Clinical spectrum associated with some structural cerebellar abnormalities

The presence of cerebellar structural abnormalities as the predominant finding on MRI often poses a diagnostic and prognostic challenge to clinicians because the anatomic abnormality itself is non-specific in most cases. The embryologic development of the cerebellum is complex, beginning at approximately 3 weeks of gestation and continuing until 20 months of postnatal life for complete cellular differentiation of the cerebellar layers in humans. The protracted development makes the cerebellum vulnerable to a broad spectrum of developmental disorders, and that is why it is found in a wide range of conditions, including infections, chromosomal abnormalities, Mendelian genetic syndromes, metabolic disorders, neurodegenerative disorders, complex malformations, and sometimes causes cannot be explained. In contrast, it seems relatively ‘resistant’ to prenatal, perinatal, and postnatal hypoxic-ischemic events.

ABSTRACT

Objectives: To review the clinical, neuroimaging, cytogenetic, and biochemical studies obtained in 20 patients with different cerebellar structural abnormalities presenting at variable ages of onset with variable signs and symptoms.

Methods: These patients visited the Clinical Genetics Department, National Research Center, Cairo, Egypt during the period from September 2002 to September 2003. All patients were subjected to complete personal and family history taking 3 generation family pedigree construction and full clinical examination, including complete eye evaluation. Metabolic screening, chromosomal examination and brain CT or MRI, or both, were also carried out.

Results: Patients with cerebellar structural abnormalities were broadly divided into those with cerebellar hypoplasia (15 patients; 75%), cerebellar atrophy (3 patients; 15%) and cerebellar white matter abnormalities (2 patients; 10%). Further, cerebellar hypoplasia was subdivided into cerebello-vermal hypoplasia (4 patients; 20%), vermal-cerebellar hypoplasia (3 patients; 15%) and associated with involvement of other features such as brain stem (4 patients; 20%), posterior fossa (1 patient; 5%); and intracranial calcification (3 patients; 15%).

Conclusion: This study showed that the type of cerebellar structural abnormality is not the main determining factor of the clinical outcome, but rather the underlying etiology. A high incidence of mostly autosomal-recessive inheritance was diagnosed in 65% of the patients with cerebellar structural abnormalities. Nevertheless, the high rate of consanguinity (18 cases; 90%) with mean inbreeding coefficient of 0.05312 and the similarly affected sibs highlights the role of the autosomal recessive gene in our country.

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but not bleeding associated with prematurity, which causes unilateral cerebellar hypoplasia.\textsuperscript{5,6} Cerebellar symptoms of truncal ataxia and dysmetria only become evident at a time when integration of higher neocerebellar functions are achieved during motor development, and these symptoms may change depending on the stage of general motor development, improving with maturation of the motor system or becoming more evident with higher demands on motor co-ordination.\textsuperscript{7} Children who never achieve motor functions such as sitting and walking may never exhibit their cerebellar dysfunction. Improving brain-imaging technologies has arisen perplexing problems of categorization and syndrome delineation, as more subtle structural anomalies can now be identified. However, the ability to predict the degree of motor and cognitive impairment based on the gross appearance of brain images has been problematic.\textsuperscript{4} Alternately, it is often difficult to be sure whether abnormal cerebella identified in children with signs and symptoms referable to the cerebellar structural abnormalities represent atrophy or hypoplasia.\textsuperscript{8} Anatomical, embryological, imaging-based classifications schemes for cerebellar structural abnormalities have been proposed.\textsuperscript{1,2,6,9,10} In broad terms, it appears that the cerebellar abnormalities could be divided into cerebellar hypoplasia (CH), cerebellar atrophy (CA), cerebellar dysplasia, and white matter abnormalities.\textsuperscript{10} Differentiation of CH from prenatal onset atrophy and even postnatal onset atrophy is not always possible on imaging.

This study aims to review the clinical, neuroimaging, cytogenetic and biochemical studies obtained in 20 patients with different cerebellar structural abnormalities that presented at variable ages of onset with variable signs and symptoms. We choose to focus on the relatively more common malformations, and those in which there has been considerable confusion regarding delineation, prognosis, or both. They are: cerebello-vermal hypoplasia, vermal-cerebellar hypoplasia, CH associated with other manifestations, CA and white matter abnormalities (WMA), and we will discuss these structural manifestations seen on MRI, in relation to the etiology, highlighting the clinical features and inheritance.

