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Observations on Intelligence and Behavior in 15 Patients with Legius Syndrome

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Abstract

Legius syndrome is a RAS-MAPK syndrome characterized by pigmentary findings similar to neurofibromatosis type 1 (NF1), but without tumor complications. Learning difficulties and behavioral problems have been reported to be associated with Legius syndrome, but have not been studied systematically. We investigated intelligence and behavior in 15 patients with Legius syndrome and 7 unaffected family members. We report a mean full scale IQ of 101.57 in patients with Legius syndrome, which does not differ from the control group. We find a significantly lower performance IQ in children with Legius syndrome compared to their unaffected family members. Few behavioral problems are present as assessed by the Child Behavior Checklist (CBCL) questionnaire. Our observations suggest that, akin to the milder somatic phenotype, the cognitive phenotype in Legius syndrome is less severe than that of NF1.

Keywords

Intelligence; behavior; Legius syndrome; SPRED1; MAPK

INTRODUCTION

Legius syndrome was initially identified as a neurofibromatosis type 1 (NF1)-like syndrome arising from heterozygous germline loss-of-function mutations in the gene *SPRED1* [Brems et al., 2007]. The phenotype consists primarily of café-au-lait macules with or without freckling, and it lacks other characteristic features of NF1, such as neurofibromas, optic pathway gliomas, iris Lisch nodules or bone abnormalities. The majority of cases are familial[Messiaen et al., 2009]. Legius syndrome and NF1 both belong to the group of RAS-MAPK pathway disorders that are caused by mutations in genes coding for proteins of the RAS-MAPK pathway. This group of disorders is characterized by an overlapping phenotype

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consisting of heart defects, facial dysmorphism, skin abnormalities and variable degrees of cognitive impairment. In addition, most RAS-MAPK syndromes have an increased predisposition to malignancy [Denayer et al., 2008b]. Overall, the phenotype associated with Legius syndrome appears to be milder than the phenotype associated with NF1. In particular, there is not an increased risk for malignancy, although the number of reported patients is modest (139 reported patients; 53 adults, and 86 older than 5 years).

Learning difficulties [Brems et al., 2007; Muram-Zborovski et al., 2010; Pasmant et al., 2009], hyperactivity [Brems et al., 2007; Messiaen et al., 2009] and language or speech delay [Messiaen et al., 2009; Pasmant et al., 2009] have been reported in several children with Legius syndrome. In NF1, the prevalence of learning disabilities is estimated between 35–70%. The mean intelligence quotient (IQ) of patients with NF1 is lower than compared to the general population and sibling controls, and ranges from the high 80's to the low 90's [Levine et al., 2006; North et al., 2002]. In addition, NF1 is associated with impairments across multiple neuropsychological domains. Deficits in visuo-spatial and visual constructive skills are considered hallmarks of NF1. Other affected domains include attention (divided, switching and sustained), memory, language and executive functions (such as planning and organization and abstract concept formation) [Levine et al., 2006; North et al., 2002].

Studies in *Nf1* heterozygous mice have focused on hippocampus-dependent visuo-spatial memory. Heterozygous *Nf1* mice show deficits in the hidden version of the Morris water maze task, in which mice have to learn the position of a hidden platform beneath the water surface based on distant visual cues. These deficits can be reversed by compensating for RAS-MAPK hyperactivation by genetic and pharmacological approaches [Costa et al., 2001; Costa et al., 2002; Silva et al., 1997]. Treatment of $Nf1^{+/-}$ mice with farnesyltransferase-inhibitors as well as statins, which interfere with RAS membrane anchorage and thus RAS activation, resulted in performance comparable to wild-type mice [Costa et al., 2002; Li et al., 2005]. These initial animal studies prompted further evaluation of pharmacological treatment for learning difficulties in children with NF1 [Krab et al., 2008]. *Spred1* knockout mice had a similar impaired learning in the Morris water maze task. Heterozygous *Spred1* mice did not have deficits in the Morris water maze; however, they stagnated at an intermediate level between wild-type and knock-out mice in the last and most difficult part of the T-maze, a visual discrimination task [Denayer et al., 2008a]. Overall, the cognitive and synaptic plasticity phenotype in $Spred1^{-/-}$ mice is remarkably similar to that in $Nf1^{+/-}$ mice.

