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Socio-Behavioral Characteristics of Children with Rubinstein-Taybi Syndrome

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Abstract Research regarding the behavioral aspects of children with Rubinstein-Taybi syndrome (RTS) has suggested some possible behavioral patterns including autistic features. Caregivers of 39 children (mean age = 8.4 years) with RTS (49% showing abnormality in *CREBBP* gene) and 39 children (mean age = 8.6 years) matched on developmental level, age and gender were administered the Child Behavior Checklist and the Children's Social Behavior Questionnaire. Children with RTS did not exhibit higher internalizing (affective and anxiety symptoms) or externalizing (disruptive symptoms) behavioral problems than expected for their age/developmental range. However, they displayed some specific behaviors: short attention span, motor stereotypies, poor coordination, and overweight. The presence of an identified *CREBBP* gene abnormality was possibly related to the motor difficulties through impaired motor skills learning.

Keywords Rubinstein-Taybi syndrome · Pervasive Developmental Disorder Not Otherwise Specified · Socio-behavioral characteristics

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Introduction

Rubinstein-Taybi syndrome (RTS) is a congenital syndrome first described in 1963 (Rubinstein and Taybi 1963) and most often occurring sporadically. Birth prevalence has been estimated at about one in 100,000–125,000 by Hennekam et al. (1990). The diagnosis of RTS is based on clinical features. It is characterized by developmental delay, postnatal growth retardation, microcephaly, typical facial appearance, broad thumbs and big toes. Other medical problems such as neonatal feeding difficulties, neonatal respiratory difficulties, and congenital heart defects may occur. Chromosomal or molecular abnormalities are found in about 55% of the cases (Hennekam 2006; Stef et al. 2007). The syndrome has been mapped to 16p13.3 (Lacombe et al. 1992) with two genes currently known to be linked to the syndrome: *CREB Binding Protein* (*CREBPP*) and *E1A Binding Protein P300* (*EP300*) (Roelfsema et al. 2005). To date, in spite of the developmental delay associated with the syndrome, little attention has been paid to the cognitive and behavioral aspects of children with RTS.

In their original report, Rubinstein and Taybi (1963) mentioned hyperactivity in three out of seven children, and significant emotional lability in three children of the same series. However, that study lacked a standardized psychometric tool. A second investigation published by Goots and Liemohn (1977) compared three children (aged seven to ten) with the syndrome to 15 counterparts with mixed mental retardation. They found that children with RTS were friendly and more readily accepted social contacts, were more emotional and excitable, had nightmares more often, were more prone to self-stimulate, were more likely to pout, had short attention span, and had more difficulties in planning motor acts and in executing locomotor and

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oculomotor skills. Inferences from this survey were somewhat limited by the small sample size.

Another study by Stevens et al. (1990) described the natural history of 50 individuals with RTS (mean age of 8.1 and age range from 1 to 26.5). Thirty-seven individuals underwent psychological testing with an average Intelligence Quotient (IQ) of 51 (range from 30 to 79). Families of individuals with RTS completed a questionnaire about the behavior of their child. A short attention span was described in 90% of the individuals. 65% of the responders reported unusual behaviors (primarily self-stimulatory such as rocking, spinning, and hand-flapping). 46% of the families reported that their child disliked loud sounds and did not tolerate crowds because of noise. Families further completed the Inventory for Client and Agency Planning. This tool provides a maladaptive behavior index and showed that 10% of individuals experienced a significant maladaptive behavior problem. Families also claimed their children to be loving, friendly and happy. The study, however, was limited by the lack of control group and by the psychometric tool used, which did not afford comparisons with psychiatric validated instruments.

