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REVIEW
PREGLEDNI RAD

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Giant Cell Lesions of the Jaws Involving RASopathy Syndromes

Gigantocelularne lezije čeljusti uključene u sindrom RAZopatije

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Abstract

Objective: Giant cell lesions of the jaws (GCLJ) may rarely occur in the setting of RASopathy syndromes such as Noonan syndrome or neurofibromatosis I. Recently, central giant cell granulomas (CGCG), the most common of the GCLJ, have been recognized as benign neoplasms characterized by Ras/MAPK signaling pathway mutations. This provides a rational basis for understanding GCLJ in RASopathy syndromes as syndromically occurring CGCG. This review aims to summarize the clinicopathologic features of syndromic CGCG and to review the salient clinical and craniofacial features of the syndromes in which they may rarely occur. **Material and Methods:** An electronic search in 3 databases was performed, looking for GCLJ/CGCG in RASopathy syndromes. **Results:** 124 CGCG in 56 patients were identified across 6 RASopathy syndromes. Median age at syndromic CGCG diagnosis is 11 years; 69.6% (39/56) patients developed two or more CGCG; 58.9% (33/56) presented with bilateral posterior mandibular CGCGs, mimicking cherubism. Of 88 CGCG with follow-up, 22.4% (13/58) of excised/resected CGCG recurred while 46.7% (14/30) of monitored CGCG showed continued growth. **Conclusion:** Syndromic CGCG involves multiple RASopathy syndromes and may mimic cherubism or, when solitary, sporadically occurring CGCG. Familiarity with other clinical findings of RASopathy syndromes is critical for appropriate diagnosis and patient management.

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Introduction

Giant cell lesions of the jaws (GCLJ) represent a group of diverse conditions occurring in the mandible or maxilla, characterized by the presence of multinucleated giant cells histopathologically (1). GCLJ may occur in sporadic or syndromic settings, or in the setting of specific metabolic alterations. Central giant cell granuloma, cherubism, brown tumor of hyperparathyroidism and aneurysmal bone cyst are the principal GCLJ.

Central giant cell granuloma (CGCG), usually occurring sporadically, accounts for the majority of GCLJ. CGCG typically occurs in the first three decades of life with a slight female predilection and is considered to have a predilection for the anterior jaws, usually mandible (2). Approximately half of cases result in cortical bone perforation and more aggressive cases show rapid growth with tooth displacement and root resorption, or may pursue a multiply recurrent clinical course (3). Histopathologically, CGCGs are characterized by a vaguely lobular proliferation of mononuclear spindle-shaped and polygonal cells with admixed multinucleated giant cells, extravasated erythrocytes, and variable osteoid production (4).

Uvod

Gigantocelularne lezije čeljusti (GCLJ) skupina su različitih stanja koja se pojavljuju u mandibuli ili maksili, a obilježava ih histopatološka prisutnost višejezgrenih gigantskih stanica (1). GCLJ može nastati zasebno ili u sklopu sindroma ili u uvjetima specifičnih metaboličkih promjena. Centralni gigantocelularni granulom, kerubizam, smeđi tumor kod hiperparatireoidizma i aneurizmatska koštana cista osnovni su oblici GCLJ-a.

Centralni gigantocelularni granulom (CGCG) obično nastaje izolirano i čini većinu GCLJ-a. CGCG obično se pojavljuje u prva tri desetljeća života s nešto malo većom zastupljenošću među ženama i smatra se da je češći u prednjem dijelu, obično donje čeljusti (2). Otprilike polovina slučajeva rezultira perforacijom kortikalne kosti, a agresivniji slučajevi pokazuju brzi rast s pomakom zuba i resorpcijom korijena ili mogu imati klinički tijek s višestrukim ponavljanjima (3). Histopatološki, CGCG karakterizira nejasna lobularna proliferacija mononuklearnih vretenastih i poligonalnih stanica s mješovitim multinuklearnim gigantskim stanicama, ekstravaziranim eritrocitima i varijabilnom osteoidnom proi-

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Therapeutic approaches are either surgical (curettage, local excision, resection) or pharmacological (intralesional injections with steroids, interferon-α, denosumab, others), (5-7). More recently, sporadically occurring CGCGs- in spite of their name- have been recognized as neoplasms unique to the jawbones that harbor *TRPV4*, *KRAS* or *FGFR1* mutations, resulting in activation of the MAPK (mitogen activated protein kinase) pathway (Fig. 1), (8). This signaling pathway influences cell proliferation, migration and differentiation, and its dysregulation increases neoplastic behavior (9). The MAPK signaling pathway is one of the most commonly dysregulated signaling pathways in human neoplasia, benign or malignant (10).