**Methods.** The study included 20 patients (12 boys and 8 girls), in which cerebellar structural abnormalities as a predominant finding (detected by MRI and CT) had been identified. These patients visited the Clinical Genetics Department, National Research Center, Cairo, Egypt during the period from September 2002 to September 2003. Cases with retro-cerebellar subarachnoid cysts were excluded. We considered the following data for all the patients: age at last observation, gender, pedigree analysis, history of similarly affected family members, pre-, peri-, and postnatal history, and psychomotor development. All patients were subjected to full clinical evaluation with special emphasis on the neurological assessment regarding tone, reflexes, Babinski sign, gross motor function, function of the lower extremities, and fine motor functions as well as examination of the cranial nerves and sensations in co-operative patients. Further, each patient was reviewed for the clinical signs associated with cerebellar abnormalities (microcephaly, macrocephaly, hypotonia, hypertonia, ataxia, impaired co-ordination, autism, strabismus, and nystagmus). All patients were subjected to complete eye evaluation. Visual evoked potentials (VEP) were carried out for patients who showed optic atrophy. Chromosomal examination from peripheral blood lymphocytes was performed for all patients according to the modified method of Verma and Babu.\textsuperscript{11} The GTG-banding technique was carried out according to Seabright.\textsuperscript{12} Karyotyping was performed according to the International System for Human Cytogenetic Nomenclature (ISCN).\textsuperscript{13} For each case, at least 30 metaphases were analyzed to detect chromosomal aberrations and to assess the stability of chromosomes. Metabolic screening for amino acids in blood and urine using thin layer chromatography was carried out for all patients. In addition, patients were selected for further investigations based on the neuro-imaging findings of cerebellar structural abnormalities. Enzymatic assay for the arylsulphatase enzyme, α and β subunits of the hexosaminidase enzyme, and blood level of lactate and pyruvate were carried out for patients that showed CA, cerebellar WMA, or both. These patients were subjected to further biochemical investigation for very long chain fatty acids (VLCFA), and phytic acid and pristanic acid using the gas liquid spectrophotometer. Serological tests for congenital infections for toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH) were carried out for all patients except those with loss of acquired milestones. Electroencephalogram (EEG) examinations, brain CT, and MRI were carried out for all patients. Electromyogram (EMG) and nerve conduction studies were carried out for selected patients (patients showing hypotonia, or high signal of the cerebral or cerebellar white matter). Based on brain CT and MRI findings, patients were divided into those with CH, CA, and cerebellar WMA. Cerebellar hypoplasia was subdivided depending on whether the main structural abnormality or lesion was confined to the vermis,
pontocerebellar, or both cerebellar hemispheres. Cerebellar hypoplasia denotes reduced cerebellar volume, whilst cerebellar shape is (near) normal and fissures are of normal size compared with the folia. An additional pattern of CH was increased interfoliar cerebrospinal fluid spaces on the vermis or hemispheres, or both, leading to a “skeleton-like” appearance of the cerebellum at the time of initial imaging when imaging was performed at the onset of symptoms or signs or showing no evidence of progression.10 Cerebellar hypoplasia associated with CSF collection that appeared continuous with the fourth ventricle with elevation of the tentorium and hydrocephalus is known as Dandy-Walker malformation (DWM). The Dandy-Walker variant (DWV) consists of malformations with less severe cerebellar vermis hypoplasia, less notable or absent upward rotation of the vermis, communication between the fourth ventricle and subarachnoid space and no hydrocephalus.10 Cerebellar atrophy was diagnosed when increased interfoliar spaces on the vermis, hemispheres, or both, and enlarged fissures developed during the course of the disease and were progressive. The “skeleton-like” appearance can also be seen in the end stage of CA. Cerebellar WMA were characterized by a focal or diffuse high signal on T2-weighted images. Abnormalities of the dentate nuclei (DN) were seen as a signal change in and around the DN due to deposition of metabolic products, calcification or demyelination.10

Statistical analysis of data was carried out using SPSS for Windows Release 6 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, mean and standard deviation of the mean were calculated.