A survey conducted by Hennekam et al. (1992) focused on the psychological aspects of 45 Dutch subjects with RTS (mean age of 13 and age range from 4.3 to 34.6). For 40 subjects, cognitive assessment showed an average IQ of 35.6 (range from 25 to 79). Behavioral data were available for 37 individuals as assessed by the Child Behavior Checklist (CBCL). The most frequently reported behavioral problems were "acts too young for age" (86%), "can't concentrate" (76%), and "poorly coordinated, clumsy" (73%). The only autistic-like behavior found with the CBCL was "likes to be alone" (68% of the subjects) and was stated by the families as the way their children coped with too much noise and crowds. "Overweight" was also found in numerous subjects (46%), predominantly in females. "Sudden changes in mood" and "temper tantrums" were found in 46% and 41% respectively. Although considered frequent in the Goots and Liemohn survey (1977), "nightmares" and "troubles with sleeping" were found in only four and seven patients respectively. Subjects with RTS were also shown to have good communication skills and social competencies, possibly higher than those of subjects with other causes of mental retardation. However, due to the absence of a comparison group, the authors could not determine whether their findings were specific for RTS.

In a more recent investigation, Levitas and Reid (1998) reported on the psychiatric evaluations of a clinical sample of 13 adult patients with RTS referred for behavioral problems. The diagnoses clustered into mood disorders and the tic/obsessive compulsive disorder spectrum. One subject also met the diagnosis of pervasive developmental disorder not otherwise specified (PDDNOS). Because the sample was highly selected (severely retarded referrals for psychiatric evaluation), and due to the lack of control group, no inferences were drawn regarding the prevalence of psychiatric disorders in subjects with RTS. Interestingly, a review and case study (Hellings et al. 2002) described the case of an adult female (aged 39) who presented with symptoms of severe over-activity, short attention span, mood lability, and aggressive outbursts in a cyclical pattern. Diagnostic criteria for PDDNOS were also met in this patient. These reports in adults therefore support a potential link between RTS and the mood disorders/obsessive compulsive disorder spectrum.

Taken together, these findings suggest a possible pattern of behavioral difficulties in children and adults with RTS. It seems relevant to focus on childhood behavioral characteristics of children with RTS since they might represent a phenotypic indicator of subsequent psychiatric conditions. To date, studies have failed to determine whether the childhood behavioral features in individuals with RTS differ from those found in children with a comparable level of cognitive impairment due to unidentified causes. Hence it has not been proved whether there is a specific behavioral profile in children with RTS, or if behavioral manifestations in such children are rather due to the developmental delay related to non-specific brain dysfunction.

We report an observational study focusing on socio-behavioral variables in children with RTS compared to a Developmental Quotient (DQ) and chronological age-matched control group. Our aim was to determine whether there is a specific pattern of behaviors in children with RTS.

Method

Participants

Participants included 39 children and adolescents with RTS (16 males and 23 females) and a control group of 39 subjects matched on gender, chronological and DQ (16 males and 23 females). Subjects with RTS were prospectively recruited (between December 2003 and January 2008) from families who participated in the meetings of the French RTS Association ($N = 13$) and from the university department of medical genetics in Bordeaux hospital in France ($N = 26$). Inclusion required a confirmed diagnosis of RTS made by two expert geneticists from Bordeaux hospital. Only classic cases were considered and all patients fulfilled strict diagnostic criteria. Molecular testing (Denaturing High Performance Liquid Chromatography and *CREBBP* gene sequencing) was performed in all subjects. Molecular abnormalities in the *CREBBP* gene were

found in 49% of the cases: nonsense mutation ($N = 4$), missense mutation ($N = 3$), mutation with frame shift (deletion or insertion) ($N = 8$), splice site mutation ($N = 3$), and complete gene deletion ($N = 1$).

Participants from the control group were recruited from the university department of medical genetics in Bordeaux hospital (France), at the same time as cases. Exclusion criteria for the control group were (i) presenting an identified neurogenetic disorder, (ii) presenting a primary diagnosis of pervasive developmental disorder or psychosis, (iii) presenting an organic etiology for developmental delay.

Parents were invited to fill out self-administered questionnaires about the socio-behavioral features of their children. The study was conducted in accordance with the French RTS association and conformed to the French bioethics and clinical research and data protection legislation. All data were de-identified. The data were collected during routine medical and psychological management, and there was no supplementary medical procedure mandated by the study. Written consent for genetic testing was obtained for all subjects, as requested by the French legislation.

