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Original Article

Congenital anosmia

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ABSTRACT

INTRODUCTION. Congenital anosmia (CA) is a rare condition among all olfactory disorders (OD). It is estimated that one in 10,000 persons is born with anosmia, and the diagnosis may be related to various syndromes, especially Kallmann (hypogonadotropic hypogonadism).

METHODS. Patients with CA were identified in the REDCap database at the University Clinic for Flavour, Balance, and Sleep; Department of Otorhinolaryngology, Goedstrup Hospital, Denmark. In addition to demographics and clinical findings, the database recorded patient-reported outcome measures, such as the Sino-Nasal-Outcome-Test 22 scores and the Major Depression Index, as well as quality of life scores and results of psychophysical tests. OD was assessed using the Danish modification of the Sniffin' Sticks, including screening for basic tastes. Furthermore, results of blood tests, BMI and imaging (magnetic resonance imaging of the brain/computed tomography of the sinuses) were included in the database.

RESULTS. The cohort (n = 100) was characterised by a slight predominance of females (n = 56) and a wide age range from six to 72 years. A total of 50% had various comorbidities – besides allergic diseases, psychiatric and neurologic disorders were frequent. In addition, 29% of patients had relatives with relevant anosmia-/hyposmia-related disposing conditions. Total threshold, discrimination identification (TDI) scores were below 16 in 90 patients.

CONCLUSIONS. Our findings underscore the importance of early identification of CA through olfactory testing and MRI, with genetic and endocrine evaluations when appropriate.

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The literature on olfactory dysfunction (OD) has risen sharply over the past two decades, with a considerable boost from the COVID-19 pandemic and its profound impact on the sense of smell and taste. The prevalence of OD in the population is estimated at 15-20%, including both quantitative and qualitative OD [1]. Quantitative OD refers to decreased olfactory sensitivity (hyposmia and anosmia), whereas qualitative OD involves changes in the perception of sensory input, most often negatively (parosmia and phantosmia) [1]. The diagnosis is usually based on subjective reporting/questionnaires, as well as various psychophysical tests, such as Sniffin' Sticks, which provide composite scores for threshold, discrimination, and identification [2, 3].

It is well known among adults that OD has a major impact on quality of life (QoL), pleasure, sexuality, nutrition, mental health, social relationships and warning against environmental hazards [4-6]. If OD is hypothesised to have an equivalent impact on children, how would this manifest? Children often lack the vocabulary to express deficits and symptoms, and may not be aware of the problem [7]. In a previous study of children referred to a flavour clinic, we concluded that attention towards OD in childhood/adolescence is quite low and that OD among

children may be underreported [7]. Furthermore, we suggested that eating disorders may be a result of or associated with OD [7]. Besides vocabulary, familiarity with odours and motivation, testing may be rather difficult [1, 7, 8].

Congenital anosmia (CA) may constitute a unique problem in OD. It is estimated that one in 10,000 persons is born with anosmia [9]. CA may be related to various syndromes, especially Kallmann (hypogonadotropic hypogonadism), Turner and Bardet-Biedl syndromes, whereas a third of cases are non-syndromic idiopathic CA of unknown aetiology [1, 9]. For differential diagnostics between congenital and "acquired" OD, magnetic resonance imaging (MRI) of the olfactory bulb and sulci is required to demonstrate hypoplastic/aplastic olfactory bulbs and olfactory sulci [1, 10]. Further diagnostics with genetic, endocrinological and paediatric examination is recommended to identify children who need hormonal substitution [1].

The aim of this study was twofold: First, to investigate the characteristics and assumed consequences of CA. Second, to explore how the management of CA can be optimised, including how awareness of the phenomenon can be improved. The study hypothesises that a limited ability to perceive nuanced flavours — for example, relying solely on the basic tastes — may lead to the development of picky eating behaviours or other eating disorders. Furthermore, we expected to find an OD-related negative impact on QoL.