We sought to better understand the cognitive and behavioral functioning in patients with Legius syndrome, and to compare this with patients with NF1 because of the significant clinical and biochemical overlap in these two conditions in humans and the overlapping cognitive and synaptic plasticity phenotypes in mice. As a preliminary study, we compared intellectual functioning in children with Legius syndrome with their unaffected siblings/family members as controls. Since learning disabilities are characterized by impairments restricted to specific domains of mental function, leading to a discrepancy between tests of intellectual capability and actual achievement, we also asked parents for data on school performance of their children.

MATERIALS AND METHODS

We contacted 5 families with Legius syndrome currently followed in the Leuven multidisciplinary Neurofibromatosis clinic, and asked the children (aged up to 18 years) if they were willing to participate in this study. Eleven patients with pathogenic *SPRED1* mutations and 7 siblings/family members without the known familial mutation from 4

different families were eligible for this study and agreed to participate. A 5th family with a *SPRED1* mutation contained only one eligible affected patient, and this family was not contacted because of practical reasons. The clinical phenotype of the affected patients has been reported before (UZL1: IV8, IV9, IV10; UZL2: III4, III8, III9; UZL3: II1, II2, II3; UZL5:III1, III4) [Brems et al., 2007]. Their intelligence was measured by means of Wechsler intelligence tests. In addition, we contacted referring doctors from 2 other small families in Belgium with Legius syndrome. Sufficient data were available on one child from one family diagnosed in UZ Brussel. Moreover, we received results from intelligence testing for one family (one child and two adults) that was the only family diagnosed at NIH, USA. Thus, the total number of affected participants in this study is 15, and the number of unaffected participants is 7. All intelligence tests and behavioral checklists were performed in the participant's native language, ie Dutch for patients from UZ Leuven and UZ Brussel (Belgium) and English for patients from NIH, USA.

Assessment of cognitive function

Wechsler scales, according to their age distribution, were used as diagnostic instruments for intelligence (Table I). The Wechsler Preschool and Primary Scale of intelligence (WPPSI) was utilized in one affected and one unaffected child. The Wechsler Intelligence Scale for Children (WISC) was used to assess 14 children in their native language: in one affected child the revised edition (WISC-R) was used, in 13 children (7 affected and 6 unaffected) the 3rd edition (WISC-III) was used. Three affected young adults were tested with the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III). Two affected adults were tested with the Wechsler Adult Intelligence Scale 4rd edition (WAIS-IV), which reports Verbal Comprehensive Index (VCI) instead of Verbal IQ (VIQ) and Perceptual Reasoning Index (PRI) instead of Performance IQ (PIQ). One child was assessed with the Mullen Scales of Early Learning (a measure used to assess developmental functioning in children from birth to 68 months).

We compared the cognitive findings in the children with Legius syndrome with their siblings as well as with a group of 103 children with NF1 (ages 6–16 years) from the Leuven multidisciplinary clinic for neurofibromatosis who had been previously tested with the Flemish version of the WISC-R test (Wechsler Intelligence Scale for Children Revised).

Assessment of behavioral symptoms

To gain insight into the learning and behavioral problems in children with Legius syndrome, a parent report measure was used to assess specific problem behaviors and competencies. The Child Behavior Checklist (CBCL) [Achenbach et al., 2001] was completed, and we asked parents about the school performance of their children. The CBCL consists of 10 syndrome scales assessing Aggressive Behavior, Anxious/Depressed, Attention Problems, Delinquent Rule-Breaking Behavior, Social Problems, Somatic Complaints, Thought Problems, Withdrawn, Externalizing, and Internalizing Behaviors. Parents of 8 affected children and 7 unaffected children diagnosed in the Leuven multidisciplinary Neurofibromatosis clinic, and one child from the NIH clinic completed the CBCL. The Young Adult Behavior Checklist (YABCL) [Achenbach, 1997] was completed by one adult, and the Adult Self Report (ASR) [Achenbach et al., 2003] was completed by one other adult. An overview of the different families and types of intelligence/behavioral tests is given in Supplementary Table S1.