Measures

To evaluate socio-behavioral characteristics in our sample, we used the CBCL (Achenbach 1991; Achenbach and Rescorla 2001) and the Children's Social Behavior Questionnaire (CSBQ) (Luteijn et al. 1998, 2000). The CBCL is a widely used psychometric tool, both in the field of developmental delay and in intellectually average children. Its factor validity for internalizing and externalizing problems in children with moderate-to-severe developmental delay was confirmed by Borthwick-Duffy et al. (1997). The CBCL allowed comparison with the findings of Hennekam et al. (1992). The French version of the CBCL was validated in previous clinical and epidemiological studies (Fombonne 1992, 1994). This instrument has been previously used by the authors in the field of neurogenetic disorders (Galéra et al. 2006). The CBCL consists of 118 items referring to various behavioral and emotional problems for the previous 6-month period as reported by parents. Each item is rated from 0 to 2 ("not true", "somewhat or sometimes true", "very true or often true"). "Total", "internalizing" (comprises items such as: cries, fears, fears school, fears doing bad, has to be perfect, feels unloved, worthless, nervous, fearful, guilty, self-conscious, talks suicide, worries, enjoys little, rather be alone, won't talk, secretive, shy, lacks energy, sad, withdrawn, nightmares, constipate, dizzy, tired, aches, headaches, nausea, eye problems, skin problems, stomach, vomits) and "externalizing" (comprises items such as: no guilt, breaks rules, bad companions, lies or cheats, runs away, sets fires, sex problems, thinks sex, steals at home, steals outside home, swears, truant, vandalism, argues, mean, demands attention, destroys own things, destroys others' things, disobedient at home, disobedient at school, fights or attacks, prefers older children, screams, stubborn, mood changes, sulks, suspicious, teases, temper, threatens, loud, alcohol or other drugs use) problems scales and six DSM (Diagnostic and Statistical Manual of Mental Disorders, APA 1994) oriented scales ("affective problems", "anxiety problems", "somatic problems", "attention deficit/hyperactivity problems", "oppositional defiant problems", "conduct problems") can be derived by summing the score items (Achenbach and Rescorla 2001). It allows raw and T-scores to be obtained for each scale. A T-score $\geq$63 in the total problems scale is clinically meaningful.

The CSBQ is a questionnaire for parents or caregivers to chart the diverse forms of social, communication, and stereotyped problem behaviors in children and adolescents aged 4–18. It was designed to explore features typical of children with milder forms of PDD. Psychometric properties of the instrument were provided by Luteijn et al. (2000) and showed good indices of reliability and validity. Preliminary validation of the French version of the CSBQ was conducted by Excoffier et al. (2007). The initial CSBQ comprised 96 items referring to the behavioral and social problems of their child during the preceding 2 months. A further refinement of the instrument reduced the number of items to 49 (Hartman et al. 2006). Each item is coded in an ordinal fashion from 0 to 2 ("does not apply", "somewhat or sometimes applies", "clearly or often applies"). The items are divided into six subscales ("behavior/emotions not optimally tuned to the social situation", "reduced contact and social interest", "orientation problems in time, place, or activity", "difficulties in understanding social information", "stereotyped behavior", "fear of and resistance to change").

To provide a DQ, all participants underwent cognitive testing with the French versions of the Wechsler Intelligence Scale for children, third version (WISC-III) or the Psycho Educative Profile-R (Wechsler 1991, 1995; Schopler et al. 1994). DQ was used rather than IQ since the Psycho Educative Profile-R does not provide an IQ measure.

Statistical Analyses

We first compared the two groups on chronological age means, DQ means (two-tailed *T*-test), and gender frequencies (two-way χ^2 analyses) to check the adequacy of the matching procedures. We then compared the RTS group to the control group for CBCL and CSBQ scale scores. We also compared the two groups for the single