The identification of MAPK pathway alterations in CGCG now provides a rational basis for understanding the rare occurrence of GCLJ in Noonan syndrome, neurofibromatosis type I, and a handful of other less common syndromes. These syndromes are all characterized by germline or post-zygotic mutations in genes important in MAPK pathway signaling, and collectively are referred to as RASopathies (Fig 1), (11, 12).The fact that RASopathies are pathogenetically related explains shared clinical features of short stature, scoliosis, osteoporosis and chest wall deformities (13).

On the basis of recently discovered genomic alterations, GCLJ occurring in RASopathies can now be understood as syndromic CGCGs and this review aims to determine their incidence and clinical presentation, as well as a comprehensive review of the salient clinical features of the syndromes in which they occur. Cherubism, an autosomal dominant disorder characterized by bilateral and self-limiting maxillomandibular expansion and by germline *SH3BP2* mutations, a gene whose function is presently unclear and with no relationship to MAPK pathway signaling, will not be reviewed (14).

zvodnjom (4). Terapijski pristupi su kirurški (kiretaža, lokalna ekscizija, resekcija) ili farmakološki (intralezijske injekcije sa steroidima, interferon-α, denosumab i drugi) (5 – 7). Posljednjih godina sporadični CGCG-ovi – unatoč njihovu nazivu – prepoznati su kao neoplazme jedinstvene za čeljusne kosti koje sadržanju mutacije TRPV4, Kras ili FGFR1, što rezultira aktivacijom MAPK puta (mitogenski aktivirane proteinske kinaze) (slika 1.) (8). Taj signalizacijski put utječe na proliferaciju stanica, migraciju i diferencijaciju, a njegova disregulacija povećava neoplastično ponašanje (9). MAPK put signalizacije jedan je od najčešće disreguliranih puteva signalizacije u ljudskim benignim ili malignim neoplazmama (10).

Identifikacija promjena MAPK puteva u CGCG-u sada pruža racionalnu osnovu za razumijevanje rijetke pojave GCLJ-a u Noonanovu sindromu, neurofibromatozi tipa I i nekoliko drugih manje čestih sindroma. Sve njih karakteriziraju germlinske ili postzigotske mutacije gena važnih u signalizaciji MAPK puteva, a zajedno se nazivaju RAZopatije (slika 1.) (11, 12). Činjenica da su RAZopatije patogenetski povezane objašnjava zajedničke kliničke značajke niskoga rasta, skolioze, osteoporoze i deformiteta stijenke prsnoga koša (13).

Na temelju nedavno otkrivenih genomskih promjena, GCLJ koji se pojavljuje u RAZopatijama sada se može shvatiti kao sindromski CGCG i cilj je ovoga preglednoga rada utvrditi njihovu incidenciju i kliničku manifestaciju te dati sveobuhvatan pregled glavnih kliničkih značajki sindroma u kojima se pojavljuju. Kerubizam, autosomno dominantni poremećaj koji obilježava bilateralna i samoograničavajuća maksilo-mandibularna ekspanzija i mutacije *germlinskoga SH3BP2*, gena čija je funkcija trenutačno nejasna i nema veze sa signalizacijom MAPK putova, neće se detaljnije prikazivati (14).