Statistical analysis

Data were compared using unpaired t-tests using Sigmastat software. To compare the WISC test results of the small group of 8 affected children with the group of 6 unaffected siblings we used the Mann-Whitney test, a non-parametric analog of the two-sample t-test. To

compare the scores on verbal and performal IQ within both groups we used the Wilcoxon signed-rank test.

RESULTS

Data from the patients from UZ Brussel and from NIH were combined with those from the patients from the Leuven multidisciplinary Neurofibromatosis Clinic. Intelligence data were first analyzed for the adolescents and adults. Three affected young adults aged 18 years had a mean full scale IQ (FSIQ) of 103.67 (SD= 14.64; median= 106) with verbal IQ (VIQ) of 110.67 (SD= 13.8; median= 116) and performance IQ (PIQ) of 98.67 (SD= 12.86; median=104). The two adults, aged 66 and 40 years had full scale IQ scores in the average and superior range (112; 128 respectively) with lower VCI (103; 127) than PRI (109;135) scores.

Data were analyzed for the group of children aged between 6 and 16 years tested with the Wechsler Intelligence Scale for Children (Table II). Mean age was 10 years in the affected group and 10.3 years in the unaffected group (p=0.835). A lower score of mean full-scale IQ (FSIQ) was obtained in the affected (95.25; SD= 18.47; median= 95.5) versus the unaffected group (113.33; SD= 13.94; median= 116), but this difference was not significant (p=0.069, Mann-Withney test). Also the VIQ was not significantly lower in the affected versus the unaffected group (p=0.195). However, children with Legius syndrome had a significantly lower PIQ than the unaffected children (p=0.028). The Wilcoxon signed-rank test showed no significant discrepancies between VIQ and PIQ within either the affected group (p=0.123), or in the unaffected group (p=0.684). One affected child had a FSIQ below 70. The affected group had the lowest mean score on all subtests; however, only in one subtest assessing performance IQ (Block Design), was the score significantly lower in the affected group (p=0.013; Mann-Withney test; without correction for multiple testing).

We analyzed the intelligence scores of 3 children (2 affected and 1 unaffected) who were too young to be tested with the Wechsler Intelligence Scale for Children. In 2 of these children (1 affected, 1 unaffected), cognitive functioning was evaluated with the WPPSI. The affected child had a FSIQ of 109 with VIQ of 118 and PIQ of 86. The unaffected child had a FSIQ of 92 with VIQ of 98 and PIQ of 88.

In one 5-year-old affected child, the Mullen Scales of Early Learning showed T-scores of 40 for visual reception, 28 for fine motor, less than 20 for receptive language and 26 for expressive language. These result in an estimated VIQ of 46, a PIQ of 68 and a FSIQ of 61.

After combining the data from all age groups tested via a Wechsler intelligence test, the significance for the difference between PIQ in the affected versus unaffected group disappears (Table III). We also compared the results of patients with Legius syndrome with the results of 103 children diagnosed with NF1 in the Leuven multidisciplinary clinic. Patients with a *NF1* microdeletion were excluded from this group. Unpaired t-test shows that the FSIQ and VIQ are significantly lower in patients with NF1 than in those with Legius syndrome, whereas there is no significant difference between PIQ in both groups (Table III).

