree of thalamic nonseparation (graded on a 0 to 3 scale[8]) correlated with the presence or absence of a dorsal cyst; patients with high degree of nonseparation were more likely to have a dorsal cyst (p = 0.029, Mann–Whitney U test).

Seven of 15 (47%) patients were microcephalic at the time of the evaluation. Of these seven, only one patient had a dorsal cyst and did not require a shunting procedure.

Midline craniofacial anomalies. None of the 15 patients had severe midline craniofacial anomalies, such as cyclopia, ethmocephaly, cebocephaly, or premaxillary agenesis. Three patients (20%) had moderate dysmorphic features (two with nonmedian cleft lip and palate and one with a median cleft palate). Nine other patients had only mild facial dysmorphisms, such as a single central maxillary incisor or hypertelorism. Our previous neuroimaging study showed that none of these patients had hypotelorism, and four had hypertelorism.[5]

Motor dysfunctions. Spasticity was the most common motor dysfunction seen in seven of 14 patients (50%) to a mild degree and five patients (36%) to a moderate degree. No patient had severe spasticity (table). Hypotonia of various degrees was the second most common motor problem seen in eight of 14 patients (57%). Dystonia was identified in half of the patients (see the table). None of the patients had choreoathetosis (involuntary movement disorder).

Developmental abnormalities. One of 14 patients (7%) greater than 1 year of age was able to ambulate independently, whereas five (36%) were able to ambulate with support (figure 2). One of 14 patients (7%) had normal upper-extremity function, whereas nine (64%) were able to use their upper-extremity with mild dysfunction.

Speech and oromotor development in MIH patients were delayed. None of 14 patients over 1 year of age had normal speech, whereas three (21%) were able to speak in short sentences and eight (57%) uttered single words (see figure 2). Oromotor feeding difficulties were noted in six (43%) patients (see the table).

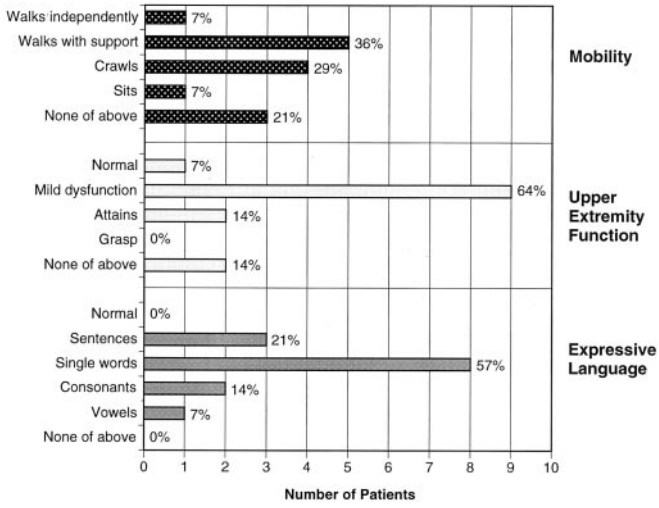


Figure 2. Distribution of developmental function of MIH patients for mobility, upper-extremity function, and expressive language. Sits = patients able to sit independently; attains = patients able to reach and attain objects; grasp = patients able to hold objects when placed in hands; sentences = patients able to speak short multiword sentences; single words = patients able to utter only single words; consonants = patients able to utter consonants sounds only; vowels = patients able to utter vowel sounds only.

Discussion. The classic classification of HPE proposed in 1964 by DeMyer et al.[2] was based on gross neuroanatomic abnormality and provided a convenient subdivision into alobar, semilobar, and lobar types. Advances in neuroimaging over the past decade have led to a better understanding of the pathogenesis of HPE and the variability of this condition.[4,5,8,9,11] In MIH, the posterior frontal and parietal lobes fail to separate in the midline despite a separation of anterior and posterior portions of the cerebral hemispheres. Basal forebrain is nearly normal with a greater formed anterior interhemispheric fissure. Despite the differences between classic HPE and MIH, they share a fundamental similarity, nonseparation of a significant portion of the cerebrum in two separate hemispheres. Mutations in *ZIC2* gene have been recently reported in 16 patients with HPE.[12] This case series was comprised mostly of alobar HPE patients, but also included one patient with MIH (also one of the current study cases). The fact that mutations in *ZIC2* cause classic HPE as well as MIH provides further evidence that MIH is a variant of HPE.