Methods

Patients with CA were identified in the Flavour REDCap database at the University Clinic for Flavour, Balance, and Sleep; Department of Otorhinolaryngology, Head and Neck Surgery, Goedstrup Hospital, Denmark. The database was established in January 2017 and contains approximately 3,500 patients who have consented to be registered, including demographic data, clinical findings and patient-reported outcome measures (PROMs) such as Sino-Nasal-Outcome-Test 22 (SNOT-22) scores and Major Depression Index (MDI) scores. Furthermore, the patient-rated degree of negative impact of OD on their QoL, measured on a Likert scale from 1 (no impact) to 10 (worst possible impact), was recorded in the database along with the results of psychophysical tests [11-13]. Olfactory threshold (T), discrimination (D) and identification (I) scores obtained by the Danish version of the Sniffin' Sticks, including a composite threshold, discrimination identification (TDI) score, were noted, as well as screening of the basic tastes: sour, bitter, sweet and salty by taste sprays. In case the child did not understand the TDI test, a smell identification test (SIT-16) was performed.

Finally, results of blood tests and brain imaging (3 T MRI)/sinuses (HRCT) were included in the database.

The database and the study were approved by the Danish Data Protection Agency (ref. no. 790983).

Statistics

Descriptive statistics are presented as means SDs, medians with ranges, or frequencies with percentages, as appropriate. Comparison between subgroups was performed by Student's t-test in case of normally distributed data; otherwise by the χ^2 test or Fisher's exact test.

Trial registration: not relevant.

Results

From January 2017 to September 2024, 100 patients were registered in the Flavour database due to clinical suspicion of CA based on patient- and/or parent-reported data. The cohort was characterised by a slight predominance of females and a relatively wide age range from 6 to 72 years (**Table 1**). However, the majority were adolescents and young adults who reported not having experienced any smell sensation in their lives,

consistent with the relatively long duration of anosmia listed in **Figure 1**. Typically, all patients had become aware of the missing sense of smell during adolescence when peers referred to perfumes and body odours due to, e.g., sweat.

TABLE 1 Demographics of 100 patients with clinical suspicion of congenital anosmia who were referred to the Flavour Clinic between January 2017 and September 2024.

Sex, n (%)	
Female	56 (56)
Male	44 (44)
Total	100
Age, yrs	
Mean (SD)	25.4 (15.9)
Median (min.-max)	19 (6-72)
Comorbidity, PROMs, n (%)	
1 comorbidity:	
Allergic diseases	20
Psychiatric/personality disturbances	13
Endocrinological/blood/heart-vessel diseases	9
Neurologic diseases	8
Subtotal	50 (50)
> 1 comorbidity	10
No comorbidity	48 (48)
Unknown	2 (2)
Medication, n (%)	39 (39)
Airway medication	16
SSRI/melatonin	10
No medication	61 (61)
Dispositions, n (%)	
Dementia	6
Metabolic	4
Parkinson	3
Depression	1
Cerebral-cardio-vascular	1
Others	14
Subtotal	29 (29)
Smokers, n (%)	7 (7%)
Other family members with OD? (N = 76)[a]	
Yes, % (n/N)	16 (12/76)
No, % (n/N)	78 (59/76)
Uncertain, % (n/N)	6 (5/76)

OD = olfactory dysfunction; PROMs = patient-reported outcome measures; SSRI = selective serotonin reuptake inhibitors.
a) The variable was not registered for all patients.

FIGURE 1 Patient-reported outcome measures.

		Distribution measure	n
Subjective duration of anosmia			
Mean (SD), yrs	24.59 (18.027)	*Duration*	
Median (min.-max), yrs	18 (1-72)	≤ 2 yrs	5
		3-10 yrs	10
		> 10 yrs	80
Subtotal			95
Impact on QoL, Likert scale score[a]			
Mean (SD)	4.56 (2.63)	*Score*	
Median (min.-max)	2 (1-10)	1	10
		2	6
		3	12
		4	7
		5	11
		6	6
		7	9
		8	5
		9	2
		10	3
Subtotal			71
SNOT-22 score			
Mean (SD)	18.22 (14.35)	*Score*	
Median (min.-max)	7 (0-62)	0-7	24
		8-20	44
		21-50	28
		> 50	3
Subtotal			99
MDI score			
Mean (SD)	8.41 (9.44)	*Score*	
Median (min.-max)	3 (0-47)	0-19	85
		20-24	6
		25-29	3
		> 29	3
Subtotal			97

MDI = Major Depression Index; QoL = quality of life; SNOT-22 = Sino-Nasal-Outcome-Test 22.
a) 1-10 (no – worst possible).

