Cerebrotendinous Xanthomatosis Presenting with Severe Externalized Disorder: *Improvement After One Year of Treatment with Chenodeoxycholic Acid*

Olivier Bonnot, MD, PhD, Matthew J. Fraidakis, MD, PhD, Raffaella Lucanto, PhD, Dominique Chauvin, PhD, Nathalie Kelley, PhD, Monique Plaza, PhD, Odile Dubourg, MD, PhD, Olivier Lyon-Caen, MD, Frédéric Sedel, MD, PhD, and David Cohen MD, PhD

ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a rare inborn disorder of sterol storage with autosomal recessive inheritance and a variable clinical presentation. We describe two siblings with an early psychiatric presentation of CTX-associated attention-deficit/hyperactivity disorder and oppositional defiant disorder, also associated with a mild intellectual disability and major behavioral impairments. In both cases, treatment with chenodeoxycholic acid improved externalized symptoms and a partial recovery of cognitive impairments was observed. This suggests that CTX is potentially reversible, demonstrating the need for early diagnosis and treatment of this disorder before irreversible neurological lesions can occur.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease of bile acid synthesis. It is caused by mutations in the cytochrome P450 (CYP) 27A1 gene, which is localized on the long arm of chromosome 2 and codes for the mitochondrial enzyme sterol 27 hydroxylase. This enzyme is involved in the synthesis of chenodeoxycholic and cholic acids from cholesterol. The metabolic block causes a progressive storage of cholesterol and its poorly soluble byproduct, cholestanol, which are deposited in many tissues, including the brain and tendons.[1] A recent review found >300 patients with CTX worldwide and identified 50 different mutations in the CYP27A1 gene associated with this disease.[2]

Clinical presentations of the disease are quite variable. The initial symptoms typically begin in childhood with non-specific mild mental retardation, juvenile cataract, chronic diarrhea, or sometimes epilepsy. Progressive neurological deterioration follows in adolescence or adulthood with acute psychiatric signs,[3,4] progressive spastic paraparesis, cerebellar ataxia, polyneuropathy, epilepsy, and cognitive deficits leading to severe handicap or death. These neurological signs can be accompanied by the appearance of tendon xanthomata, which is mainly visible at the level of the Achilles' tendons. A magnetic resonance image (MRI) of the brain typically shows a specific pattern with high signals in the dentate nuclei of the cerebellum on T2 weighted sequences.[5]

Chenodeoxycholic acid is the primary treatment for CTX. It blocks the accumulation of cholestanol by replenishing the pool of bile acid in the liver and enterhepatic circulation. It also shuts down the abnormal bile acid synthetic pathway in the liver. Although it is efficient at normalizing circulating levels of cholestanol and clearly stabilizes disease progression, it does not improve already existing neurological signs and xanthomata do not decrease in size. The permeability of the blood-brain barrier is established with the chenodeoxycholic acid treatment.

Because the initial developmental and psychiatric manifestations are inconsistent, patients with CTX are usually diagnosed during adulthood when neurological symptoms and tendinous xanthomata are already present, and when treatment is less effective. In contrast, there are some reports describing the effects of treatment at early stages of the disease. Here we describe two siblings, a boy and his younger sister, diagnosed with CTX as a result of severe psychiatric

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press

presentations and mild neurological symptoms. With treatment, we observed a marked improvement of psychiatric symptoms in both siblings.

METHOD

Lifetime and current psychiatric diagnoses were assessed using the Diagnostic Interview for Genetic Studies (DIGS) version 2.0, a semi-structured diagnostic interview developed by the Human Genetics Initiative of the National Institute of Mental Health (French translation by Claudine Laurent). Along with suicidal behaviors, the DIGS elicits information necessary to diagnose psychotic, mood, anxiety, substance use, and eating disorders by *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Editon criteria. Given that the DIGS does not include a section for externalized disorders, we added the corresponding section from the Diagnostic Interview-Schedule for Children, version 4.0 (French translation by Lebreton and colleagues).[6]

Both patients and their mother were interviewed to obtain the best estimates for lifetime diagnoses. Their current clinical state was assessed using the following: the Child Behavior Checklist (CBCL)[7] to index global psychopathology, the Bush-Durkee Hostility Inventory (BDHI)[8] to score hetero-aggressiveness and hostile behaviors, the Nisonger Child Behavior Rating (NCBR)[9] to index global behavioral and social impairments, and the Conners' scales to assess symptoms of attention-deficit/hyperactivity disorder (ADHD).[10] All psychiatric and medical charts as well as school notes were collected to confirm the clinical information both in terms of symptoms and time course.