items of interest (i.e. highly prevalent or described in previous research findings). For these single items and in order to assess clinically relevant problems, we constructed the dichotomous dependent variables by considering the rating 0 and 1 vs. 2. To take into account the matching procedures, we performed unconditional multivariate regressions (linear or logistic models) with DQ, age and gender as covariates. The model fit was assessed through graphical examination of residuals for linear models, and with the Hosmer and Lemeshow goodness-of-fit statistic for logistic models. Pearson's r correlations were performed to examine the relationship between cognitive level, chronological age, and socio-behavioral problems in each group. When applicable, we calculated effect sizes in order to assess the magnitude of significant differences observed between groups. For quantitative variables we computed Cohen's d-ratio. For binary variables we used the coefficient Phi. To examine a possible gene-behavior link, we finally described significant behaviors by genetic abnormalities in the *CREBBP* gene (RTS group with genetic abnormalities in *CREBBP* versus RTS group without genetic abnormalities in *CREBBP*). An alpha level of 0.05 (two-tailed) was adopted as the criterion for statistical significance. Statistical analyses were performed with S.A.S. Version 9.1. (Statistic Analysis System, version 9.1., SAS institute, Inc., Cary, NC).

Results

Matching procedures were successful regarding chronological age [$t(76) = 0.28$, $p = 0.78$; RTS group: mean = 8.4 years, range = 4.3–15.8 years, SD = 3.4; control group: mean = 8.6 years, range = 4.4–15.5 years, SD = 3.3], DQ [$t(76) = 0.75$, $p = 0.45$; RTS group: mean = 46.1 SD = 16.9; control group: mean = 49.1, SD = 17.7], and gender ($\chi^2(1) = 0$, $p = 1.0$).

Table 1 shows the results of multivariate regression analyses for CBCL scales.

Children with RTS did not display higher scores than controls on DSM-oriented scales or broad band scales. Children with RTS displayed lower scores than their counterparts in anxiety problems (statistically significant difference). Regarding total problems scores, there was no difference between the two groups, with 49% of children with RTS and 49% of controls showing total problems scores in the clinical range.

Table 2 shows the results of multivariate regression analyses for CBCL single items of interest.

Statistically significant differences were found for "acts too young for his/her age", "can't concentrate/pay attention for long", "overweight", and "poorly coordinated or clumsy", with higher rates reported in children with RTS. Coefficients Phi for these CBCL items were respectively 0.34, 0.22, 0.22, and 0.39, which represented a moderate association. In the RTS group we found a statistically significant positive correlation between overweight and age (RTS group: Pearson's $r = 0.48$, $p < 0.01$; Control group: Pearson's $r = 0.12$, $p = 0.45$) and a significant negative correlation between poor coordination and DQ (i.e. worse coordination with lower DQ) (RTS group: Pearson's $r = -0.39$, $p = 0.02$; Control group: Pearson's $r = -0.08$, $p = 0.62$). In the control group there was a significant negative correlation between short attention and DQ (i.e. worse attention with lower DQ) (RTS group: Pearson's $r = -0.02$, $p = 0.88$; Control group: Pearson's $r = -0.39$, $p = 0.01$).

Table 3 shows CSBQ scale scores in subjects with RTS and in controls.

Most of the scale scores and total problems scores were not significantly different between the two groups. A

Table 1 Child Behavior Checklist (CBCL) scales in subjects with Rubinstein-Taybi syndrome (RTS) and in control subjects

Variable	RTS group ($N = 39$)	Control group ($N = 39$)	p
Age in years, mean (SD)	8.4 (3.4)	8.6 (3.3)	NS
Developmental Quotient (DQ)	46.1 (16.9)	49.1 (17.7)	NS
DSM oriented scales, mean (SD)			
Affective problems	3.9 (3.1)	3.7 (3.4)	NS
Anxiety problems	3.3 (2.2)	4.4 (2.3)	0.0314
Somatic problems	1.4 (1.9)	1.5 (2.2)	NS
Attention deficit/hyperactivity problems	4.5 (2.1)	4.2 (2.3)	NS
Oppositional defiant problems	3.4 (2.2)	3.5 (2.1)	NS
Conduct problems	2.5 (3.1)	3.0 (3.2)	NS
Broad band scales, mean (SD)			
Internalizing	9.3 (6.6)	12.2 (6.9)	NS
Externalizing	10.8 (6.6)	11.8 (7.6)	NS
Total problems score	46.5 (21.9)	45.7 (20.3)	NS
Total problems in the clinical range, N (%)	19 (49%)	19 (49%)	NS