Results. Twenty patients (12 boys and 8 girls) presenting with different cerebellar structural abnormalities were examined in the present study. Their ages ranged from 4 months to 21 years with the mean of 4.01 ± 0.69 years. The gender ratio was 0.6 in the total group showing male predominance. The mean maternal age at the birth of an affected child was 26.6 years, and the mean paternal age was 33.4 years. Consanguinity was documented in 18 patients (90%) and our sample included 2 sibships from consanguineous marriages. Patients are classified according to the brain CT and MRI findings into: 1. Patients with cerebellar hypoplasia (15 patients; 75%): Cerebello-vermal hypoplasia; first 4 patients (4 patients; 20%). Vermal-cerebellar hypoplasia; patients 5, 6, and 7 (3 patients; 15%). Cerebellar hypoplasia associated with involvement of other features: Brain stem hypoplasia; patients 8, 9, 10, and 11 (4 patients; 20%). Posterior fossa malformation; patient 12 (1 patient; 5%). Intracranial calcification; patients 13, 14, and 15 (3 patients; 15%). 2. Cerebellar atrophy: patients 16, 17, and 18 (3 patients; 15%). 3. Cerebellar WMA; patients 19 and 20 (2 patients; 10%). Table 1 summarizes the clinical features associated with the 20 patients with structural cerebellar abnormalities. Serological tests showed high IgM for cytomegalovirus in patients 13, 14, and 15, while metabolic screening showed the presence of branched chain amino acids detected with the 2,4-dinitrophenylhydrazine (DNPH) test in the urine of patient 16, suggesting the diagnosis of maple syrup disease. In addition, patient 17 had high C26 (4.35 µg/ml n=0.3-0.9 µg/ml), C26/C22 (1.74 µg/ml; n=0.01-0.44 µg/ml), C24/C22 (1.64 µg/ml; n=0.655-1.01 µg/ml), and pristanic acid (4.28 µg/ml; n=0.1-0.25), but normal phytanic (0.73 µg/ml; n=0.1-4 µg/ml) suggesting the diagnosis of peroxisomal disorder. An enzymatic assay for patient 18 showed low enzymatic activity of α subunits (1.2 µmol/l/h normal range 50-200 µmol/l/h), but normal levels of β subunit (716 µmol/l/h normal range 700-3500 µmol/l/h) of the hexosaminidase enzyme suggesting Tay-Sachs disease, while patient 19 had evident low enzyme activity of α (1.6 µmol/l/h normal range 50-200 µmol/l/h) and β (386 µmol/l/h normal range 700-3500 µmol/l/h) subunits of the hexosaminidase

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Developmental delay or learning difficulty</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Loss of acquired milestones</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Microcephaly (&gt; -3SD)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Macrocephaly (&gt; +2SD)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Seizures</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Hypertonia or spasticity</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Abnormal movements, intention tremors, head nodding</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Autistic features</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Bilateral optic atrophy</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Peripheral neuropathy, radiculopathy* (for 8 cases)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Abnormal VEP* (for 12 cases)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

*Carried out for a limited number of patients, VEP - visual evoked potentials
enzyme indicating Sandhoff disease. Chromosomal examinations for all patients showed normal results, but one with spontaneous breaks.