Cognitive function before and after treatment was assessed using a battery of tests (Table). General cognitive skills, attention, and visual-spatial abilities were assessed with the Wechsler Adult Intelligence Scale,[11] the Conners' continuous performance test,[12] and the Rey figure. Oral language assessment included phonology and verbal fluency scores with the bilan neuropsychologique de l'enfant, a neuropsychological test for children[13]; lexical knowledge scores with the test de denomination d'images, a test of picture naming[14]; and oral morphosyntax score with the epreuve de compréhension morphosyntaxique, a test of morphosyntactic comprehension.[15]

Academic skills (written language and mathematical abilities) were also assessed. Regarding reading tasks, several tasks were proposed to score word identification, narrative comprehension, and information seeking. Word identification was assessed with the batterie d'évaluation du langage écrit, a written language evaluation battery.[16] This task assesses oral reading. The subject is asked to read 48 words aloud which vary in terms of frequency, length, and complexity, and 24 non-words which vary in the same characteristics except for frequency. Word identification is scored using the number of words correctly read by the subject. Another test used was the epreuve de la competence en lecture, a reading proficiency test.[17] It is a 1 minute reading test scoring speed and the number of errors according to age.

Global reading tasks (comprehension and information seeking) were assessed with the Journée Appel Défense battery, which is a French battery for adolescents and young adults.[18] It includes two written prose texts: Mortelle matinée, a long but easy text, and Jacques Lentide, a shorter but complex text. Global comprehension and comprehension of contradictions, actions, resolution, history, etc., in the narrative are assessed using a multiple-choice question paradigm. Both tasks are scored by the percentage of correct answers. Literacy is obtained for scores superior to 71%. It also tested by a TV schedule test that requires a selective understanding of written information. In the task, the subject is asked to seek information in a document (TV schedule for one day). Several abilities are tested: scanning by using graphical features (bold, italic, etc.), understanding of the logic of a list or a table, and comparison of time slots. Seven multiple choice questions are administered and the task is scored by the percentage of correct answers. Spelling was assessed using a dictation task validated in French, the Tempête au Sahara, for adolescents $\geq$12 years.

Regarding mathematical abilities, we used three tasks. The construction et utilisation du nombre (construction and utilization of number)[19] to assess logical thinking, spatial organization, and conservation of volume, length, weight, and substance. This task is based on Piagetian principles. The Neuropsychological Test Battery for Number Processing and Calculation in Children[20] was used to assess size estimation. And the test diagnostique des competences de base en mathematiques (diagnostic test of basic mathemathics),[21] assessed basic numeration skills.

All examinations and cognitive evaluations were performed during psychiatric follow-up for both patients. Neither were hospitalized for pretreatment or follow-up examination.