Models regarding CBCL variables were adjusted for age, DQ, and gender

NS No significance

Table 2 Child Behavior Checklist (CBCL) single items in subjects with Rubinstein-Taybi syndrome (RTS) and in control subjects

Variable	RTS group ($N = 39$)	Control group ($N = 39$)	p
CBCL single items, *N* (%)			
Acts too young for his/her age	29 (74%)	16 (41%)	0.0033
Can't concentrate/pay attention for long	31 (79%)	23 (59%)	0.0454
Would rather be alone than with others	2 (5%)	5 (13%)	NS
Nightmares	0 (0%)	0 (0%)	NS
Sleeps less than most kids	2 (5%)	0 (0%)	NS
Sleeps more than most kids	6 (14%)	4 (10%)	NS
Trouble sleeping	2 (5%)	1 (3%)	NS
Overweight	6 (15%)	1 (3%)	0.0521
Poorly coordinated or clumsy	25 (64%)	10 (26%)	0.0015
Sudden changes in mood or feelings	1 (3%)	4 (10%)	NS
Temper tantrums or hot temper	1 (3%)	1 (3%)	NS

Adjusted for age, DQ, and gender

NS No significance

Table 3 Children's Social Behavior Questionnaire (CSBQ) scores in subjects with Rubinstein-Taybi syndrome (RTS) and in control subjects

Variable	RTS group ($N = 39$)	Control group ($N = 39$)	p
CSBQ scores, mean (SD)			
Total problems	29.2 (11.6)	29.0 (11.1)	NS
Not optimally tuned to social situation	6.9 (4.4)	7.5 (4.2)	NS
Reduced contact or social interest	4.5 (3.9)	6.3 (4.4)	0.0491
Orientation problems in time/place/activity	4.7 (2.6)	4.0 (2.5)	NS
Difficulties understanding social information	6.3 (3.6)	6.0 (2.8)	NS
Fear and resistance to changes	2.2 (1.4)	2.4 (1.6)	NS
Stereotyped behavior	4.5 (3.6)	2.8 (3.1)	0.0361

Adjusted for age, DQ, and gender

NS No significance

significantly higher score was found in children with RTS with regard to the stereotyped behavior scale. There was a medium d-ratio of 0.50 for this group difference. Regarding correlations between DQ and CSBQ scores, a significant negative correlation was found between DQ and stereotyped behavior scores in both groups (RTS group: Pearson's $r = -0.34$, $p = 0.03$; Control group: Pearson's $r = -0.42$, $p < 0.01$). Scores for reduced contact and social interest were significantly lower in children with RTS, which means better contact and social interest in RTS children versus control children.

Table 4 shows CSBQ items of interest frequencies in subjects with RTS and in controls.

Significant differences were found for the motor stereotypies items "flaps arms/hands when excited", "makes odd/fast movements with fingers/hands", and "extremely pleased by certain movements/keeps doing them", with coefficients Phi equal to 0.24, 0.29 and 0.24 respectively (moderate associations). There was no significant correlation in any group between the CBCL item poor coordination and the CSBQ items for motor stereotypies.

Within the RTS group, there was no significant difference between the groups with and without abnormalities in the *CREBPP* gene regarding chronological age [$p = 0.09$; RTS group with genetic abnormalities: mean = 7.5 years, SD = 3.0; RTS group without genetic abnormalities: mean = 9.4 years, SD = 3.5], DQ [$p = 0.36$; RTS group with genetic abnormalities: mean = 48.4, SD = 13.9; RTS group without genetic abnormalities: mean = 43.9, SD = 19.4], and gender ($\chi^2(1) = 0.02$, $p = 0.89$). Table 5 shows significant socio-behavioral features according to genetic status.

Regarding poor coordination, there was a significantly higher prevalence in the RTS group with identified genetic abnormalities in the *CREBPP* gene when compared to the RTS group without genetic abnormalities, when adjusting for chronological age, DQ, and gender. We conducted further analyses by comparing each RTS subgroup to the control group for poor coordination problems. The RTS group with identified genetic abnormalities in the *CREBPP* gene displayed significantly worse coordination problems than the control group ($p = 0.0005$, coefficient phi = 0.51). The difference between the RTS group without identified genetic abnormalities in the *CREBPP* gene and the control group did not reach statistical significance ($p = 0.1013$).