In the second part of the study, we assessed school performance and behavioral problems in the group of patients with Legius syndrome. Concerning the school performance, 2 affected children were enrolled in special education programs because of learning problems and 3 other affected children were enrolled in vocational education programs. Two affected children had learning problems for mathematics, but were in a regular education classroom. In comparison, all 7 unaffected children were enrolled in regular education programs and no learning difficulties were reported. Concerning behavioral problems, one affected child diagnosed at NIH (individual IV3 from NIH, see supplementary table S1; 4 years, 10

months old at time of testing) was enrolled in a pre-school for children with autism spectrum disorder (ASD). He had a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). This child also had symptoms of Attention Deficit Hyperactivity Disorder (ADHD), but the diagnosis was not fully assessed because of his young age at the time of testing. In 2 affected siblings followed in the Leuven multidisciplinary Neurofibromatosis clinic (individuals UZL: III8 and III9, supplementary table S1), autistic features were noticed by observation and history, but no formal diagnosis of ASD had been made because the parents were not interested in additional testing. Two affected children were diagnosed with AD(H)D. In the group of unaffected children no symptoms of ASD or ADHD were indicated.

In addition, we compared the mean T-scores on the CBCL/YABCL/ASR forms between the affected and unaffected groups. This failed to show significant differences in the total score on any of the syndrome scales (anxious depressed, withdrawn/depressed, somatic complaints, rule breaking behavior, aggressive behavior, social, attention, thought problems). One affected male with a suspected diagnosis of ASD (patient UZL2: III8) had a total score in the borderline range with subscores for social problems and attention in the clinical range. The ASR form showed a score for withdrawn behavior in the clinical range for the affected adult. One unaffected male (patient UZL2: III6) also had a borderline total score with the subscore for rule-breaking behavior in the clinical range. These data indicate that there are no major behavioral problems in this small group of children with Legius syndrome as indicated by the responses on the CBCL. We compared these data to results of the CBCL in 114 children with NF1 followed in the Leuven multidisciplinary Neurofibromatosis clinic (Table 4). Given the small number of patients with Legius syndrome, there is insufficient power to conclude that the number of patients that fall in the clinical range for certain subscales is significantly lower than in NF1. Comparison of the mean T-scores on the different subscales shows significantly more somatic complaints and social problems in the group of children with NF1.

DISCUSSION

In conclusion, in this preliminary study we report a mean FSIQ of 101.57 (SD= 17.57; median= 107; IQR= 23) in 15 patients with Legius syndrome, which does not differ significantly from the control group, and is higher than the mean FSIQ in 103 patients with NF1. These preliminary data suggest that in addition to the somatic phenotype [Messiaen et al., 2009], the cognitive phenotype is milder in Legius syndrome than in NF1 and other RAS-MAPK syndromes. In Legius syndrome, the standard deviation was larger than expected, indicating a large variability in mean FSIQ in patients with Legius syndrome. Our data show a significantly lower performance IQ in children with Legius syndrome than in unaffected family members. In comparison with NF1, there were few behavioral problems as assessed by the CBCL. These results should be considered as preliminary since this study suffers from several limitations including; small patient group size, non-random ascertainment of included patients, and the use of various measures that spanned a wide age range. Moreover, the assessment of global intellectual functioning by means of Wechsler intelligence scales likely does not represent the full cognitive profile associated with Legius syndrome. In addition to studies assessing intelligence in larger numbers of patients, further studies using comprehensive neuropsychological testing consisting of specific tests for attention, memory, visuo-spatial abilities and executive functions are needed to increase our understanding of the cognitive profile. Therefore, these results indicate a need for larger studies addressing the cognitive and behavioral problems associated with Legius syndrome. Since Legius syndrome is rare – Messiaen et al. found an incidence for *SPRED1* mutations of 1.9% in patients fulfilling NF1 diagnostic criteria [Messiaen et al., 2009] suggesting that

the prevalence of Legius syndrome is 1/150,000 – additional studies will have to recruit patients from many centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

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Sarah L. Ruppert is a board certified genetic counselor who received her B.S. in Biology from Duke University and her M.S. in Genetic Counseling from the University of Minnesota. She is a current member of the editorial board of the Journal of Genetic Counseling and is a clinical protocol coordinator within the Genetic Disease Research Branch of the National Human Genome Research Institute at the National Institutes of Health.