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press

TABLE.
Summary of Clinical Scores and Psychological Test Results

	Patient 1		Patient 2	
Ability and Tests Used	***Pre-treatment score****	***Post-treatment score****	***Pre-treatment score****	***Post-treatment score****
Clinical scales				
Buss-Durke Hostility Inventory	54	↓ (39; 40%)	57	↓ (19; 60%)
Child Behavior Check List-mother	70	↓ (21, 70%)	38	↓ (19; 50%)
Nisonger Child Behavior Rating	57	↓ (14; 75%)	50	↓ (20; 60%)
Conners-mother	50	↓ (14; 72%)	27	↓ (11; 59.3%)
WAIS III				
Verbal IQ	75	Stable (74)	54	Stable (56)
Performance IQ	78	Stable (79)	56	Stable (51)
Verbal comprehension	89	Stable (86)	58	↑ (65)
Perceptual organization	75	Stable (76)	60	Stable, slightly ↓ (56)
Working memory	67	Stable (67)	50	Stable, slightly ↑ (56)
Proceeding speed	50	Stable (50)	50	↑ (58)
Global IQ	75	Stable (75)	53	Stable (52)
Other cognitive abilities				
Attention	Pathological (2/8)	↑ (7/8)	Pathological (3/8)	Stable, slightly ↑ (5/8)
Impulsivity	Pathological (1/3)	↑ Stable (3/3)	Pathological (2/3)	Stable
Vigilance	Normal (2/2)	Stable	Normal	Stable
Communication	122 (10.4)	Stable	125 (12.0 years)	Stable
Daily living skills	152 (12.3)	Stable	154 (12.9 years)	Stable
Socialization	101 (9.2)	Stable	124 (17.9 years)	Stable
Rey figure				
Copy organization	Type 1	Stable	Type 1	Stable
Copy accuracy	32 (71 cent)	↑ (5, <10° cent)	34 (75 cent)	Stable
Delayed organization	Impossible	↑ (Type I)	Impossible	↑ (Type I)
Delayed accuracy	Impossible	↑ (8, <10° cent)	Impossible	↑ (11, <10° cent)
Oral language				
Phonology	81% (normal)	Stable	74% (normal low)	Stable
Lexic	96% (normal)	Stable (97%)	87% (normal)	↑ (93%)
Verbal fluency	>75% (normal)	Stable	>75% (normal)	Stable
Oral morpho-syntax	94% (normal)	Slightly ↑ (96%)	>75% (normal)	Stable
Written language				
Word identification	68% (+0.6SD)	Stable	78% (-1.3SD)	Stable
Word identification speed	70 seconds	↑ (62 seconds)	110 seconds	↑ (75 seconds)
One minute reading	103 (3 errors; +1SD)	↑ 105 (3 errors; +1.15SD)	72 (7 errors; -1SD)	↑ 93 (3 errors; +0.5SD)
Short prose comprehension	100%; normal	Stable	0% (<-2SD)	↑ (100%; normal)
Long prose comprehension	57% (<-2SD)	Stable	57% (<-2SD)	Stable
Information seeking	14% (<-2SD)	↑ 57% (<-2SD)	57% (<-2SD)	Stable
Spelling	10% (<-2SD)	↑ 35%(<-2SD)	57% (low)	Stable
Mathematical Abilities				
Conservation				
Substances	Patient refused tests		Acquired (>9 years)	Stable
Length			Delay (8 years)	↑ (acquired; 10 years)
Weight			Delay (7 years)	↑ (delay; 9 years)
Volume			Delay (7 years)	↑ (delay; 9 years)
Logical Thinking				
Seriation			Delay (6 years)	↑ (acquired; 7 years)
Classification			Delay (8 years)	Stable
Inclusion			Delay (9 years)	↑ (acquired; 11 years)
Transitivity			Delay (<7 years)	↑ (delay; 10 years)
Mathematical reasoning			Very low (16.6%)	↑ (50%)
Spatial Organization				
Spatial organisation			Delay (4 years)	↑ (acquired; 7 years)
Découpage			Acquired(>10 years)	Stable
Numeration				
Size estimation			Low (70%)	↑ (83%)
Addition			37%	↑ (50%)
Subtraction			Not acquired	↑ (37%)
Multiplication			Not acquired	↑ (100%)
Division			Not acquired	Not acquired

* Indications are given where scores were below normal compared to the norms for that test (when available). For example, (7 years) means the score corresponds to an age of development of 7 years; (↓2SD) means the score is below two standard deviations from the mean of a same age normative sample; Not acquired (<10 years) means the dimension tested was not acquired, whereas it should have been acquired by 10 years of age.

WAIS=Wechsler Adult Intelligence Scale.

Bonnot O, Fraidakis MJ, Lucanto R, Chauvin D, Kelley N, Plaza M, Dubourg O, Lyon-Caen O, Sedel F, Cohen D. CNS *Spectr.* Vol 15, No 4. 2010.

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press

CASE REPORTS

Patient 1 was a 13-year-old boy at his first admission in a psychiatric setting. He was born to non-consanguineous parents. His early development was unremarkable (no motor or language delay). At 6 years of age, his mother noticed a tendency to fall frequently as well as clumsiness in writing and fine motor movements. Impairments in drawing, writing, spelling, and mathematics were then noticed. He began attending the local child development center at the end of first grade and attended regular sessions with a reading specialist and a physical therapist until adolescence. Behavioral disturbances were also reported. He became hyperactive, impulsive, and sometimes violent. He was able to attend regular school despite his learning difficulties and behavioral disturbances. At 13 years of age, he was hospitalized after an episode of aggressiveness towards his mother during a family quarrel when he threatened her with a knife. He was subsequently admitted to a day-hospital for 4 years. Psychiatric diagnosis at adolescence was borderline intelligence associated with dysgraphia, ADHD predominant hyperactive-impulsive subtype, and oppositional defiant disorder (ODD). No pharmacological treatment was employed. He was never able to attend special education because of his aggressive and oppositional behavior, and left the hospital at 16 years of age to return home.