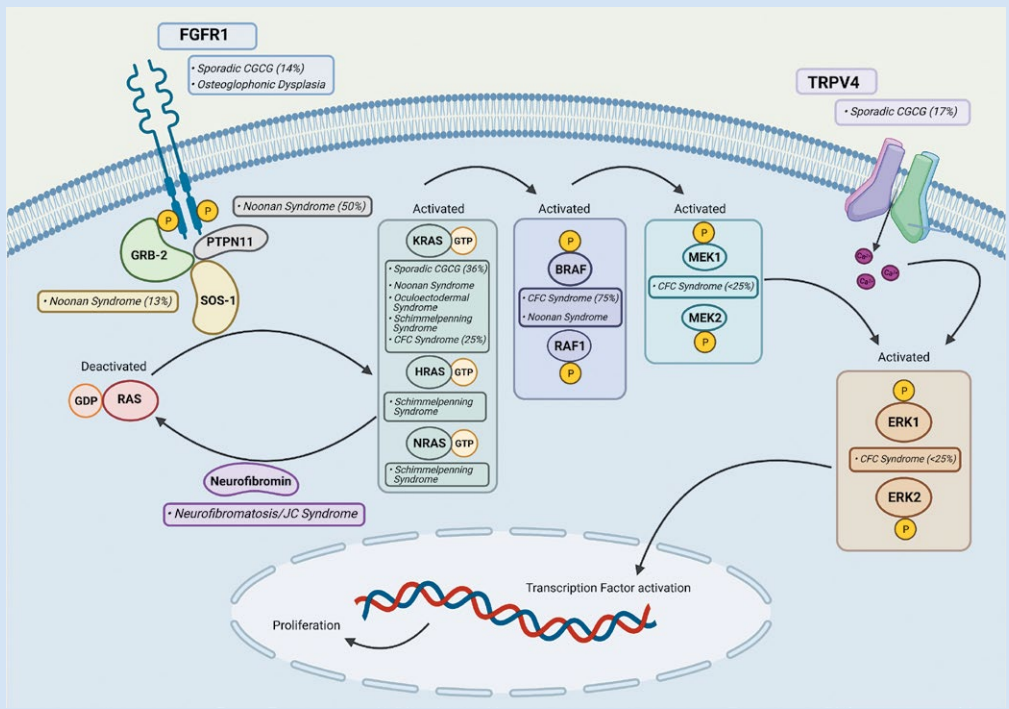

Figure 1 MAPK pathway alterations in sporadic CGCG and RASopathies involved by syndromic CGCG.
Slika 1. Promjene MAPK puteva kod izoliranoga CGCG-a i CGCG-om u sklopu RAZopatijskih sindroma

Material and methods

PubMed, Medline and Scopus databases were searched for articles published up to December 31, 2021. The authors screened titles and abstracts of all studies that included the terms: Noonan, neurofibromatosis, Jaffe-Campanacci, oculoectodermal, Ramon, Schimmelpenning, Costello, cardio-facio-cutaneous, osteoglophonic dysplasia and RASopathy, in combination with the term giant cell. Inclusion criteria included: primary research in the English language; adequate clinical, radiographic, histologic, and/or molecular information to confirm the diagnosis of GLCJ/CGCG as well as the parent syndrome; involvement of mandible or maxilla. Exclusion criteria included sporadically occurring GLCJ/CGCG; giant cell lesions involving bones other than the mandible/maxilla (non-ossifying fibromas); secondary research; retracted articles; non-English language.

Full-text articles screened for eligibility identified a total of 41 relevant primary research articles. Extracted data consisted of: parent syndrome, age, gender, number of CGCG, location and, when included, treatment and follow-up information. Data were presented as descriptive statistics to present, for the first time, an overview of the clinical and demographic presentation of syndromic CGCG. These findings were compared against the clinical and demographic features of sporadic CGCG, as recently reviewed in 2018, for statistical significance using a Student's t-test or Mann-Whitney test, depending on the normality (2).

CGCG occurrence in RASopathies

Following comprehensive review of the English language literature in PubMed, a total of 124 syndromic CGCGs, in 56 patients, were identified in the following RASopathy syndromes (Table 1): Noonan syndrome /77/ (15-37), neurofibromatosis type I /22/, (38-47), oculoectodermal syndrome /11/ (48, 49), Schimmelpenning syndrome /6/ (50-52), cardio-facio-cutaneous syndrome /5/ (53), and osteoglophonic dysplasia /3/ (54, 55). In light of a recent systematic review of 2270 CGCG published in the literature by Chrcanovic et al, 5.1% (121/2391) of all published CGCG have occurred syndromically, though this presumably reflects substantial publication bias since sporadically occurring CGCG are no longer commonly reported, and the proportion is likely much smaller (2).

The median age of syndromic CGCG diagnosis is 11 years, with wider age ranges reported in Noonan syndrome (4-22 years) and neurofibromatosis type I (7-38 years) than in other syndromes where CGCGs have been reported exclusively in the first two decades of life. There is a 1.25 to 1 M:F ratio, with some variation by syndrome. Seventeen patients (30.4%) had one CGCG and 39 (69.6%) had two or more CGCGs. Mandibular involvement was noted in 92/124 (74.2%) of CGCG, with only 5 CGCGs (5.4%) occurring anterior to the canine. Anterior maxillary involvement (5/32, 15.6%) was also uncommon. Bilateral mandibular CGCGs occurred in 33/56 (58.9%) patients, leading to mischaracterization of the patient as (also) having cherubism in many instances.