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Table I

Characteristics of patients with Legius syndrome in this study

Group	Legius syndrome	Unaffected
No of patients	15	7
Males/females	11/4	5/2
Type of intelligence test		
WPPSI (3–7y)	1	1
WISC-R/WISC-III (6–16y)	1/7	0/6
WAIS-III/WAIS-IV (>16y)	3/2	0
Mullen Scales of Early Learning	1	0

WPPSI: Wechsler Preschool and Primary Scale of intelligence; WISC-R: Wechsler Intelligence Scale for Children-Revised; WISC-III: Wechsler Intelligence Scale for Children-3rd edition; WAIS-III: Wechsler Adult Intelligence Scale-3rd edition; WAIS-IV: Wechsler Adult Intelligence Scale-4th edition; y: year

Table II

Results of IQ testing by means of Wechsler Intelligence Scales for Children in children with Legius syndrome compared to family members

Group	Legius syndrome (SD; median; IQR) (n=8)	Unaffected (SD; median; IQR) (n=6)	p-value (Mann-Whitney test)
FSIQ	95.25 (18.47; 95.5; 23)	113.33 (13.94; 116; 18)	0.069
VIQ	99.75 (19.18; 97; 25)	111.83 (12.29; 112,5; 18)	0.195
PIQ	91.38 (16.81; 96,5; 23)	111.67 (13.37; 112; 16)	0.028

FSIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient. SD: standard deviation; IQR: interquartile range

Table III

Results of IQ testing by means of Wechsler intelligence tests in children and adults with Legius syndrome compared to family members and to children with NF1

Group	Legius syndrome (SD; median; IQR) (n=14)	Unaffected (SD; median; IQR) (n=7)	p-value (unpaired t-test)	NF1 (SD) (n=103)	p-value (unpaired t-test)
FSIQ	101.57 (17.57; 107; 23)	110.28 (15.06; 115; 20)	0.277	88.74 (15.18)	0.01
VIQ/VCI	105.57 (17.38; 105.5;26)	109.86 (12.38; 110; 23)	0.569	90.95 (15.65)	0.003
PIQ/PRI	97.64 (17.87; 100; 24)	108.29 (15.13; 109; 22)	0.193	88.40 (15.62)	0.068

FSIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; VCI: verbal comprehensive index; PIQ: performance intelligence quotient; PRI: perceptual reasoning index; SD: standard deviation; IQR: interquartile range

Table IV

Comparison of number of patients with Legius syndrome and NF1 that score in the clinical range for the different syndrome scales of the Child Behavioral Checklist and mean T-score on different syndrome scales

	Legius syndrome		NF1		P-value (t-test)
	No in clinical range (%)	Mean T- score (SD)	No in clinical range (%)	Mean T-score (SD)	
Withdrawn	1/11 (9.09)	55.5 (9.4)	7/111 (6.31)	55.5 (7.3)	0.989
Somatic complaints	0/11 (0.00)	51.3 (1.6)	17/114 (14.91)	58.9 (8.4)	0.003
Anxious/depressed	0/11 (0.00)	51.7 (3.9)	9/113 (7.96)	55.7 (7.9)	0.102
Social problems	1/11 (9.09)	54.7 (6.6)	31/111 (27.93)	62.4 (10.8)	0.038
Thought problems	0/11 (0.00)	52.2 (2.9)	7/111 (6.31)	55.6 (7.9)	0.185
Attention problems	1/11 (9.09)	56.4 (8.9)	28/111 (25.23)	62.4 (10.1)	0.060
Rule breaking behavior	0/11 (0.00)	52.1 (3.7)	10/110 (9.09)	54.9 (7.3)	0.226
Aggressive behavior	0/11 (0.00)	52.7 (3.6)	13/114 (11.40)	56.8 (9.1)	0.149