With regard to linear regression models, graphical examination of residuals indicated that the hypotheses of normality and homoscedasticity were acceptable. Hosmer and Lemeshow goodness-of-fit statistics were not significant, which indicated a good fit for the logistic models.

Table 4 Children's Social Behavior Questionnaire (CSBQ) single items in subjects with Rubinstein-Taybi syndrome (RTS) and in control subjects

Variable	RTS group ($N = 39$)	Control group ($N = 39$)	p
Single items (Stereotyped behavior scale), *N* (%)			
Flaps arms/hands when excited	13 (33%)	5 (13%)	0.0464
Makes odd/fast movements with fingers/hands	12 (31%)	3 (8%)	0.0190
Sways to and fro	0 (0%)	1 (3%)	NS
Unusually sensitive to certain sounds	8 (21%)	3 (8%)	NS
Pleased by movements/keeps doing them	13 (33%)	5 (13%)	0.0437
Smells objects	3 (8%)	3 (8%)	NS
Constantly feels objects	6 (15%)	5 (13%)	NS
Fascinated by certain colors/forms/moving objects	5 (13%)	1 (3%)	NS

Adjusted for age, DQ, and gender

NS No significance

Table 5 Child Behavior Checklist (CBCL), Children's Social Behavior Questionnaire (CSBQ) single items, and stereotyped scores within Rubinstein-Taybi syndrome (RTS) by genetic status

Variable	Identified abnormality in *CREBBP* ($N = 19$)	No. identified abnormality in *CREBBP* ($N = 20$)	p
CBCL single items, *N* (%)			
Acts too young for his/her age	15 (79%)	14 (70%)	NS
Can't concentrate/pay attention for long	15 (79%)	16 (80%)	NS
Overweight	2 (11%)	4 (20%)	NS
Poorly coordinated or clumsy	15 (79%)	10 (50%)	0.0368
CSBQ score, mean (SD)			
Stereotyped behaviours	4.3 (3.7)	4.8 (3.7)	NS
CSBQ single items, *N* (%)			
Flaps arms/hands when excited	7 (37%)	6 (30%)	NS
Makes odd/fast movements with fingers/hands	7 (37%)	5 (25%)	NS
Pleased by certain movements/keeps doing them	6 (32%)	7 (35%)	NS

Adjusted for age, DQ, and gender

NS No significance

Discussion

Regarding behavioral and emotional problems, CBCL results showed relatively high prevalence rates. However, CBCL scores were not significantly higher in the RTS group than in the control group. Anxiety problems were even significantly slightly lower in the RTS group. In addition, rates of behavioral problems in our study were comparable to previous findings in people displaying intellectual disability. Using the same psychometric tool (i.e. the CBCL), Dekker et al. (2002) found that almost 50% of children with intellectual disability had a CBCL total problem score in the deviant range. When we examined the CBCL data item by item, we found that the short attention span repeatedly described in former studies was replicated here. Interestingly, while the concentration/attention problem was highly prevalent in the two groups, it was significantly more frequently reported as a very true or often true problem by parents of the RTS group, and was thus indicative of a possible clinically relevant issue. Furthermore, whereas a short attention span was negatively correlated with DQ in the control group, the rate was higher in the RTS group regardless of DQ. This finding of attention problems in RTS children is valuable since attention problems may impact behavioral and educational outcomes negatively. There is hence the need to consider the possible attention difficulties in children with RTS in order to take them specifically into account in the behavioral and educational management of the syndrome and to think about medication if warranted. Remarkably, some previous findings were not corroborated in our study. In particular, we did not find any significantly higher prevalence of sleep problems, mood or temper disturbances in the RTS group. Nevertheless, sleep problems should not be disregarded since obstructive sleep apnea has been found to be quite prevalent in children with RTS (Stevens 2007).