Materijali i metode

Baze podataka PubMed, Medline i Scopus pretražene su da bi se našli radovi objavljeni do 31. prosinca 2021. Autori su pregledali naslove i sažetke svih istraživanja koja su uključivala pojmove: Noonan, neurofibromatoza, Jaffe-Campanacci, okuloektodermalno, Ramon, Schimmelpenning, Costello, kardio-faciokutani, osteoglofonska displazija i RAZopatija, u kombinaciji s pojmom *gigantska stanica*. Kriteriji za uključivanje bili su primarno istraživanje na engleskome jeziku, odgovarajuće kliničke, radiografske, histološke i/ili molekularne informacije za potvrdu dijagnoze GLCJ-a/CGCG-a i roditeljskoga sindroma, te zahvaćenost mandibule ili maksile. Kriteriji za isključivanje bili su sporadično pojavljivanje GLCJ-a/CGCG-a, gigantocelularne lezije koje uključuju kosti, osim mandibule/maksile (neosificirajući fibromi), sekundarna istraživanja i radovi koji nisu na engleskome jeziku.

Provjerom cjelovitih tekstova pronađen je ukupno 41 relevantni primarni istraživački članak. Izvučeni podatci sastojali su se od roditeljskoga sindroma, dobi, spola, broja CGCG-a, lokacije i, ako su bile uključene, informacije o liječenju i praćenju. Podatci su prikazani kao deskriptivna statistika kako bi se prvi put dao pregled kliničke i demografske prezentacije sindroma CGCG-a. Ti su nalazi uspoređeni s kliničkim i demografskim značajkama izoliranoga CGCG-a koje su nedavno prikazane 2018. (2), a statistička značajnost utvrđena je s pomoću Studentova t-testa ili Mann-Whitneyjeva testa, ovisno o normalnosti.

Pojava CGCG-a U RAZopatijama

Nakon sveobuhvatnoga pregleda literature na engleskome jeziku na PubMedu, ukupno 124 sindromna CGCG-a ustanovljena su kod 56 pacijenata u sklopu sljedećih sindroma RAZopatije (tablica 1.): Noonanov sindrom /77/, (15 – 37), neurofibromatoza tipa I /22/, (38 – 47), okuloektodermalni sindrom /11/, (48, 49), Schimmelpenningov sindrom /6/, (50 – 52), kardiofaciokutani sindrom /5/ (53) i osteoglofonijska displazija /3/, (54, 55). U nedavno objavljenom sistematiziranom preglednom radu Chrcanovica i suradnika u kojemu je obrađeno 22 270 CGCG-a, sindromskih je bilo 5,1 % (121/2391), iako to vjerojatno odražava znatnu pristranost autora jer se o zasebnoj pojavi CGCG-a manje izvješćuje i udio je vjerojatno mnogo manji.

Medijan dobi pacijenata s dijagnozom sindroma CGCG-a iznosi 11 godina, a širi dobni raspon zabilježen je kod Noonanova sindroma (4 – 22 godine) i neurofibromatoze tipa I (7 – 38 godina) nego kod drugih sindroma kod kojih je CGCG prijavljen isključivo u prva dva desetljeća života. Postoji omjer 1,25 prema 1 M : Ž, s određenim varijacijama, ovisno o sindromu. Sedamnaest pacijenata (30,4 %) imalo je jedan CGCG, a 39 (69,6 %) dva ili više. Zahvaćenost mandibule zabilježena je kod 92/124 (74,2 %) pacijenta s CGCG-om, a samo 5 CGCG-a (5,4 %) pojavilo se anteriorno od očnjaka. Zahvaćenost anteriorne maksile (5/32, 15,6 %) također je bila manje česta. Bilateralni mandibularni CGCG-i pojavili su se kod 33/56 (58,9 %) pacijenata što je u mnogim slučajevima pogrešno smatrano kao (također) kerubizam.

Table 1. Clinical features of RASopathy patients with CGCG
Tablica 1. Kliničke značajke pacijenata s RAZopatijom s CGCG-om

Patients	NS	NF1/JC	OES	SS	CFC	OGD	Total
	34	12	2	3	3	2	56
Median age (range)	**10 years (4-22 years)**	**12 years (7-38 years)**	**3.5 years (3-4 years)**	**11 years (5-14 years)**	**8 years (5-14 years)**	**4.5 years (3-12 years)**	**11 years (3-38 years)**
Gender							
Male	23	3	1	0	2	1	30
Female	11	9	1	3	1	1	26
Number of CGCG per patient							
1	6	6	1	2	1	1	17 (30.4%)
2+	28	6	1	1	2	1	39 (69.6%)
Patients with:							
Bilateral mandibular (cherubism-like) presentation	25	5	1	0	2	0	33 (58.9%)
Additional CGCGs following initial CGCG diagnosis	3	2	1	1	0	0	7 (12.5%)
Total CGCG reported[a]	77	22	11	6	5	3	124
Maxilla	17 (22.1%)	7 (31.8%)	2 (18.2%)	5 (83.3%)	0 (0.0%)	1 (33.3%)	32 (25.8%)
Anterior	2	1	0	2	0	0	5
Posterior	15	6	2	3	0	1	27
Unknown	0	0	0	0	0	0	0
Mandible	60 (77.9%)	15 (68.2%)	9 (81.8%)	1 (16.7%)	5 (100.0%)	2 (66.7%)	92 (74.2%)
Anterior	1	2	1	0	0	1	5
Posterior	56	13	4	1	4	1	79
Unknown	3	0	4	0	1	0	8