In addition to these cognitive and psychiatric manifestations, he was found to have pes cavus at 13 years of age, necessitating a bilateral anterior tarsectomy. At 18 years of age, physical examination revealed a bilateral extensor plantar response, distal muscular atrophy of the anteroexternal aspect of the legs, and distal hypoesthesia at the lower extremities up to the ankles. An electroneuromyograph showed a sensorimotor axonal polyneuropathy affecting all extremities. The MRI was considered normal. By 21 years of age, the association of psychiatric symptoms together with pyramidal signs and polyneuropathy led to a metabolic workup and his plasma cholestanol was found to be elevated (ratio cholestanol:cholesterol=1:100, N<1:1000).

Subsequent sequencing of the CYP27A1 gene in the patient and his parents revealed that he had the Arg 395 / Cys point mutation inherited from his mother and the Arg 479 / Cys point mutation from his father. Both mutations have previously been described in association with CTX.[22] Other biological abnormalities included low cholesterol (1.3 g/L; normal=1.60–2.60 g/L), low high-density lipoprotein (0.40 g/L normal=0.40–0.65 g/L) and low-density lipoprotein (0.40 g/L; normal=0.70–1.40 g/L), and high triglycerides (2.75 g/L; normal=0.45–1.90 g/L). Mild lens opacity was found during an ophthalmological examination. Finally, a second MRI showed mild hyperintensities in both dentate nuclei of the cerebellum. MR spectroscopy revealed an elevation of choline and inositol at the level of the centrum semiovale. Cerebellar peaks were within normal limits. Treatment with chenodeoxycholic acid (250 mg TID) was then started.

Patient 2 is the sister of patient 1. She had an unremarkable early development. Her medical history was non-specific except for pes cavus and hammer toes discovered at 7 years of age, as well as chronic diarrhea. During the school years, the patient was purportedly active in sports, but had underperformed academically and exhibited oppositional behaviors and deficits in attention. She received methylphenidate (10–20 mg/day) for ADHD from 9–11 years of age. The treatment was discontinued because of increases in learning disability, impulsivity, aggressiveness and suspicion of low cognitive functioning, forcing her to leave school. The diagnosis of CTX was made after her brother's diagnosis. Neurological examination and electroneuromyography found mild signs of sensorimotor axonal peripheral neuropathy. Brain MRI and ophthalmological examinations were normal.

EVOLUTION WITH TREATMENT

Patient 1

At initiation of treatment, symptoms of ADHD/ODD were still present and severe. Neuropsychological testing performed a few weeks before treatment, revealed borderline intelligence, difficulties with abstract reasoning, a deficit in attention, and dysexecutive syndrome affecting inhibition. The observed impairments in social behaviors were significant. Improvement after 1 year of treatment was impressive for all clinical variables, ranging from 40% to 72% at the 1 year follow-up (Figure 1). We found no difference in general cognitive function. The patient, however, did exhibit improved writing language scores (word identification speed, 1 minute reading score, spelling, and information seeking) and visual spatial skills (Rey figure). After 2 years of treatment, he is now able to devote himself to a handicraft job and lives alone in an apartment.