Nor did we find that children with RTS would rather be alone than with others when compared to controls. It should be underlined, however, that suggestions made in other surveys arose from non-comparative data so no firm conclusions could be made.

Beyond the scope of psychopathological items, the CBCL also tapped some more general problems. Consistent with earlier knowledge, we found higher rates of parentally reported overweight and coordination/motor problems in children with RTS. With regard to growth, feeding difficulties are common in infants with RTS due to oral-motor coordination difficulties and failure to thrive. Initial growth retardation with poor weight gain during infancy often gives way to overweight in childhood and adolescence due to overfeeding (Hennekam 2006; Stevens 2007). Our results corroborate this reported tendency since we found a positive significant correlation between age and overweight in the RTS group. For this reason, growth and dietary monitoring is necessary to prevent overweight.

The finding of a significantly higher rate of motor difficulties in RTS children suggests the existence of a specific motor deficit that is not explained only by developmental delay. This is coherent with previous studies suggesting difficulties in planning motor acts and in coordination in RTS children (Goots and Liemohn 1977; Hennekam et al. 1992). Interestingly, the group with identified abnormalities in the *CREBBP* gene drove the significant result in the group comparison between RTS and controls for motor difficulties. This result suggests a possible *CREBBP*-specific effect. Prior research in animal models showed that mice bearing a mutation in the *CREBBP* gene exhibited impaired motor skill learning (Oliveira et al. 2006). Homozygous and heterozygous mice bearing a *CREBBP* mutation, homozygous and heterozygous mice bearing an *EP300* mutation, and wild-type mice (without mutation) were examined on the accelerating rotarod task. Only mice bearing a *CREBBP* mutation (whether homozygous or heterozygous) displayed significantly decreased time on the rotarod. The authors suggested that these results were due to motor learning deficits and not to defects in muscle or locomotor capability. They hypothesized that CREB and CBP proteins could play a role in motor skill learning, possibly through transcriptional activation of genes involved in motor skill learning. Our survey is consistent with the possibility of a motor phenotype in RTS children, especially in those with a *CREBBP* abnormality. This hypothesis of a defect in motor skill learning is strengthened by the negative correlation between DQ and poor coordination problems in RTS children in our sample. This finding should raise awareness of the need for early identification and intervention to target motor skills in this population. It should also promote further research on motor development and learning in RTS subjects.

With regard to CSBQ dimensions, the stereotyped behavior scale score was significantly higher in the RTS group. This difference was mainly attributable to three repetitive motor behaviors, namely "flaps arms/hands when excited", "makes odd/fast movements with fingers/hands", and "extremely pleased by certain movements/keeps doing them", which were rated as "clearly or often applies" by one third of parents of RTS children. In both groups, the stereotyped behavior score was significantly negatively correlated with DQ. However, since DQ was taken into account in group comparisons, children with RTS seemed to display specific developmentally inappropriate repetitive and stereotyped movements. This is coherent with prior research that found frequent self-stimulatory behaviors such as rocking, spinning and hand-flapping (Stevens et al. 1990), thus raising the question of a possible autistic-like behavior pattern in these children. This is all the more relevant since a diagnosis of PDDNOS was evoked in one out of 13 RTS adults in the case series of Levitas and Reid (1998), and in a case report of an adult woman (Hellings et al. 2002). However, children with RTS have been repeatedly described as friendly and having good social competencies and communication skills. In addition, the other autistic dimensions explored by the CSBQ were not significantly higher in the RTS group. Contact/social interest was even better in RTS children since they had lower scores on the scale "reduced contact or social interest" (scale exploring the following: need for contact, quality of eye contact, comfort-seeking when upset, acceptance of physical contact, response to initiative by others, initiating play with other children, expression of feelings by face and body, not living in one's own world, looking up when spoken to), a result that was statistically significant. On the whole, our data do not suggest the existence of a social communication deficit in children with RTS. However, the finding of a possible specific motor stereotypies problem is noteworthy. Motor stereotypies, described not only in people with developmental disabilities but also in children without developmental problems, are thought to be due to dysfunction in cortico-striato-thalamocortical circuits (Kates et al. 2005). The possible association between motor stereotypies and RTS suggests there may be some specific effect of RTS gene defects on the pathways mediating motor stereotypies. This finding should promote further genetic and clinical investigation in this area in order to confirm this motor pattern and its molecular correlates, and to determine its eventual impairment and duration throughout development. Other findings from the CSBQ were that, contrary to previous findings, children with RTS were not significantly more often unusually sensitive to certain sounds, nor did they exhibit fear and resistance to change.