NS denotes Noonan syndrome; NF1/JC denotes neurofibromatosis type 1/Jaffe-Campanacci syndrome; OES denotes oculoectodermal syndrome; SS denotes Schimmelpenning syndrome; CFC denotes cardiofaciocutaneous syndrome; OGD denotes osteoglophonic dysplasia
[a] Patients described as having 'multiple' lesions were quantified as having 3 CGCG for tabulation purposes
NS – Noonanov sindrom; NF1/JC – neurofibromatozu tip 1/Jaffe-Campanaccijev sindrom; OES – okuloektodermalni sindrom; SS – Schimmelpenningov sindrom; CFC – kardiofaciokutani sindrom; OGD –osteoglofonska displazija
a Pacijenti za koje je opisano da imaju „višestruke" lezije kvantificirani su kao da imaju 3 CGCG za potrebe tablice

Table 2. Management of syndromic CGCG
Tablica 2. Liječenje sindroma CGCG-a

	NS	NF1/JC	OES	SS	CFC	OGD	Total
Number of CGCGs with management/ follow-up information	43	22	11	6	5	1	88
Conservative excision	12	11	11	4	0	0	38
Recurrence	1	4	3	0	0	0	8 (21.1%)
Resection	8	5	0	2	5	0	20
Recurrence	1	3	0	1	0	0	5 (25%)
Observation only	23	6	0	0	0	1	30
Continued growth	9[a]	4	0	0	0	1[b]	14 (46.7%)

NS denotes Noonan syndrome; NF1/JC denotes neurofibromatosis type 1/Jaffe-Campanacci syndrome; OES denotes oculoectodermal syndrome; SS denotes Schimmelpenning syndrome; CFC denotes cardiofaciocutaneous syndrome; OGD denotes osteoglophonic dysplasia
[a] Makis, et al reported continued CGCG growth in setting of radiation therapy, antiangiogenic therapy, and steroid therapy
[b] White, et al reported continued CGCG growth in setting of vinblastine and methotrexate therapy but with response to IV bisphosphonate
NS – Noonanov sindrom; NF1/JC – neurofibromatozu tip 1/Jaffe-Campanaccijev sindrom; OES – okuloektodermalni sindrom; SS – Schimmelpenningov sindrom; CFC – kardiofaciokutani sindrom; OGD – osteoglofonska displazija
a Makis i suradnici izvijestili su o kontinuiranom rastu CGCG-a u uvjetima terapije zračenjem, te antiangiogene i steroidne terapije
b White i suradnici izvijestili su o kontinuiranom rastu CGCG-a u postavljanju terapije vinblastinom i metotreksatom, ali s odgovorom na IV. bisfosfonat

Of the 88 CGCGs with follow-up information, 38 (43.2%) were conservatively excised, 20 (22.7%) were resected and 30 (34.1%) were observed (Table 2). Recurrences were noted in 8 (21.1%) excised and 5 (25%) resected CGCGs, while continued growth was noted in 14 (46.7%) CGCG managed by observation. One Noonan syndrome patient[24] had continued CGCG growth in spite of radiation therapy, antiangiogenic therapy and steroid therapy while one patient

Od 88 CGCG-a s naknadnim praćenjem, 38 (43,2 %) je konzervativno ekscidirano, 20 (22,7 %) je resecirano, a 30 (34,1 %) je promatrano (tablica 2.). Recidivi su zabilježeni kod 8 (21,1 %) ekscidiranih i 5 (25 %) reseciranih CGCG-a, a kontinuirani rast zabilježen je kod 14 (46,7 %) CGCG-a koji su promatrani. Kod jednoga pacijenta s Noonanovim sindromom (24) CGCG je nastavio rasti unatoč terapiji zračenjem, te antiangiogenoj i steroidnoj terapiji, a kod drugoga

