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ORIGINAL

Hypothyroidism and Down's syndrome

C. Claret [a,b,*], **J.M. Corretger** [c] **and A. Goday** [a,b,c]

[a] *Servicio de Endocrinología, Hospital del Mar, Barcelona, Spain*
[b] *Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Centre Mèdic Down, Fundació Catalana Síndrome de Down, Barcelona, Spain*

KEYWORDS
Hypothyroidism;
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Abstract
Introduction: Subclinical hypothyroidism is common in the first years of life of children with Down's syndrome (DS). The aim of this study was to analyse the natural evolution of this disease and to identify the factors that predict its spontaneous remission.
Material and methods: A retrospective, observational study conducted on patients with DS and hypothyroidism diagnosed before 5 years of age, who were seen in a DS reference medical centre.
Results: A total of 53 patients, 28 boys and 25 girls, with a mean age 2.4 ± 1.1 years, were identified with subclinical hypothyroidism. The hypothyroidism resolve spontaneously in 39 cases (73.6%), in a mean time of 13.2 ± 11.1 months, this resolution rate being significantly higher in the patients without goitre: 94.9% (95% confidence interval [CI]: 81.2-99.3%) vs 28.6% (95% CI: 4.4-37.7%), $p < .05$, and with negative antithyroid antibodies: 89.7% (95% CI: 74.6-96.2%), vs 42.9% (95% CI: 20.7-56%), $p < .05$). Fifteen patients (28.3%) were treated with levothyroxine.
Conclusions: The subclinical hypothyroidism that appears in early infancy in DS is usually transient. The absence of goitre and antibodies is associated with a higher spontaneous resolution rate.

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* Correspondence author.
E-mail: doctoraclaret@gmail.com (C. Claret).

PALABRAS CLAVE
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Tiroides;
Infancia;
Subclínico

Hipotiroidismo y síndrome de Down

Resumen
Introducción: el hipotiroidismo subclínico es frecuente en los primeros años de vida de los niños con síndrome de Down (SD). El objetivo del estudio fue analizar la evolución natural de esta patología identificando los factores que predicen su remisión espontánea.
Material y métodos: estudio observacional retrospectivo sobre pacientes con SD e hipotiroidismo diagnosticado antes de los 5 años de edad, atendidos en un centro médico de referencia para SD.
Resultados: se identificó a 53 pacientes con hipotiroidismo subclínico, 28 niños y 25 niñas, con una media de edad de 2,4 ± 1,1 años. El hipotiroidismo se resolvió espontáneamente en 39 casos (73,6%), en un tiempo medio de 13,2 ± 11,1 meses, y la tasa de resolución fue significativamente superior en los pacientes sin bocio: 94,9% (intervalo de confianza [IC] del 95%: 81,2-99,3%) frente a 28,6% (IC del 95%: 4,4-37,7%), $p < 0,05$, y con anticuerpos antitiroideos negativos: 89,7% (IC del 95%: 74,6-96,2%) frente a 42,9% (IC del 95%: 20,7-56%), $p < 0,05$. Un total de 15 pacientes (28,3%) fueron tratados con levotiroxina.
Conclusiones: el hipotiroidismo subclínico que aparece en la primera infancia en el SD suele ser transitorio. La ausencia de bocio y anticuerpos se asocia a una mayor tasa de resolución espontánea.

Introduction

The prevalence of medical disorders in individuals with Down's syndrome (DS) is higher than in the general population, and has a negative impact on their quality of life and life expectancy. Thyroid disease features prominently among these medical problems. Both hyper- and hypothyroidism, mainly of autoimmune origin, occur more often in DS[1-3], the latter being 6 times more common than the former[4,5].