Patient 2

Evaluation at baseline before treatment

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press

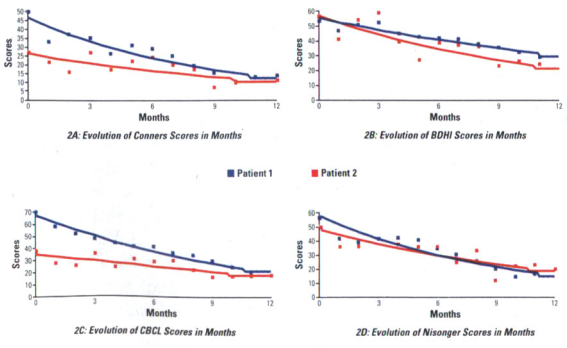
showed a severe ADHD comorbid with ODD and an excellent insight towards her behavioral problems that she was unable to control. Cognitive evaluation confirmed that she had mild intellectual disability, but more focal testing was inconsistent. She showed lower scores than expected in processing speed, visual spatial abilities, memory, and mathematical abilities, whereas she had much better scores in oral language and reading tests. After 1 year of treatment with chenodeoxycholic acid, she showed marked improvement in both clinical behavior and cognitive function. Post-treatment clinical scores showed improvement in the BDHI, CBCL, NCBR, and Conners, (Figure 1). She also improved markedly in visual memory, word identification speed, reading comprehension, information seeking, and most mathematical abilities, including some believed not to be acquired before treatment (Table). Furthermore, she was able to return to a vocational school for the first time in 3 years.

DISCUSSION

CXT is a rare metabolic disease associated with non-specific psychiatric and physical symptoms including tendinous xanthomas, cataracts, diarrhea, and neurological signs. Acute psychotic episodes have been described but most psychiatric symptoms are non-specific, and occur during childhood and/or adolescence.[3,4] Given the overall effect of cholestanol accumulation, the course of symptoms is quite characteristic and parallels diagnostic delay. Our first patient illustrates this point as molecular diagnosis was reached only after several major behavioral episodes and the decline of his neurological status. Figure 2 summarizes the symptom course according to age in the two siblings. The association of the subtle cognitive impairments following a normal early development, learning disabilities, externalized disorders coupled with chronic diarrhea should have led to an early metabolic investigation as chronic diarrhea is an important, although neglected, clinical sign of metabolic disease.[23]

Early diagnosis of CTX is crucial for the use of chenodeoxycholic acid as a specific treatment. The earlier the treatment is started, the more quickly the disease progression is stopped. The two cases described here have shown that externalized disorders exhibited in CTX patients can improve dramatically after treatment, allowing for better social insertion. Notably, Patient 2 did not respond to a 2 year trial of methylphenidate, even though its mean effect size for ADHD symptoms is among the highest in child psychopharmacology. Furthermore, Patient 2 showed a remarkable improvement in logical and mathematical processes, visual memory, and cognitive speed. This is critical; since early treatment leads to improvement in learning capacities, that may explain the improvements observed in oral and writing language scores. Although cognitive impairments are found in neurolipidoses[24] and CTX,[1] studies reporting a significant improve-

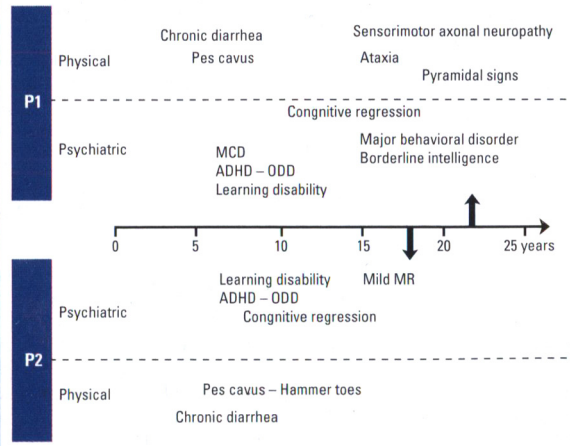
FIGURE 1.
Evolution of clinical scores at 1 year follow-up



BDHI=Buss-Durke Hostility Inventory; CBCL=Child Behavior Check List-mother.

Bonnot O, Fraidakis MJ, Lucanto R, Chauvin D, Kelley N, Plaza M, Dubourg O, Lyon-Caen O, Sedel F, Cohen D. *CNS Spectr.* Vol 15, No 4. 2010.

FIGURE 2.
Summarized view of the course of CTX symptoms according to age*



* Age at molecular diagnosis is indicated with arrow.

CTX=cerebrotendinous xanthomatosus; MCD=motor coordination disorder; ADHD=attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; MR=mental retardation.

Bonnot O, Fraidakis MJ, Lucanto R, Chauvin D, Kelley N, Plaza M, Dubourg O, Lyon-Caen O, Sedel F, Cohen D. *CNS Spectr.* Vol 15, No 4. 2010.

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press

ment of cognitive functioning after treatment are scarce. The current cases illustrate how early molecular diagnosis before the occurrence of neurological signs is important for prognosis.