A total of 23% of patients had a positive reaction towards a standard allergen panel, especially grass, house dust and birch. Furthermore, 50% had various comorbidities – besides allergic diseases, psychiatric and neurologic disorders were frequent (Table 1). In addition, 29% of patients had relatives with relevant anosmia-/hyposmia-related disposing conditions. Concerning family history, 16% had other relatives with known OD, which exceeds the prevalence of subjective OD in the general population [14] (Table 1). Notably, in eight of the nine cases with known anosmia in the family, the relatives were females, i.e., mothers, grandmothers or maternal aunts.

More than two-thirds had rated the impact of anosmia on their QoL (Figure 1). Among these, over half reported experiencing no or little negative influence on their QoL due to anosmia. Most patients had total SNOT-22 scores

within the normal range, and those with scores indicative of chronic rhinosinusitis (CRS) had developed these symptoms independently of their anosmic condition. Six patients (three adolescents and three adults) had MDI scores corresponding to moderate to severe depression: two were known with a psychiatric diagnosis and in medical treatment; four were undiagnosed and untreated at the time of the clinical visit.

Test results listed in **Figure 2** show a total TDI score in 92 patients, as it was not possible to conduct the identification test among eight children and adolescents. Thus, these eight identification scores were obtained by the SIT-16. Among the eight patients for whom only the SIT-16 or an identification score on the Sniffin Sticks was available, the scores ranged from 0 to 10 out of 16. Overall, the TDI scores verified the presence of anosmia according to the definition, except in two cases with TDI scores of 17 and 19, respectively.

FIGURE 2. Test results of the Sniffin' Sticks, taste spray test, imaging and biochemistry.

Objective test measures		Distribution score	n
T score			
Mean (SD)	1.08 (0.43)	-	
Median (min.-max)	1 (1-4.25)	-	
Subtotal			97
D score			
Mean (SD)	4.9 (2.05)	-	
Median (min.-max)	5 (1-11)	-	
Subtotal			93
I score			
Mean (SD)	4.5 (2.44)	-	
Median (min.-max)	4 (0-10)	-	
Subtotal			98
TDI score			
Mean (SD)	10.5 (3.23)	≤ 16	90
Median (min.-max)	10 (4-19)	17	1
		19	1
Subtotal			92[a]
Taste spray test score			
Mean (SD)	3.89 (0.379)	4	83
Median (min.-max)	4 (2-4)	2 and 3	5
Subtotal			88
Allergy test, n			
Positive		-	23
Negative		-	64
Not performed		-	13
Subtotal			100
CT sinuses, n			
Not performed[b]		-	25
Patients with normal findings		-	69
Patients with abnormal findings		-	6
Subtotal			100
3 T MR-C, n			
Not performed		-	23
Patients with normal findings		-	10
Patients with abnormal findings		-	64
1.5 MR-C with normal findings of the brain		-	3
Subtotal			100
Biochemistry, n			
Patients with abnormal findings		-	2
Subtotal			15

D = discrimination; I = identification; MR-C = magnetic resonance imaging of the cerebrum; SIT-16 = Sniffin' Sticks 16 Identification Kit; T = threshold.
a) 8 identification scores were obtained by SIT-16.
b) Computed tomography was avoided in children and adolescents as a routine procedure.

In contrast, all patients had normal sensation of the basic tastes, except in five cases, in which especially bitter and sour were confused.