As well as the increased risk of developing hypothyroidism with age[2,6], children with DS have a higher probability of presenting with two other thyroid problems in their first months of life: congenital hypothyroidism[7], which can be easily detected by neonatal screening, and, more frequently, an isolated mild increase in thyrotropin (TSH) or subclinical hypothyroidism[8,9]). This latter disorder is usually transient and rarely progresses to clinical stages, and normally self-resolves without the need for treatment[10,11]. But there are few systematic studies on this disorder, and the factors associated with this self-resolution are not clear. There are also doubts on the possible benefits of hormonal treatment on the development of these patients, despite it being a subclinical, and even transient, disorder. In this sense, the results of a double-blind randomised clinical trial with 196 children with DS were innovative compared to previous studies. Based on the theory that all subjects with DS are slightly hypothyroid at birth[12,13], this study evaluated the effect of systematic treatment with levothyroxine started in the neonatal period and during the first two years of life, compared with placebo. The treatment with levothyroxine showed a slight improvement in psychomotor development and somatic growth at 24 months, and thus concluded that hormonal treatment should be considered in neonates with DS to obtain optimal development and growth[14].

The primary aim of the current study is to characterise and analyse the progression of the hypothyroidism diagnosed in a population of children under 5 years-old with DS, and to determine the main factors that predict the spontaneous resolution of the disorder.

Material and methods

Patients

A retrospective study was conducted on a clinical series of patients with DS and hypothyroidism. The data were collected by reviewing the clinical histories of patients with DS from the *Fundació Catalana Síndrome de Down* (FCSD), registered between 1993 and 2008. The FCSD, established in 1984, is a non-profit organisation that has as its aim to promote the full development of subjects with DS in Catalonia. It provides support to patients from prenatal diagnosis to adulthood, but does not have a complete populational record of all patients with DS. The medical program of the Foundation includes the annual systematic screening for thyroid diseases, including the annual determination of TSH. The FCSD data base was analysed, and all patients with hypothyroidism were identified, whether it was clinical (elevated TSH with decreased levels of total triiodothyronine (TT3) and/or free thyroxine (FT4), or subclinical (elevated TSH with normal TT3 and FT4 levels). All patients were less than 5 years-old at the time of diagnosis, and had been assessed by the same endocrinologist.

Clinical data

Among the variables collected from the clinical histories included: age when diagnosed with hypothyroidism, sex, the presence of thyroid disease in the family history, the

genetic variation associated with the DS, and associated medical disorders. The signs and symptoms of the hypothyroidism on diagnosis, and in the follow-up were recorded, using the score on a scale validated by Billewicz[15]. This scale adds or subtracts points depending on the presence or absence of various signs and symptoms. Individuals with hypothyroidism usually score over +29 and the euthyroids less than −4. Scores between −4 and +29 are considered indeterminate. We determined the presence and grade of goitre at diagnosis and during follow-up. The record of signs and symptoms was made by looking at the laboratory results, with their interpretation not being blind.

Anthropometric measurements

Weight and length/height at diagnosis was obtained by direct measurement in light clothes and without footwear, along with the percentiles corresponding to the Spanish population with DS[16], and the evolution of these parameters in the two years following the diagnosis. The body mass index (BMI) was calculated for the patients over 2 years-old.

Laboratory data

The laboratory data included the determination of TSH, FT4 and TT3, as well as anti-peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies. The reference interval of TSH differed according to the age of the patient: 0.01-5.5 µU/mL (6 months-4 years), and 0.57-4.13 µ/mL (4-7 years). We recorded whether the TT3 and FT4 were normal, elevated or decreased according to the normal intervals related to the age. The reference interval for FT4 was: 0.89-1.87 ng/dL (6 months-4 years) and 0.96-1.86 ng/dL (4-7 years). The reference interval for TT3 was 0.75-2.05 ng/dL (6 months-4 years) and 1-1.78 ng/dL (4-7 years).

Similarly, whether the antibodies were positive or negative was also determined as a categorical variable.

Resolution and treatment dose

The remission of hypothyroidism was defined as the return of the TSH levels to normal without the need to start hormone treatment, or at least after having stopped it for 12 months. The time passed until the resolution and the associated factors were determined.

The criteria that the endocrinologist had used to start hormone replacement treatment were to have a TSH ≥ 10 µ/mL, a decrease in peripheral hormones T3 and/or T4, or due to the indication of cardiac surgery, given the importance of achieving a strictly normal thyroid function in this situation.

For the cases on treatment with levothyroxine, the mean initial dose and that during follow-up according to age and sex (total and per kg weight) were recorded, as well as the annual changes in these doses.