Discussion. The cerebellum is involved in more than just motor control, which is further suggested by this clinical series of 20 patients with cerebellar structural abnormalities. Defining and classifying congenital abnormalities of the cerebellum can be difficult and confusing. Cerebellar hypoplasia accounts for most of the congenital abnormalities that affect the cerebellar hemispheres. It is a heterogeneous group of disorders. It can be either clastic or neurodegenerative in origin, unilateral or bilateral. It could be an isolated finding or associated with posterior fossa, brain stem, or cerebral malformations or as a part of multiple congenital abnormalities. The neuroimaging of 3 patients, 2 sibs (patient 1 and 2) and a sporadic patient (patient 3), showed cerebello-vermal hypoplasia of variable severity. The anterior lobulus of the vermis is affected in mild forms, whereas the whole vermis is involved in more pronounced forms, frequently together with mild to moderate involvement of the neocerebellum. The most severe case (patient 3), showed marked hypoplasia of the vermis and hemispheres. There was no patient with isolated hemispheric involvement. The question that arises in describing these patients is what is the best diagnosis? A general approach is to call them non-progressive congenital ataxia (NPCA) because they presented with hypotonia and developmental delay, followed by ataxia. Non-progressive congenital ataxia is a rare but well-recognized chronic encephalopathy. With progression of the disease, the 2 patients (patients 2 and 3) developed mild spasticity, hypertonia, and occasionally these children develop mildly focal or segmental dystonia, which is similarly observed in children with NPCA. Ataxia is a non-progressive, but persistent symptom. Similarly to our patients, major problems arise in the majority of these subjects related to cognitive impairment, and less to neurologic symptoms. Clinical and neuroimaging findings do not help in defining any subgroups of NPCA (CH of the granular cell layer or disequilibrium syndromes), and it seems most likely that only progress in the genetics of ataxias will give more information. In accordance with the established literature, our study showed that the degree of clinical symptoms was neither concordant with the severity of neuroimaging findings, nor with the degree of ataxia, and it does not predict cognitive outcome. In patient 3, seizure disorder was present and it seems most likely that seizures are related to poor cognitive outcome. Alternately, occasional reports of patients with CH without any obvious clinical symptoms were reported. In the literature, there are families with autosomal recessive, autosomal dominant, and X-linked inheritance, as well as sporadic, single cases. Based on consanguinity and the affected girl and boy (patients 1 and 2), autosomal recessive inheritance was suggested. As regard to the male patient (patient 3), it is very difficult to judge whether it is a sporadic case or that of autosomal recessive, dominant mutation, or X-linked inheritance.

Cerebellar hypoplasia appears to be a frequent additional feature in many Mendelian syndromes, as reviewed by Bordarier and Aicardi. Although patient 4 had CH, brain atrophy, and hypogenesis of the corpus callosum, she presented with psychomotor retardation and failure to thrive. In addition, she had mask-like face with high forehead, blepharophimosis nystagmus, upturned nostrils, low set ears, high-arched palate, low-set ears, congenital joint contractures, and arachnodactyly. These phenotypic manifestations meet with the diagnostic criteria of Marden-Walker syndrome. Moreover, the constellation of clinical features and the MRI findings has left no doubt about the diagnosis of Marden-Walker syndrome, since cerebellar malformations are widely reported in association with this syndrome. Not only cerebellar hypoplasia was reported in association with Marden-Walker but also Dandy-Walker malformation (DMW). The variability of the type of the structural abnormalities of the cerebellum associated with this syndrome suggests that prenatal CNS dysfunction, mainly of the cerebellum, may play a significant role in the pathogenesis of Marden-Walker syndrome. Patients 5, 6, and 7 had vermo-cerebellar hypoplasia, however, it is associated with normal position of the cerebellar vermis relative to the brainstem or minimal upward rotation due to a mildly enlarged 4th ventricle, without elevation of the tentorium cerebelli. The retrocerebellar fluid collection (not technically a cyst) is generally smaller than that seen in true DWM, but does communicate directly with the 4th ventricle, as in DWM. These conditions are rare, but are likely to be under diagnosed and often misdiagnosed as “Dandy–Walker variant.” Patients 5, 6, and 7 presented with developmental delay, hyperactivity, autistic behavior, ataxic gait and negative molecular test for fragile-X. These patients were diagnosed as idiopathic autism (diagnosis of autism was based on DSM-IV criteria, confirmed primarily by the Autism Diagnostic Interview). The cerebello-vermal hypoplasia evident in the neuroimaging is of variable severity associated with increase of the retrocerebellar fluid. The whole
vermis is affected in mild forms, whereas the posterior (mainly lobules VI and VII) vermis is involved in more pronounced forms. Our data confirm these recent associations between idiopathic autism and cerebellar vermal abnormalities.\textsuperscript{24,25} However, these abnormalities are independent of cognitive status. Our findings emphasize the possible role that the posterosuperior vermis plays in the pathogenesis of some of the characteristic features of autistic behavior.