Allergy tests showed positive reactions in 23 patients (23%), particularly to grass, house dust and/or birch, consistent with the background population [15, 16]. Among the 75 patients undergoing CT of the nasal sinuses, only six revealed signs of CRS. Three of these patients were known to suffer from CRS/upper airway allergy. MRI was conducted in 77% of patients, of whom the majority (77/64; 83%) had aplasia of the olfactory bulb, usually associated with hypoplasia/aplasia of the olfactory sulci. The typical reasons for omitting MRI were the patient's/parent's preferences, the patient's young age or rejection of the MRI referral because the patient

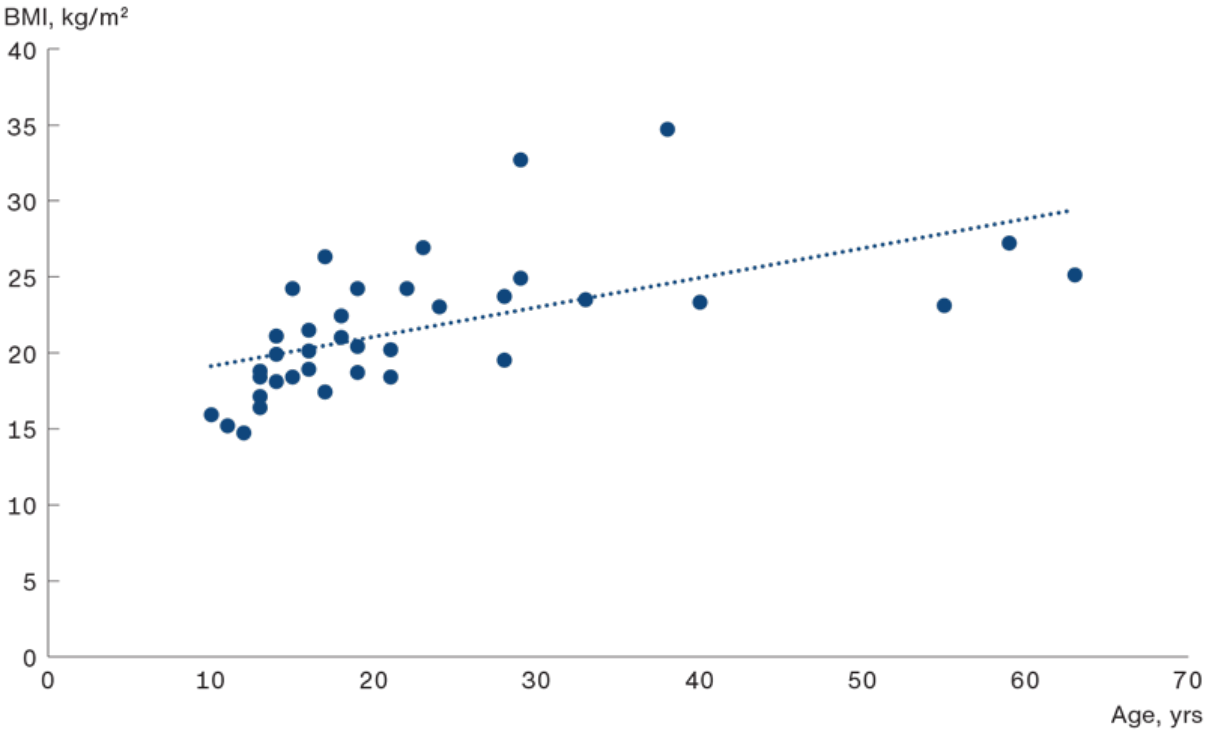
resided in another geographical region. A minority had devices resulting in disturbing artefacts on MRI, such as braces.

Before undergoing genetic assessment, patients underwent endocrine screening via blood tests. For women, the tests included follicle-stimulating hormone, luteinising hormone, oestradiol, haemoglobin, androstenedione, sex hormone-binding globulin and dehydroepiandrosterone sulphate. For men, the screening included the same tests, plus total and free testosterone.

Supplementary workup revealed that genetic testing had been performed in 15 patients, of whom two showed a mutation associated with Kallmann syndrome (*ANOS1*); another child had a rare mutation in a gene associated with Kallmann syndrome.

It was possible to calculate BMI for a total of 37 patients using electronic patient record information. The mean BMI was 21.7 kg/m^2 (median: 21; range: 14.7-34.7), with a tendency for BMI to increase with age (**Figure 3**). Eleven patients had BMI values below normal (18.5 kg/m^2). The mean age (13.8 years; range: 10-21 years) of these patients was significantly lower than that of the remaining group (mean: 26.7 years; range: 14-63 years) (t = –3.01188, p = 0.002399). Four patients had a current or prior history of an identified eating disorder (anorexia) or picky eating.