Statistical analysis

The differences between groups were analysed using the χ^2 test for the categorical variables, the independent samples *t* test for continuous variables with a normal distribution, and the Mann-Whitney U test for the variables that did not follow a normal distribution (TSH, FT4 and TT3). The results are presented as means ± SD and percentages with CI. We considered the significance level as $p < .05$. The analyses were performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL).

The study was approved by the FCSD Clinical Research Ethics Committee.

Results

Baseline characteristics

Out of a total of 1903 clinical histories from the FCSD, 149 patients were identified with an alteration in thyroid function, which is a prevalence of 7.8% (95% CI: 6.6-9%), 12 of them with hyperthyroidism[3], and 137 with hypothyroidism (fig. 1). Of the 137 patients with hypothyroidism, 54 (28 boys and 25 girls) were diagnosed before 5 years of age; 1 of them had clinical hypothyroidism with a low FT4, while the remaining 53 fulfilled the criteria of subclinical hypothyroidism, and were included in the study. The follow-up time was 54 ± 19 months. The mean age was 2.4 ± 1.1 years. Table 1 shows the baseline characteristics at the time of diagnosis.

There was a family history of thyroid disease in 13 patients (24.5%; 95% CI: 12.3-37.7%), multinodular goitre and hypothyroidism in the majority of the cases, with a predominance of the maternal line. Karyotype analysis was available in all cases, which confirmed trisomy 21 as the most common genetic abnormality (n = 48, 90.5% [95% CI: 80.5-97.3%]), followed by mosaicism (n = 4, 7.5% [95% CI: 0.4-14.4%]) and 14/21 translocation (n = 2, 3.7% [95% CI: −1.3-8.7%]). There was a high prevalence of concomitant medical disease, particularly congenital heart diseases, which affected 23 cases (43.4% [95% CI: 29-56.2%]).

Signs and symptoms

A total of 19 patients (35.8% [95% CI: 22.4-47.9%]) had some symptom or sign of hypothyroidism on diagnosis. The most frequent symptoms described were, constipation (23.6%), rough, dry or cold skin (22.1%), and weight increase (11.1%). Other, less frequent, symptoms were: intolerance to cold, decrease in sweating, asthenia, hearing loss, or drowsiness. The mean score on the Billewicz scale was −13.9 ± 11.9 (non-specific). There were no differences in the mean values of TSH between the patients with and without symptoms (mean 8.2 ± 2.9 µU/ml vs 8 ± 2.8 µU/ml, respectively, p = .5). The neck examination showed the presence of goitre in 12 cases (22.6% [95% CI: 15.2-65%]), which, in the majority of cases (91.7%), was of low grade (Grade I).

Anthropometric data

The mean weight percentile compared to the Spanish population with DS was 55 ± 24.2 at the time of diagnosis, and a mean length/height percentile of 45.7 ± 26.6. The BMI at diagnosis, excluding patients less than 2 years-old, was 16.5 ± 1.3, with a mean percentile BMI compared to the general