Table 3 Comparison of clinical features between syndromic and sporadic CGCG
Tablica 3. Usporedba kliničkih značajki između sindromskog i sporadičnog CGCG

	Syndromic CGCG	Sporadic CGCG[a]	P value
Mean age ± SD (range)	10.5 ± 6.68 years (3-38 years)	25.8 ± 15.3 years (0-85 years)	< 0.001
Gender[b]			0.030
Male	30/56 (53.6%)	876/2233 (39.2%)	
Female	26/56 (46.4%)	1357/2233 (60.8%)	
Location[b]			0.243
Mandible	92/124 (74.2%)	1503/2171 (69.2%)	
Maxilla	32/124 (25.8%)	668/2171 (30.8%)	
Recurrence following surgical treatment[c]			
Yes	13/58 (22.4%)	232/1316 (17.6%)	0.885
No	45/58 (77.6%)	1084/1316 (82.4%)	

[a]Data derived from Chrcanovic BR, et al. *J Oral Pathol Med*. 2018;47:731 (reference 2). •

[b]Cases with unknown gender or location were excluded, as in primary analysis by Chrcanovic, et al. •

[c]Among cases with follow-up •

with osteoglophonic dysplasia had continued CGCG growth while on vinblastine and methotrexate but demonstrated response to IV bisphosphonate (54).

The number of reported syndromic cases is small and precludes confident statistical comparison between syndromic and sporadic CGCG; however, certain trends are noted (Table 3). The mean age of diagnosis of syndromic CGCG was 10.5 years, which was significantly younger than the mean age of diagnosis of 25.8 years for sporadic CGCG ($p < 0.001$), though the wide standard deviation of ± 15.3 years for sporadic CGCG renders this clinical characteristic, in isolation, unlikely to be helpful in patient evaluaton (2). Also of statistical significance was the 1.15:1 M:F ratio in syndromic CGCG compared to 1:1.55 M:F ratio for sporadic CGCG ($p = 0.03$). Syndromic and sporadic CGCG share a mandibular predilection (74.2% and 69.2%, respectively), though it is noteworthy that the vast majority (91.7%) of syndromic CGCG occur posterior to the maxillary or mandibular canines. In contrast, sporadic CGCG appears to show no clear anterior or posterior predilection and only a minority of cases cross the midline of the jaws, as is often considered characteristic (2). More detailed clinical information such as size and presenting symptoms were rarely reported in syndromic cases and not amenable to comparison.

The occurrence of multiple CGCGs, seen in approximately 70% of syndromic patients, appears strongly suggestive of an underlying syndrome as multiple CGCGs were not reported in the 2018 review (2). Of note, over half of syndromic patients (58.9%) presented with bilateral involvement of the posterior mandible, suggesting that distinction from cherubism, which also presents with giant cell-rich lesions of the posterior mandible, is critical in the pediatric setting and requires careful clinical evaluation for other syndromic features or genetic testing for correct diagnosis.

There were no statistically significant differences between recurrence rates of syndromic (22.4%) versus sporadic (17.6%) CGCG ($p = 0.89$). However, sporadic CGCG may present with aggressive and non-aggressive variants, and subgroup analysis of these two variants yielded recurrence rates of 22.8% and 7.8%, respectively, as reported previously (2).

s osteoglofonskom displazijom (54) nastavio se rast CGCG-a dok je primao vinblastin i metotreksat, ali je pokazao odgovor na intravenski administrirani bisfosfonat.

Broj prijavljenih slučajeva sindroma malen je i isključuje pouzdanu statističku usporedbu između sindroma i izoliranoga CGCG-a, no uočeni su određeni trendovi (tablica 3.). Srednja dob za dijagnozu sindromnoga CGCG-a bila je 10,5 godina, što je bilo znatno manje od srednje dobi za dijagnozu izoliranoga CGCG-a od 25,8 godina ($p < 0,001$), iako široka standardna devijacija od ± 15,3 godine za izolirani CGCG čini tu kliničku karakteristiku malo korisnom u procjeni pacijenata (2). Također je statistički značajan omjer 1,15 : 1 M : Ž u sindromnom CGCG-u u usporedbi s omjerom 1 : 1,55 M : Ž za izolirani CGCG ($p = 0,03$). Sindromski i izolirani CGCG skloni su se pojaviti u mandibuli (74,2 %, odnosno 69,2 %), iako je vrijedno napomenuti da se velika većina (91,7 %) sindromnih CGCG-a pojavljuje posteriorno od gornjih ili donjih očnjaka. Suprotno tomu, čini se da izolirani CGCG ne pokazuje jasnu sklonost za pojavljivanje u prednjemu ili stražnjemu segmentu čeljusti i samo manji broj slučajeva prelazi srednju liniju čeljusti, što se često smatra karakterističnim (2). Detaljnije kliničke informacije, poput veličine i prisutnih simptoma, rijetko su prijavljene u sindromskim slučajevima i nisu podložne usporedbi.