Cerebellar hypoplasia with pontine hypoplasia, and possible cerebral atrophy, demyelination of white matter, or both, was evident in 4 patients. The constellation of these features was known as pontocerebellar hypoplasia. It is a separate group of autosomal recessive neurodegenerative disorders with fetal onset.\textsuperscript{11} Barth,\textsuperscript{11} distinguished 2 forms of pontocerebellar hypoplasia, PCH1 and PCH2, on the basis of clinical and neuroradiological patterns. It is important to stress that they cannot be differentiated by neuroradiologic findings alone.\textsuperscript{14} The hallmark of PCH1 is the presence of spinal anterior horn degeneration similar to Werdnig-Hoffmann disease. Presentation in the neonatal period is characterized by respiratory insufficiency, frequent congenital contractures, and a combination of central and peripheral motor signs. Patients usually die during the infantile period.\textsuperscript{26} In contrast, the characteristic features of PCH2 are the presence of chorea/dystonia, which is often severe, without the impaired spinal anterior horn cells, microcephaly and severely delayed mental and motor development. They frequently die during childhood.\textsuperscript{26} Neuronal degeneration in both types of PCH is non-specific. The diagnosis of pontocerebellar hypoplasia type II could be confirmed in patients 8, 9, 10, and 11 by the typical clinical and MRI findings.\textsuperscript{14,21,27} In these patients, the MRI showed, in addition to pontocerebellar hypoplasia, cortical atrophy and delayed myelination in 3 patients. This is in accordance with the reported literature,\textsuperscript{26,28} and suggests that delayed myelination can occur in some patients with PCH2. Febrile seizures, and possibly severe epilepsy with paroxysmal multifocal activity, have also been reported in the literature.\textsuperscript{14,21,28} However, the absence of seizures does not rule out the diagnosis of PCH2.\textsuperscript{29} The 4 patients had not developed seizures until we examined them. It is noteworthy to mention that; pontocerebellar hypoplasia is also present in carbohydrate-deficient glycoprotein syndrome and olivopontocerebellar hypoplasia/atrophy (OPCH/A).\textsuperscript{30} The presence of postnatal microcephaly and fat pads above the buttocks and lipoatrophy affecting the thighs can easily be distinguished from PCH. Differently from PCH, the pons and medulla are only slightly atrophic in cases of OPCH/A. Another newly discovered entity; progressive cerebello-cerebellar atrophy, which bears some similarity to PCH2. However, this disorder can be ruled out because the cerebellar changes were progressive and not recognized at birth with no pontine involvement, and these patients develop severe spasticity.\textsuperscript{31} Based on consanguinity and similarly affected sibs, autosomal recessive inheritance has been recognized.

Cerebellar hypoplasia may be associated with malformations of the posterior fossa, including the DWM/DWV. In fact, DWM/DWV is a distinct malformation occurring in at least 1 in 5000 live born infants.\textsuperscript{31} Despite over a century of experience with DWM, our understanding of the etiology, classification, outcomes and underlying biology of this and related malformations remains limited. Of the 20 cases with cerebellar abnormalities, one patient (5%) had evident DWM/DWV. This patient had all the features consistent with DWM. The DWM/DWV could be an isolated finding or in association with single gene disorders, clinically recognizable genetic syndromes, or other multifactorial conditions.\textsuperscript{32,33} Further, it was found as an associated finding in a wide array of chromosomal anomalies, most commonly trisomy 18, trisomy 9, and trisomy 13.\textsuperscript{34} The MRI findings in the present patient showed in association with DWM, agenesis of the corpus callosum, and this was in accordance with the literature.\textsuperscript{10,35} The prognosis for children with DWM/DWV is guarded. The long term outcome of DWM/DWV is very variable: from marked ataxia and cognitive delay through mild involvement to a few exceptional patients with normal motor and cognitive development.\textsuperscript{4} Patients in the present study with DWM/DWV had moderate developmental delay and ataxia. Moreover, the heterogeneous nature of DWM/DWV makes counseling for recurrence risks difficult. Our patient had isolated DWM. In the absence of a family history, this patient is most likely sporadic with an empiric risk of 1-5%.\textsuperscript{30} Familial patients with isolated DWM/DWV are rare.