CONCLUSION

CTX is a treatable metabolic disease that requires early molecular diagnosis to prevent cognitive regression and neurological lesions. The reported cases suggest that the association of slow cognitive regression after normal early development, learning disabilities, externalized disorders, and chronic diarrhea should lead to specific metabolic investigation. Our knowledge in the field of neurometabolic diseases has grown since the last decade. Prevalence is around 1/2,500 births and 80% of diagnosis are pediatric.[23] Moreover, psychiatric manifestation revealing inborn errors of metabolism in adolescent or adults are not rare, and some diseases are treatable, such as CTX, Homocystinuria, Wilson Disease, or Urea Cycle Disorder, which are known for possibly presenting with psychiatric symptoms.[23] Early treatment may lead to psychiatric, cognitive, and behavioral improvement, and will also stop the metabolic induced physical signs of the disease. To confirm the clinical validity of our proposal, however, more research in adult CTX patients is needed in order to carefully describe the course of symptoms during childhood and adolescence. ***CNS***

REFERENCES

1. Moghadasian MH, Salen G, Frohlich JJ, Scudamore CH. Cerebrotendinous xanthomatosis: a rare disease with diverse manifestations. *Arch Neurol.* 2002;59:527-529.
2. Gallus GN, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. *Neurol Sci.* 2006;27:143-149.
3. Berginer VM, Foster NL, Sadowsky M, Townsend JA 3rd, Siegel GJ, Salen G. Psychiatric disorders in patients with cerebrotendinous xanthomatosis. *Am J Psychiatry.* 1988;145:354-357.
4. Estrov Y, Scaglia F, Bodamer OA. Psychiatric symptoms of inherited metabolic disease. *J Inherit Metab Dis.* 2000;23:2-6.
5. Barkhof F, Verrips A, Wesseling P, et al. Cerebrotendinous xanthomatosis: the spectrum of imaging findings and the correlation with neuropathologic findings. *Radiology.* 2000;217:869-876.
6. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry.* 2000;39:28-38.
7. Biederman J, Monuteaux MC, Kendrick E, Klein KL, Faraone SV. The CBCL as a screen for psychiatric comorbidity in paediatric patients with ADHD. *Arch Dis Child.* 2005;90:1010-1015.
8. Buss AH, Durkee A. An inventory for assessing different kinds of hostility. *J Consult Psychol.* 1957;21:343-349.
9. Aman MG, Tassé MJ, Rojahn J, Hammer D. The Nisonger CBRF: a child behavior rating form for children with developmental disabilities. *Res Dev Disabil.* 1996;17:41-57.
10. Conners CK. *Conners' Rating Scales-Revised Technical Manual.* Cheektowaga, NY: Multi-Health Systems; 1997.
11. Wechsler, D. *Wechsler Adult Intelligence Scale-Third Edition* (WAIS III). New York, NY:Pearson; 1991.
12. Conners CK and MSH Staff. *Conners Continuous Performance Test II: Computer Program for Windows Technical Guide and Software Manual.* Cheektowaga, NY: Mutli-Health Systems; 2000.
13. Korkman M, Kirk U, Kemp S. *Bilan neuropsychologique de l'enfant* (NEPSY). Paris, France: Edition du Centre de Psychologie Appliquée; 2003.
14. Kremin H, Hamerel M, Dordain M, De Wilde M, Perrier D. Age of acquisition and name agreement as predictors of mean response latencies in picture naming of French adults. *Brain Cog.* 2000;43:286-291.
15. Lecocq P. (1996). *L'ECOSSE: une épreuve de compréhension syntaxico-sémantique.* Villeneuve d'Ascq, France: Presses Universitaires du Septentrion; 1996.
16. Mousty P, Leybaert J, Alegria J, Content A, Morais J. *Batterie d'évaluation du langage écrit et de ses troubles* (BELEC). Brussels, Belgium: Laboratoire de psychologie expérimentale, Université libre de Bruxelles; 1994.
17. Khomsi A. *Epreuve d'Evaluation de la Compétence en Lecture-Forme Révisée* (LMC-R). Paris, France: Edition du Centre de Psychologie Appliquée; 1999.
18. Cohen D, Plaza M, Perez-Diaz F, et al. Individual cognitive remediation of reading disability in adults with mild mental retardation. *Res Dev Disabil.* 2006;27:501-516.
19. Meljac C, Lemmel G. *UDN-II : Construction et utilisation du nombre.* Paris, France: Edition du Centre de Psychologie Appliquée; 1980.
20. Van Nieuwenhoven C, Grégoire J, Noël MP. *TEDI-MATH, test diagnostique des compétences de base en mathematiques.* Paris, France: Editions du Centre de Psychologie Appliquée; 2001.
21. von Aster MG. *ZAREKI (Neuropsychological Test Battery for Number Processing and Calculation in Children).* Amsterdamn, Neth: Swets & Zeitlinger; 2001.
22. Cali JJ, Hsieh CL, Francke U, Russell DW. Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. *J Biol Chem.* 1991;266:7779-7783.
23. Sedel F, Baumann N, Turpin JC, Lyon-Caen O, Saudubray JM, Cohen D. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inherit Metab Dis.* 2007;30:631-641.
24. Turpin JC, Baumann N. Presenting psychiatric and cognitive disorders in adult neurolipidoses. *Rev Neurol* (Paris). 2003;159:637-647.