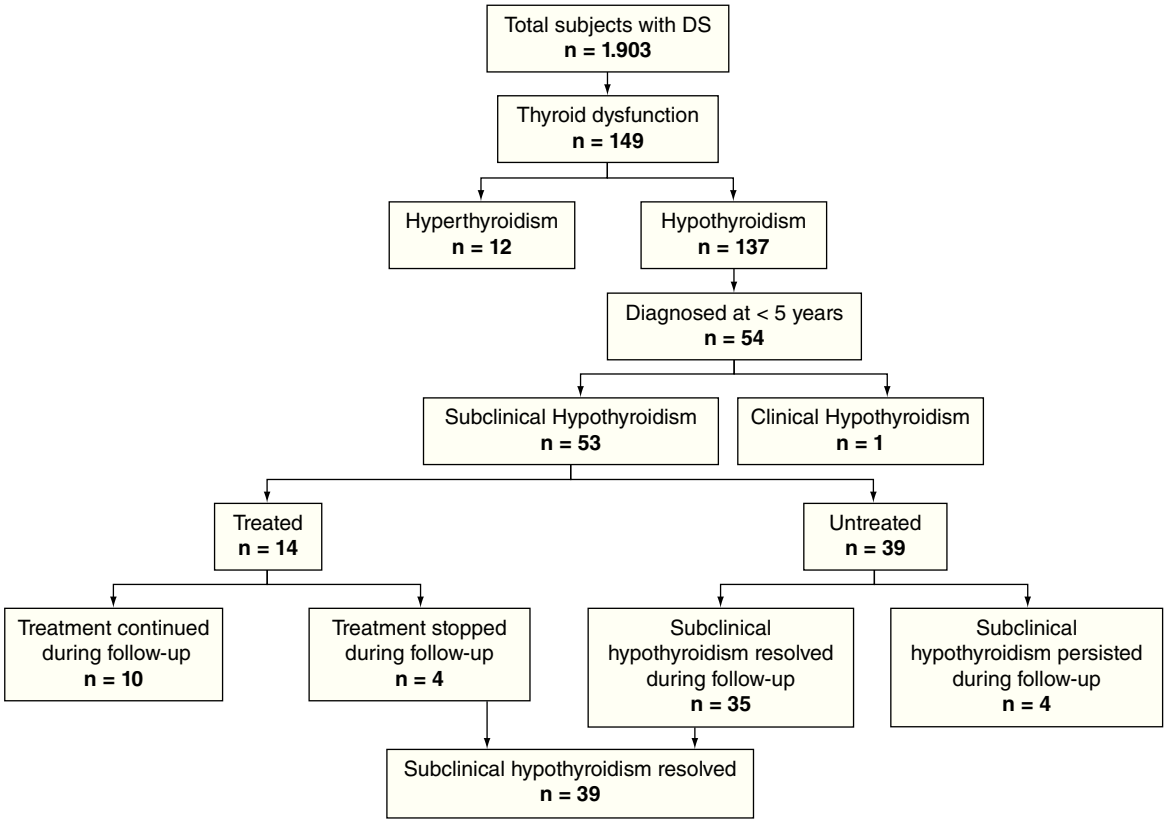

Figure 1 Flow diagram of all the patients with Down's syndrome and hypothyroidism from the Fundació Catalana Síndrome de Down data base.

Table 1 Baseline characteristics of the patients with Down's syndrome and subclinical hypothyroidism diagnose before 5 years of age

n	53
Age (years)	2,4 ± 1,1
Sex (M/F) *n*	28/25
Family history of thyroid disease *n* (%)	13 (24,5%)
Karyotype: trisomy 21 *n* (%)	48 (90,5%)
Congenital heart disease *n* (%)	23 (43,4%)
Hypothyroidism symptoms/signs *n* (%)	19 (35,8%)
Weight (percentile according to the Spanish Population with DS)	55 ± 24,2
Length/height (percentile according to the Spanish Population with DS)	45,7 ± 26,6
TSH (µU/mL)	8 ± 2,8
Positive TPO and Tg antibodies *n* (%)	12 (22,6%)

DS: Down's syndrome; Tg: anti-thyroglobulin; TPO: anti-thyroid peroxidase.

Spanish population of 59.3 ± 31.2. The percentage of overweight patients at the time of the diagnosis was 22.9% (95% CI: 9.1-37%), and there was 11.4% with obesity (95% CI: 0.6-21.4%).

There were no significant differences between the 2 groups in the initial weight and length/height percentiles, nor at one year or two years of onset.

Laboratory data and rate of resolution

The mean TSH at diagnosis was 8 ± 2.8 µU/ml. The subclinical hypothyroidism was resolved in 39 of the 53 cases (73.6% [95% CI: 61.7-85.4%]), spontaneously in 35 patients, and after withdrawing the levothyroxine medication in 4 cases. The mean time required for the resolution was 13.2 ± 11.1 months from the diagnosis. The majority of these cases were resolved between 4 and 5 years (fig. 2). No patient progressed to clinical hypothyroidism during the observation period. In the group in which the hypothyroidism resolved, the mean TSH in the last recorded visit was 3.6 ± 1.9 µU/ml, and the age was 6.8 ± 1.4 years.

Twelve cases (22.6% [95% CI: 11.4-33.9%]), had positive anti-TPO and/or anti-Tg antibodies at diagnosis or during the follow-up.