FIGURE 3 BMI versus age in 37 patients, based on electronic patient record information.



Discussion

Principal findings

This paper presents one of the largest cohorts of patients with clinically suspected CA, highlighting a wide age range and a predominance of adolescent and young adult presentations. Most patients reported lifelong absence of olfactory perception, confirmed in most cases by clinical history, objective psychophysical testing and MRI

findings demonstrating olfactory bulb aplasia or hypoplasia. Despite the condition's congenital nature, diagnosis was often delayed until adolescence or adulthood.

Comparison with existing literature

The reported prevalence of familial anosmia (16%) is higher than expected based on previous estimates of isolated CA in the general population (~ 0.01%) [9, 17]. This may indicate underdiagnosis or limited awareness of olfactory loss among children and parents. Similar to earlier studies [4, 5], the present study showed that while many patients reported little impact on QoL, a considerable minority rated the negative influence as moderate to severe. These findings support the hypothesis that olfactory function plays a more subtle yet meaningful role in psychosocial development than is typically acknowledged, particularly in adolescence, when social cues such as body odour and perfume become important.

Pathophysiological insights

The majority of patients who underwent MRI exhibited olfactory bulb and sulcus aplasia, consistent with current diagnostic criteria [1]. However, a small subgroup presented with intact olfactory bulbs despite anosmic symptoms, suggesting either limitations in imaging resolution or the possibility of alternative genetic or cortical mechanisms. Indeed, studies have shown that olfactory function can occasionally be preserved despite apparent bulb absence [18]. Genetic evaluation was rarely conducted in our cohort. However, in the few tested cases, mutations associated with Kallmann syndrome *ANOS1* and candidate genes such as *CNGA2* and *SREK1IP1* were identified, as recently described by Kamarck et al. [9].

Clinical implications and consequences

Although many patients appeared to adapt functionally, objective testing revealed complete anosmia in almost all cases. Interestingly, normal basic taste perception was preserved, but a subset of patients - particularly younger individuals – had a low BMI or a history of eating disorders, possibly reflecting reduced food enjoyment or picky eating. These findings mirror previous work suggesting that congenital olfactory loss may disrupt normal eating behaviour in children [7, 8].

Mental health screening revealed elevated MDI scores in a small but notable group, reinforcing the notion that congenital sensory deficits may be associated with psychosocial vulnerability, particularly when undiagnosed. This underscores the need for early detection and supportive counselling, even in the absence of curative treatments.

Strengths and limitations

The strengths of this study include its relatively large cohort, detailed PROMs and multimodal diagnostic approach combining clinical history, psychophysical testing and MRI. Limitations include incomplete genetic and endocrine workups, potential referral bias and limited availability of BMI data. Furthermore, the lack of a control group and reliance on retrospective data preclude conclusions about causality regarding eating and mood disorders.

Recommendations for screening and management

Given the frequent delay in diagnosis and the potential impact on eating behaviour, mental health and social integration, CA may be considered in children with unexplained picky eating, poor response to odours or absent olfactory reactions. However, eating disorders are likely multifactorial and should be interpreted within a broader clinical context. Routine olfactory screening – possibly alongside vision and hearing tests at school entry age – could facilitate earlier detection. A diagnostic algorithm following positive screening should include thorough olfactory testing. After anosmia is verified, further evaluation should include an MRI of the olfactory

system and referral for genetic/endocrine evaluation, where indicated [1].

Future directions

Future studies should prospectively evaluate cohorts with suspected CA using systematic genetic and endocrinological assessments. Longitudinal studies are also needed to examine developmental trajectories, compensatory mechanisms and the role of targeted interventions (e.g., dietary guidance or psychosocial support).

Conclusions

CA is a rare but likely underrecognised condition with potentially significant developmental and psychosocial consequences. Our findings underscore the importance of early identification through structured olfactory testing and MRI, with genetic and endocrine evaluations when appropriate. Although many individuals report minimal impact, a substantial subset experiences challenges related to food behaviour, QoL and mental health. Increased clinical awareness and systematic screening – especially in children with unexplained picky eating or absent smell perception – may improve diagnosis, support and long-term outcomes.

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