Cerebellar development is affected by congenital infection most commonly CMV infections.\textsuperscript{3} A wide spectrum of abnormalities were reported, ranging from normal anatomy to almost complete cerebellar agenesis. It varied directly with the time of infection prenatally. The appearance of complete lissencephaly, periventricular calcification and cerebellar hypoplasia in patient 13 are in favor of infection early in pregnancy.\textsuperscript{36,37} In contrast, CMV infection acquired late in pregnancy are clinically less prominent. Patients 14 and 15 had CH and periventricular calcification suggesting late pregnancy infection for these patients.\textsuperscript{38}
Metabolic disorders frequently affect the cerebellum, and some are characterized by rather specific, others by more general imaging features. Patient 16 was diagnosed as maple syrup disease (based on biochemical analysis) at the age of 16 years. Taking into consideration that maple syrup urine disease is characterized by rather specific cerebellar manifestations, which show (on MRI) severe reversible cerebellar and brain stem edema during acute metabolic decompensation. After the acute metabolic decompensation subsides, then cerebral and cerebellar manifestations may disappear totally, or leave a well-defined, low-density zone around the lateral ventricles and small, low-attenuation lesions within the cerebellum and brainstem. With the disappearance of the edema, some loss of brain substance becomes obvious. However, this could explain why this patient presented at the age of 16 years with cerebral and cerebellar atrophy rather than edema. Maple syrup disease is an autosomal recessive metabolic disorder caused by deficiency of branched chain o xo- (or keto-) acid dehydrogenase. It has either severe classical (75% of all affected patients) or intermediate clinical phenotypes. Typically, our patients’ complaint was seizures that started at the age of 6 years (but was diagnosed as idiopathic epilepsy), drowsiness, and went into unexplained progressive coma, which aroused the suspicion of CNS infection (unproven). At a more advanced stage, neuro-vegetative signs with respiratory distress, hiccups, apneas, bradycardia, and frequent coma state were the causes of referral of this patient for further evaluation. Indeed, this patient is of the intermittent type, which could explain the late age of diagnosis.

Although the MRI features of CA are often non-specific, systematic analysis of the finer details of disease involvement may permit a narrower differential diagnosis, which the clinician can then further refine with knowledge of patient history, clinical testing, and metabolic analysis. Patient 17 gave a history of loss of acquired milestones at the age of 1.5 years, optic atrophy and mild sensorineural hearing loss. In addition, biochemical tests showed high C26, C26/C22, C24/C22 and pristanic acid, suggesting peroxisomal disorder. The phenotypic variability in peroxisomal disorders can be wide and varied based on the existence of an expanding number of genetic diseases in which there is an impairment of one or more peroxisomal functions. Neuronal involvement in the peroxisomal disorders is divided into 2 main groups: developmental and post developmental or degenerative. The post developmental neuronal lesions involve specialized sensory neurons of the retina and the inner ear, resulting in visual defects and sensorineural hearing deficits. Neuronal atrophy or loss, or both, is seen in both the dorsal-root ganglia of adrenomyeloneuropathy and cerebellum. Cerebellar atrophy in our patient was symmetrical, but the vermis displayed more severe atrophy than the lateral hemispheres. The distal tips of folia showed the greatest neuronal loss. Residual Purkinje cells showed progressive degeneration, and this is in accordance with the literature. The underlying pathophysiology of these neuronal lesions is postulated to be caused by the incorporation of abnormal fatty acids into neuronal membranes, leading to an unresponsiveness to neurotrophic factors necessary for normal function and survival, or to increased permeability of calcium channels and cell death.