The factors significantly associated to the resolution of the hypothyroidism were the absence of goitre and antithyroid antibodies at diagnosis and during follow-up. Other factors analysed, but had no significant association were,

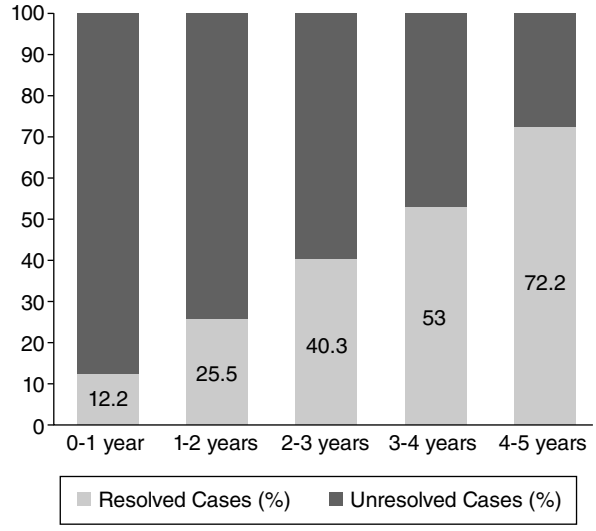

Figure 2 Hypothyroid remission according to age interval.

age, sex, family history, absence of symptoms, and the mean TSH at diagnosis (table 2). When goitre was absent, the resolution rate was 94.9% (95% CI: 81.2-99.3%), while if it was present, the hypothyroidism resolved in 28.6%of the patients (95% CI: 4.4-37.7%) ($p < .05$). The resolution rate was 89.7% (95% IC: 74.6-96.2%) in the group with negative antithyroid antibodies, while it was 42.9% (95% CI: 20.7-56%) ($p < .05$), in the group with positive antithyroid antibodies.

Treatment

A total of 15 (28.3%) patients received treatment with levothyroxine. In the majority of cases, the reason that indicated treatment was a TSH higher than 10 µU/ mL (in 1 case there was a decrease in peripheral hormones, and 1 case required cardiac surgery due to a congenital heart defect. The mean age at the start of treatment was 4.4 ± 3 years, and the mean TSH was 10.9 ± 1.3 µU/ ml. The mean initial dose of levothyroxine per kilogram was 1 ± 0.4 µg/ kg/ day (1.1 ± 0.3 µg/ kg in boys and 0.9 ± 0.5 µg/ kg in girls).

Discussion

In the present study it has been observed that the hypothyroidism characteristic of early infancy in DS usually presents as a subclinical disorder. The distribution of the disorder in this initial stage is similar between sexes, which contrasts with that which occurs in the population without DS, where the hypothyroidism is clearly predominant in the female sex[17-20]. The majority of cases are resolved without treatment, and the persistence or progression to clinical stages appears to be linked to the presence of autoimmune factors.

The cause of subclinical hypothyroidism in the first years of life of DS patients is not clear. Among the different hypotheses are that it is due to, a local peripheral defect in the production or action of T3[9], thyroid insensitivity to TSH[10,11], or an inadequate secretion, or less active TSH at central level, although in some studies the bioactivity of the TSH molecule appears to be normal in these patients[21,22]. The findings by Karlsson indicated that autoimmunity did not seem to play an essential role in this disorder, although this normally appears later on, at school age[17]. Van Trotsenburg suggested that virtually all individuals with DS had a congenital defect in the regulation at the level of the thyroid gland itself, which would be in a direct relationship with the trisomy state of chromosome 21. This approach is the result of a longitudinal study conducted on 97 neonates with DS, who were followed-up until up to 26 months of age. The results showed that the distribution of the TSH and FT4 values were normal or Gaussian, but dis-