Čini se da pojava višestrukih CGCG-a, opažena kod približno 70 % pacijenata sa sindromom, snažno upozorava na osnovni sindrom jer višestruki CGCG-i nisu prijavljeni u preglednom radu iz 2018. godine (2). Napominjemo, više je od pola pacijenata sa sindromom (58,9 %) s bilateralnim zahvaćanjem stražnjega dijela donje čeljusti, što sugerira da je važno razlikovanje od kerubizma koji se također manifestira gigantocelularnim lezijama u stražnjem dijelu mandibule, što za ispravnu dijagnozu zahtijeva pozornu kliničku procjenu drugih sindromskih značajki ili genetsko testiranje.

Nije bilo statistički značajnih razlika između stopa recidiva sindromskoga (22,4 %) i izoliranoga (17,6 %) CGCG-a ($p = 0,89$). No izolirani CGCG može se pojaviti u agresivnim i neagresivnim varijantama, a analiza podskupina tih dviju varijanti rezultirala je stopama recidiva od 22,8 %, odnosno 7,8 %, kao što je već objavljeno (2). To sugerira da

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This suggests that syndromic CGCG may have biologic behavior more similar to aggressive CGCG and raises the interesting question as to whether underlying germline predisposition may account for more rapid growth. Definitive conclusions regarding optimal patient management are precluded by the small number of cases with follow-up information, but these findings suggest a primary role for excision/resection of syndromic CGCGs as opposed to close observation in which approximately half of cases (46.7%) demonstrated continued growth. Long-term follow-up for the development of additional CGCGs was documented infrequently (12.5% of patients), but appears prudent.

Given that syndromic CGCG occurs rarely and may have substantial overlap with sporadic CGCG or cherubism at presentation, familiarity with the clinical features of the syndromes, in particular craniofacial features, in which they may present is requisite for diagnosis and patient management.

Noonan and Noonan-like syndrome

Syndromic CGCGs have been most frequently reported in Noonan Syndrome (NS), a common RASopathy first described by Jaqueline Noonan in 1968 (56). NS presents with a variable degree of distinctive features including craniofacial dysmorphia, short stature, webbed neck and congenital heart defects (57). Individuals are usually diagnosed after birth, but certain prenatal findings can suggest the diagnosis (58). Infants frequently present with feeding difficulties (can lead to failure to thrive) and sporadic episodes of nausea/vomiting that improve or resolve by the age of 15 months. Other common early-discovered traits include scoliosis, pectus excavatum or carinatum, hematologic disorders, and cryptorchidism (60-80% of boys). Short stature typically comes to attention in puberty but adult height is not always compromised (59). Cardiac abnormalities are a main clinical manifestation of NS (50%-90%), the most frequently described being pulmonary stenosis (50-60%) followed by hypertrophic cardiomyopathy (20%) and atrial septal defect (6-10%). Other less common manifestations include auditory deficits (10-25%) and lymphatic abnormalities (less than 20%), (57,59). Intelligence is generally within normal range, but intellectual impairment has been reported in 20% of cases (59).

The incidence of NS is estimated to be 1 in approximately every 1000-2500 births (59,60). NS is usually inherited in an autosomal dominant fashion but can occur *de novo* as well (60). Germline mutations in several genes of the MAPK signaling pathway have been identified in NS: *PTPN11* (50%), *SOS1, RAF1* and *RIT1* being responsible for 93% of the cases (61,62). Less frequently, mutations have been found in *KRAS*, *NRAS*, *BRAF*, *MAP2K1* and *SOS2* (63). Before the advent of genetic testing definitive diagnosis was challenging due to the tremendously variable expressivity of the disease. As a result, numerous syndromic presentations emerged with an uncertain relationship to NS. However, Noonan-like syndrome, NS with multiple lentigines/LEOPARD, NS with loose anagen hair and NS with giant cell lesions are all now considered phenotypic variants of NS instead of separate entities on the basis of shared genetic findings (62,63). Cardio-facio-cutaneous syndrome (described below) and Costel-

sindromski CGCG može imati biološko ponašanje sličnije agresivnom CGCG-u i postavlja se zanimljivo pitanje o tomu može li osnovna predispozicija zametne linije utjecati na brži rast. Konačne zaključke, kad je riječ o optimalnoj skrbi za pacijente, onemogućuje mali broj slučajeva s informacijama o praćenju, ali ti nalazi upućuju na primarnu ulogu ekscizije/resekcije sindromnih CGCG-a, za razliku od pomnoga promatranja u kojemu je približno polovina slučajeva (46,7 %) pokazala kontinuirani rast. Dugoročno praćenje razvoja dodatnih CGCG-a rijetko je zabilježeno (12,5 pacijenata), ali se čini razboritim.