A recent neuroimaging study highlighted the frequent involvement of deep brain structures in classic HPE, such as basal ganglia, thalamic nuclei, hypothalamic nuclei, and mesencephalon.[8] There is a different nonseparation pattern of the deep gray nuclei in MIH. The most commonly affected basal nucleus is the thalamus, whereas the caudate, lentiform, and hypothalamus nuclei are known to be well separated.[5] In the current study, 8 of 15 (53%) had nonseparation of

the thalamic nuclei. Because of these differences, we expected to find a contrasting pattern of clinical problems in MIH patients. The clinical differences between MIH and classic HPE are discussed below.

For the comparison group, we used the 68 patients with classic HPE types (13 alobar, 43 semilobar, and 12 lobar HPE patients) that were evaluated in a similar manner during the same time period. The clinical characteristics of these classic HPE patients have been recently described.[10] For motor and developmental variables, the comparison group was comprised of 46 classic HPE patients who were 1 year or older at the time of evaluation (5 alobar, 30 semilobar, and 11 lobar).

The incidence and severity of endocrinopathies were much lower in MIH (0%) than those of classic HPE (72%) ($p < 0.0001$, Mann–Whitney U test). The degree of nonseparation of the hypothalamus in HPE is consistent with this finding, as MIH patients had a relative lack of hypothalamic involvement but hypothalamic nonseparation was a common finding in classic HPE.[5,8] There was also lack of temperature dysregulation problems in MIH patients, compared with 32% incidence in classic HPE. This may also be due the absence of hypothalamic abnormalities in this subtype.

The frequency of seizures was comparable with the classic types of HPE. Overall, there was no significant difference in the presence of any seizures between the MIH group (40%) and classic HPE (49%). Although the proportion of patients with difficult-to-control seizures in the MIH group was smaller than that of the classic HPE group, this difference was not significant.

Forty percent of patients with MIH had a dorsal cyst. This was lower than the incidence of dorsal cyst in alobar HPE (11 of 12, 92%) but higher than in semilobar HPE (12 of 43, 28%) and lobar HPE (1 of 11, 9%) ($p < 0.0001$, χ^2).[10] The presence of a dorsal cyst in MIH may be due to the relatively frequent involvement of the thalamic nonseparation in MIH as compared with other basal nuclei. A previous neuroimaging study showed that the presence of a dorsal cyst correlated strongly with the presence of nonseparation of the thalamus.[9] The potential mechanisms for the formation of dorsal cyst in HPE have been reported.[6,9] We and others have postulated that the nonseparated thalami block CSF egress from the third ventricle, resulting in expansion of the posterodorsal portion of the ventricle (the path of least resistance) to form the cyst. This in conjunction with a possible dysgenesis of the aqueduct of Sylvius would likely result in hydrocephalus. Thus, the presence of a dorsal cyst is a risk factor for requiring CSF shunting in classic HPE. Since all the MIH patients who required shunting had a dorsal cyst, it appears to have the same prognostic significance in MIH.

The frequency of hypotonia and dystonia in MIH patients was similar to that of lobar HPE patients (Appendix 1). The frequency of spasticity in MIH patients was as high as those of more severe types of classic HPE, possibly reflecting the abnormal cleavage near the motor cortex in MIH. The lack of choreoathetoid involuntary movements in MIH patients may reflect sparing of the caudate and lentiform nuclei in MIH.[5] These structures appear well formed and separated in MIH.

Our previous study showed a high degree of correlation between the grade of classic HPE and the developmental function including mobility, upper-extremity function, and expressive language.[10] For the 14 MIH patients 1 year or older, the developmental grades were similar to those of the least severe form of HPE, i.e., lobar type (Appendix 2). This is not surprising since the extent of interhemispheric nonseparation is similar in lobar HPE and MIH, although the topographic distribution is quite different (basal for lobar and dorsal middle hemisphere for MIH).