Table 2 Factors associated with the remission of the subclinical hypothyroidism

	Hypothyroidism remission	Hypothyroidism persistence	*p*
n (%)	39 (73,6%)	14 (26,4%)	–
Mean age at diagnosis (years)	2,5 ± 1,1	2,3 ± 1,2	0,95
Mean age at the last recorded visit (years)	6,8 ± 1,4	6,6 ± 1,4	0,67
Sex (%girls)	47,4%	50%	0,29
Family history of thyroid disease *n* (%)	8 (20,5%)	5 (35,7%)	0,33
Hypothyroidism symptoms/ signs *n* (%)	11 (28,2%)	8 (28,6%)	0,72
Mean TSH at diagnosis (µU/ ml)	3,6 ± 1,9	9,1 ± 3,5	0,13
Absence of goitre *n* (%)	37 (94,9%)	4 (28,6%)	**< 0,05**
Negative TPO/ Tg antibodies *n* (%)	35 (89,7%)	6 (42,9%)	**< 0,05**

Tg: anti-thyroglobulin; TPO: thyroid peroxidase antibody; TSH: thyrotropin.

placed to the right and to the left, respectively[12]. Along the same lines, another recently published study also showed that the TSH levels in neonates with DS were higher than those in the control group, particularly in the males[23].

In these cases of subclinical hypothyroidism detected in these initial stages, the most usual approach consisted of performing an analytical follow-up with no initial therapeutic intervention, given its frequent remission[24]. The longitudinal study by Gibson showed that only one of the 20 cases of children with DS and an isolated increase in TSH developed clinical hypothyroidism in a second hormone determination performed 4-6 years later. Furthermore, the TSH returned to normal in the majority of patients in a short period of time[10]. Similarly, in our study only 1 patient had decreased T3 and T4, and the disorder resolved spontaneously in the majority of cases.

The presence of goitre or antibodies suggests the development of an autoimmune thyroiditis process, of such a different nature to the hypothyroidism observed in the majority of these children[17]. Rubello demonstrated that, in patients with subclinical hypothyroidism and positive antibodies, the possibilities of developing frank hypothyroidism in the follow-up are much higher than in those with negative antibodies[6]. The absence of goitre and antibodies are factors that predicted a higher probability of hypothyroidism remission in our study.

It has been postulated that subclinical hypothyroidism can be an added factor that could contribute to the growth delay in these patients, or could have an effect on the intellectual development, aggravating the mental retardation common to DS. The results of previous studies on this aspect are variable. Papendieck was unable to demonstrate that patients with DS and an elevated TSH had abnormal growth or improved with thyroid hormone treatment[1]. Another study could not find any differences either, when comparing the growth and intellectual development of children with compensated (subclinical) hypothyroidism with a control group with normal thyroid function[11]. On the other hand, in a longitudinal study by Karlsson, the children with hypothyroidism, in the year before starting treatment with FT4, had a lower growth rate compared to euthyroid children with DS of the same age and sex (controls), and this growth rate improved during the first year of treatment[17]. Also, the results of the trial by van Trotsenburg encouraged early treatment in the neonatal stage, considering that all individuals with DS are slightly hypothyroid at birth[14]. But, although the treated group of neonates showed an improvement in development at 2 years compared with the group treated with placebo, it has to be said that these differences were slight and probably of limited clinical relevance, particularly those referring to somatic growth. In our study, we did not observe any differences as regards the growth curves between treated and untreated children, although it has to be taken into account that the weight and height percentiles are not a good indicator of the possible effectiveness of the treatment on growth, and that the analysis of these variables are only limited to a period of 2 years.

We attempted to apply a systematic signs and symptoms score scale to the patients[15]; this correlation method is of little practical use, given that the mean score on the scale was negative, which is to say, non-specific. It should be taken into account that almost all these cases are diagnosed in the early stages of thyroid hypofunction, in theory, before the symptoms appear. This means that the clinical signs may not be of much value for the diagnosis, even in cases of very high TSH, and a T4 below the normal limit[25]. Effectively, our only patient with a decrease in T3 and T4 did not present with symptoms of hypothyroidism. Besides, the symptoms of hypothyroidism are very non-specific due to the overlap with those common to DS[26].

The limitations of the present study are mainly due to its observational and retrospective design, and the absence of a control group. The number of cases is relatively small, and we have no data available on the psychomotor development of the patients studied.

In conclusion, hypothyroidism in the first years of life in patients with DS is shown as a subclinical and mainly transient disorder, with the principal predictive factors of spontaneous remission being the absence of goitre and anti-thyroid antibodies.

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Conflict of interests

Authors declare not to have any conflict of interests.

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