Dr. Bonnot is a hospital practitioner in the Department of Child and Adolescent Psychiatry at Groupe Hospitalier Pitie Salpetriere in Paris, France. Dr. Fraidakis is a clinical and research fellow in neurology in the Department of Neurology at Groupe Hospitalier Pitie Salpetriere. Dr. Lucanto is a psychologist in the Department of Child and Adolescent Psychiatry at Groupe Hospitalier Pitie Salpetriere in Paris, France. Dr. Chauvin is speech therapist in the Department of Child and Adolescent Psychiatry at Groupe Hospitalier Pitie Salpetriere. Dr. Kelley is speech therapist in the Department of Child and Adolescent Psychiatry at Groupe Hospitalier Pitie Salpetriere. Dr. Plaza is a researcher at the CNRS and Groupe Hospitalier Pitie Salpetriere. Dr. Dubourg is a neurologist at Groupe Hospitalier Pitie Salpetriere. Dr. Lyon-Caen is Professor in the Department of Neurology at Groupe Hospitalier Pitie Salpetriere and University Pierre et Marie Curie in Paris, France. Dr. Sedel is a hospital practitioner in the Department of Neurology at Hôpital de la Salpêtrière. Dr. Cohen is Professor in the Department of Child and Adolescent Psychiatry at Groupe Hospitalier Pitie Salpetriere and University Pierre et Marie Curie.

Faculty Disclosures: The authors report no affiliation with or financial interest in any organization that might pose a conflict of interest.

Funding/Support: The work was supported by the French Ministry of Health (Plan Maladies Rares 2007).

Submitted for publication: January 1, 2009; Accepted for publication: March 1, 2010.

Please direct all correspondence to: David Cohen, MD, PhD, Département de Psychiatrie de l'Enfant et de l'Adolescent, Université Pierre et Marie Curie, AP-HP, Hôpital Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75651, Paris Cedex 13, France; Tel: 33-1-42162351, Fax: 33-1-42162353; E-mail: david.cohen@psl.aphp.fr.

CME 1 Now Available Online at www.cnsspectrums.com CME 1

CME-ACCREDITED SUPPLEMENT

AN EXPERT PANEL REVIEW OF CLINICAL CHALLENGES IN NEUROLOGY

Case in Point: Evidence-Based Insights for Epilepsy Management–*Pharmacologic Treatment of Epilepsy*

Andrew J. Cole, MD, FRCPC
Chair; Nathan B. Fountain, MD

To request a print supplement, please e-mail ks@mblcommunications.com

This activity is supported by an educational grant from GlaxoSmithKline, Pfizer Inc, and Shire

---

CME 2 Now Available Online at www.cnsspectrums.com CME 2

CME-ACCREDITED SUPPLEMENT

AN EXPERT PANEL REVIEW OF CLINICAL CHALLENGES IN PSYCHIATRY

Recognition and Treatment Strategies for Bipolar Disorder Across the Life Cycle

Joseph F. Goldberg, MD, Charles L. Bowden, MD, Claudia Baldassano, MD, Noreen Reilly-Harrington, PhD

To request a print supplement, please e-mail ks@mblcommunications.com

This activity is supported by an educational grant from Bristol-Myers Squibb and Pfizer, Inc.

https://doi.org/10.1017/S1092852900000067 Published online by Cambridge University Press