Our survey has methodological limitations. First, the sample size was rather small, which may have obscured

group differences in socio-behavioral features. However, prior studies were of comparable size or smaller and generally did not have any control group. Second, a selection bias might have arisen since a large number of patients were recruited through the French RTS association. Members of syndrome associations may not be representative of the whole RTS population since they are possibly the most severe cases, which could lead to an overestimation of group differences with regard to psychopathology. However, since psychopathology was not higher in children with RTS in our sample, this bias might not have applied to our data. Third, a measurement bias was possible through the use of self-administered questionnaires to collect the data. The CBCL and CSBQ did not allow formal psychiatric diagnoses. In particular, it would have been interesting to explore the diagnostic criteria of mood disorders, obsessive/compulsive disorders, and autism spectrum through standardized diagnostic interviews. Since parents tend to underestimate psychiatric problems in their behavior-disordered children, the study could likely have been improved by having each subject assessed by a psychiatrist specializing in individuals with developmental disabilities. Nevertheless, the validity and reliability of the CBCL and CSBQ questionnaires have been verified (Achenbach and Rescorla 2001; Luteijn et al. 2000). Fourth, the finding of a short attention span in RTS children cannot be assimilated to a diagnosis of attention deficit hyperactivity disorder because items are missing (i.e. symptoms of impulsivity and hyperactivity) and criteria of duration and impairment were not available. Fifth, we could not provide the socio-economic status of the parent group as a possible indicator of their observational abilities. Sixth, regarding motor skills and motor stereotypies, assessment was based on mere parental self-report measures. Hence, caution is needed regarding the putative association between *CREBBP* gene abnormality and motor problems or motor stereotypies since this conclusion was reached through weak measures. More refined evaluation using standardized tools focusing on different aspects of motor development are needed in order to confirm and characterize possible motor deficiencies or abnormal movements. Finally, we might have missed some specific behavioral patterns due to the young age of the sample. It has been suggested that behavior changes may occur in early adulthood (Hennekam 2006). In particular, sudden mood changes, uncertain behavior, aggressiveness, and mood bipolar disorders might emerge during aging (Hellings et al. 2002; Levitas and Reid 1998). Interestingly, except for short attention span and motor stereotypies, our data did not suggest any early pattern of behaviors that could be related to subsequent psychopathology. For example, children with RTS did not exhibit higher rates of internalizing or externalizing problems, mood lability or temper tantrums. Since adult studies were based on non-representative and non-comparative data, there is a clear need to follow-up samples of RTS and control children prospectively to catch the eventual emergence of behavioral/psychiatric difficulties and observe RTS-specific evolution with age, and to try to determine which behavioral problems in childhood are possibly indicative of subsequent psychiatric conditions. If a negative psychiatric evolution arises in adulthood, it could suggest a postnatal dysfunctioning of *CREBBP/EP300* genes, as hypothesized by Alarcón et al. (2004) and Hennekam (2006).

Despite its limitations, this report is the first sizable comparative study to focus on the socio-behavioral aspects of children with RTS. By using a matched control group of similar DQ and chronological age, we controlled for confounding factors, especially at the cognitive level. Children with RTS did not exhibit higher internalizing or externalizing behavioral problems than expected for their age/developmental range. However, some specific behaviors were more frequently reported and are possibly of clinical relevance: (1) short attention span, (2) motor stereotypies, (3) poor coordination, and (4) overweight. Within the RTS group, the presence of an identified *CREBBP* gene abnormality was possibly specifically related to the motor difficulties through impaired motor skills learning. These results are important for families and professionals who may wish to address these issues. They point to the need for early assessment and management in order to enhance quality of life in children with RTS.

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