Patients 18 and 19 are good examples that the same metabolic disorder can cause different imaging findings, as different amounts of residual enzyme result in presentation at different stages of cerebellar development. Both of our patients presented with severe psychomotor retardation and ataxia. At the progressive stage of the disease, dystonia, choreiform movements, and athetoid posturing were observed. The MRI of the former showed cerebral and CA. In contrast to the latter, that had demyelination of the cerebellum and the demyelination process of the neural tracts of mesencephalon (extending from the midbrain to the medulla). Based on the enzymatic assay, marked deficiency of both hexosaminidase A and B in patient 19 but only hexosaminidase A in patient 18 suggested the diagnosis of Sandhoff and Tay-Sachs disease. The GM2 gangliosidosis is an autosomal recessive lysosomal storage disease, in which lysosomal enzyme substrates accumulate and cannot be eliminated from the cells. It is caused by the deficiency of both hexosaminidase A and B, and characterized by marked CA with only mild cerebral atrophy in Tay-Sachs disease, while patients with Sandhoff disease also had bilateral homogeneous thalamic hyper density. There are 3 major biochemically distinct types: B, O, AB. Among the B and O types, infantile, juvenile, and adult forms can be distinguished. The 2 most common forms are Tay-Sachs disease, which results from a deficiency of the lysosomal isoenzyme b-hexosaminidase A, and Sandhoff disease, which is attributable to a deficiency of both the b-hexosaminidase A and B isoenzymes. Cerebellum white matter involvement and brainstem structure were not surprising in patient 19, as it was evident in the reported patients in various quantities. Brainstem involvement appeared as a construction from the internal capsule involvement and descended downward along the long fiber tracts of the pons through the crus cerebri. Therefore, brainstem involvement was regarded secondary to...
the primary supratentorial white matter abnormality. Absence of seizures and Cherry-red spot macula in our patients made the clinical diagnosis very illusive, as seizures were reported in most of the cases. However, the authors considered that cherry red spot is not pathognomonic although, one of them had optic atrophy, which was similarly reported in these patients. No correlation between the clinical findings of the disease (severity of the developmental delay) and central nervous system involvement (evident on MRI) has been observed.

Patient 20 had cerebellar WMA in addition to his characteristic clinical picture (growth failure after a normal delivery, microcephaly and facial dysmorphisms, neurodevelopmental and later neurological dysfunctions, mental retardation, ocular abnormalities, and chromosomal analysis showed multiple spontaneous chromosomal breaks in 30% of the studied cells). No specific chromosomal sites were detected. The total number of chromosomal breaks/number of studied cells (break/cell) was 0.56. These features suggest the diagnosis of Cockayne syndrome. Cockayne syndrome is a rare autosomal recessive disorder characterized by progressive multisystem degeneration and severe neurological impairment that begins in early infancy, and death usually occurs before the age of 12 years. It has a wide range of phenotypical expressions and it was classified into 4 main categories, classical, severe, mild and unusual, whose clinical diagnosis requires the collection of clinical signs, laboratory data and investigations. Our patient represents the classical and severe form of Cockayne syndrome. In accordance with the established literature, the MRI of our patient showed diffuse cerebral and cerebellar white matter hypomyelination. With the progress of the disease, cerebral and cerebellar atrophy will take place, with possible calcification throughout the brain, especially in the basal ganglia. Although, polyneuropathy with varying degrees of axonal loss was observed in our patient, there was no correlation between neuropsychologic impairment and MRI white matter changes.

In conclusion, although it is small brain (cerebellum), but with large confusion. Major questions concerning the etiology, prognosis, and possibility of genetic transmission of such conditions often arise and can only (but not always) be addressed after extensive diagnostic exploration. Therefore, for differential diagnosis and planning of investigations the whole constellation of known clinical, imaging, and neurophysiological features should be correlated and considered. An understanding of the spectrum of cerebellar structural abnormalities will help in counseling, anticipation of potentially emergent problems, and recognize unrelated symptoms and signs that would require further investigation. Our study revealed that there is a high incidence of mostly autosomal recessive inheritance disorders that could be diagnosed in patients with cerebellar structural abnormalities in our society. Also, a high rate of consanguinity and similarly affected sibs highlight the role of autosomal recessive genes in our country.

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**References**

Structural cerebellar abnormalities ... Abdel-Salam et al