It is not uncommon that a physician with less experience in HPE will incorrectly interpret neuroimaging studies of a patient with MIH as lobar HPE. Indeed, it has been the experience of our neuroradiologists that nearly half of all patients referred with "HPE" have not been accurately diagnosed on neuroimaging studies (unpublished data). An accurate diagnosis is crucial, as we have demonstrated differences in outcome and clinical problems between lobar HPE and MIH. Moreover, it is important to distinguish HPE from other conditions with which it is commonly confused, such as genesis of corpus callosum with interhemispheric cyst, since the prognosis and outcome is quite different.

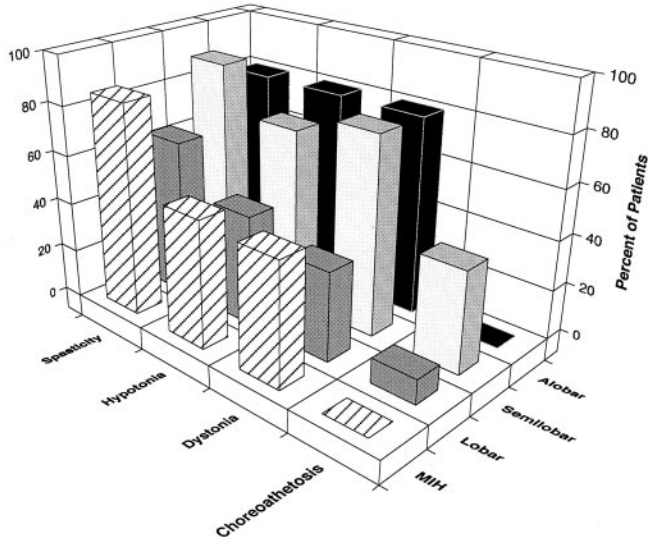
In certain aspects, such as upper-extremity function and expressive language, the MIH patients perform better than classic HPE patients do. Recently, the maturation of cerebral white matter has been noted to be delayed on MRI in most children with classic HPE, while normal in MIH (A.J. Barkovich, personal communication, July 2002). This contrast may be due to difference in underlying mechanisms responsible for classic HPE and MIH (see below). The normal myelination in MIH may play a role in better developmental outcomes in MIH patients.

The pattern of neuroanatomic abnormalities suggests that MIH is caused by impaired induction or patterning of the embryonic roof plate. In mice, expression of *Zic2* is considered important in neural tube closure and roof plate differentiation. Knockdown mutation of *Zic2* in mice results in HPE and defects in neural tube closure (anencephaly and spina bifida).[13] Our previous work also reported an increased incidence of cephalocele formation (a defect of rostral neural tube closure) in MIH patients.[5] Therefore, a defect in dorsal induction is a plausible mechanism for the formation of MIH in humans. The recent discovery of a MIH patient with *ZIC2* mutation further supports this hypothesis.[12] In addition, monosomy 13q was recently demonstrated in five patients with MIH.[14] In this neuropathologic series, it was postulated that a haploinsufficiency of the human *ZIC2* gene, which maps to a critical region 13q32,[15] is responsible for MIH.

While there are no clinical or neuroanatomic features that clearly distinguish HPE patients with *ZIC2* mutations from those without, there are some differences. HPE patients with *ZIC2* mutations lack significant craniofacial malformations, even if the HPE is severe (alobar type).[12] In general, they have a normal or mildly dysmorphic faces, possibly explained by the primarily dorsal effects of *ZIC2*. Since dorsal structures are primarily affected by *ZIC2* mutations, one would expect lesser effects on basal structures, such as face and hypothalamus. This is supported by our previous report that none of the MIH patients had hypotelorism as determined by neuroimaging measurements.[5] In the current series, severe midline craniofacial abnormalities were not observed. This may be due to lack of defects in the induction of neural crest tissue in the mesencephalic neuromere, destined to form the midface.[6] Nevertheless, a small number our patients had clefts of lip and palate. One explanation for this observation is the fact that *ZIC2* mutations account for a small proportion of patients with MIH (only one patient had a documented *ZIC2* mutation). Multiple genetic or environmental etiologies are likely responsible for MIH.

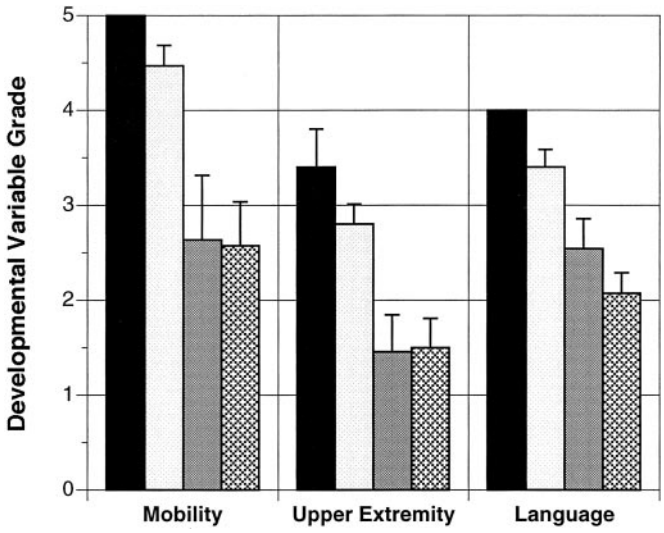
With advances in neuroimaging technology, we have been able to better understand brain malformations. HPE is an example of a disorder that has benefited tremendously from this technology. In addition to the classic HPE types (alobar, semilobar, and lobar), we have been able to characterize the neuroanatomic and clinical features of MIH. Because of the differences in pattern of neuroanatomic abnormalities in MIH, there is a very low incidence of endocrinopathies, hypothalamic dysfunction, and choreoathetosis, while there is a relative high incidence of dorsal cysts and spasticity. Accurate diagnosis of HPE is crucial since the overall outcome and the associated problems are highly dependent on the type of HPE. Through this study, we have shown that correlation of specific morphologic features of MIH with the clinical data allow identification of specific problems.

Appendix 1



Percent of patients with presence of hypotonia, dystonia, spasticity, and choreoathetosis by type of HPE. Variables were dichotomized so that, for all variables, the presence and degree of abnormality (mild, moderate, or severe) were considered positive.

Appendix 2



Mean grades of mobility, upper-extremity function, and language by HPE type. Grades ranges from 0 to 5 for all variables, with 0 indicating normal function and higher grades indicating higher disability. Error bars represent standard error. For MIH patients 1 year or older, developmental grades were superior to those of alobar and semilobar types ($p < 0.01$ for each comparison of alobar vs MIH and semilobar vs MIH). No significant difference in developmental grades between MIH and lobar HPE groups were found. ■ *= alobar;* □ *= semilobar;* ▩ *= lobar;* ▩ *= MIH.*

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Mutations in *GDAP1*

Autosomal recessive CMT with demyelination and axonopathy

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Abstract—*Background:* Mutations in the ganglioside-induced differentiation-associated protein 1 gene (*GDAP1*) were recently shown to be responsible for autosomal recessive (AR) demyelinating Charcot–Marie–Tooth disease (CMT) type 4A (CMT4A) as well as AR axonal CMT with vocal cord paralysis. Methods*:* The coding region of *GDAP1* was screened for the presence of mutations in seven families with AR CMT in which the patients were homozygous for markers of the CMT4A locus at chromosome 8q21.1. *Results:* A nonsense mutation was detected in exon 5 (c.581C>G, S194X), a 1-bp deletion in exon 6 (c.786delG, G262fsX284), and a missense mutation in exon 6 (c.844C>T, R282C). *Conclusions:* Mutations in *GDAP1* are a frequent cause of AR CMT. They result in an early-onset, severe clinical phenotype. The range of nerve conduction velocities (NCV) is variable. Some patients have normal or near normal NCV, suggesting an axonal neuropathy, whereas others have severely slowed NCV compatible with demyelination. The peripheral nerve biopsy findings are equally variable and show features of demyelination and axonal degeneration.

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Charcot–Marie–Tooth disease (CMT) is the most common inherited peripheral neuropathy, affecting 1 in 2,500.[1] The disease is characterized by distal muscle weakness and atrophy, predominantly involving the legs. Demyelinating CMT is characterized by segmental de- and remyelination, onion bulb formation, and severely slowed motor and sensory nerve conduction velocities (NCV). Axonal CMT is characterized by signs of axonal degeneration and normal or slightly reduced NCV.[2]

Molecular genetic analyses showed that CMT is genetically heterogeneous. Autosomal dominant, autosomal recessive (AR), as well as X-linked forms are described.[2] For the AR CMT types, so far 10 loci and

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