S obzirom na to da se sindromski CGCG pojavljuje rijetko i može se znatno preklapati s izoliranim CGCG-om ili kerubizmom, za dijagnozu i liječenje pacijenata prijeko je potrebno poznavati kliničke značajke sindroma, posebno kraniofacijalnih u kojima mogu biti prisutni.

Noonanov sindrom

Sindromski CGCG najčešće se susreće u slučaju Noonanova sindroma (NS), česte RAZopatije koju je prvi opisao Jaqueline Noonan 1968. godine (56). NS se manifestira promjenjivim stupnjem karakterističnih značajki, uključujući kraniofacijalne dismorfije, nizak rast, mrežasti vrat i prirođene srčane mane (57). Dijagnoza se obično postavlja nakon rođenja, ali na nju mogu upućivati i određeni prenatalni nalazi (58). Dojenčad često ima poteškoće s hranjenjem (to može dovesti do zaostajanja u napredovanju) i sporadične epizode mučnine/povraćanja koje se poboljšavaju ili povlače do dobi od 15 mjeseci. Ostale uobičajene rano otkrivene značajke uključuju skoliozu, *pectus excavatum* ili *carinatum*, hematološke poremećaje i kriptorhidizam (60 – 80 % dječaka). Nizak rast obično se očituje u pubertetu, ali katkad se dosegne i odrasla visina (59). Srčane anomalije glavna su klinička manifestacija NS-a (50 % – 90 %), a najčešće su opisane plućna stenoza (50 – 60 %), zatim hipertrofična kardiomiopatija (20 %) i atrijski septalni defekt (6 – 10 %). Ostale manje česte manifestacije su deficiti sluha (10 – 25 %) i limfne abnormalnosti (manje od 20 %) (57,59). Inteligencija je općenito unutar normalnoga raspona, ali u 20 % slučajeva prijavljeno je i takvo oštećenje (59).

Incidencija NS-a procjenjuje se otprilike u omjeru 1 : 1000 do 2500 porođaja (59, 60). NS se obično nasljeđuje na autosomno-dominantan način, ali može se pojaviti i *de novo* (60). Kod toga sindroma identificirane mutacije germlina u nekoliko gena signalizacijskoga puta MAPK-a: *PTPN11* (50 %), *SOS1, RAF1* i RIT1 kao odgovorni za 93 % slučajeva (61,62). Mutacije su rjeđe pronađene na??? *Kras*, NRA, *BRAF* , MAP2K1 (63). Prije pojave genetskoga testiranja postavljanje konačne dijagnoze bilo je izazovno zbog iznimno varijabilne ekspresivnosti bolesti. Zbog toga su se pojavile mnogobrojne sindromske manifestacije s nesigurnim odnosom prema NS-u. No sindromi slični Noonanovu – NS s labavom anagenom kosom i NS s gigantocelularnim lezijama – smatraju se fenotipskim varijantama NS-a umjesto odvojenih entiteta na temelju zajedničkih genetskih nalaza (62, 63). Kardiofaciokutani sindrom (opisan u nastavku) i Costellov sindrom (kod kojega nije prijavljen CGCG) dvije su različi-

lo syndrome (in which CGCGs have not been reported) are two distinct, less common RASopathies with substantial clinical overlap (61-64).

Distinctive craniofacial features observed in NS include frontal bossing, low-set-posteriorly-rotated ears, ptosis, hypertelorism, epicanthal folds, down slanting palpebral fissures, and deeply grooved philtrum (59,60). Additional characteristics include low posterior hairline, light-colored irises, and curly-coarse hair (64). The oral phenotype is significant for a high-arched palate (55%-100%), temporomandibular disorders (72%), class II malocclusion, open bite/posterior crossbite (50%-67%), and micrognathia. Multiple CGCG in NS associate with *PTPN11* or *SOS1* mutations (65).

Neurofibromatosis type I and Jaffe-Campanacci syndrome

Neurofibromatosis type 1 (NF1) is the most common of the three neurofibromatosis syndromes (neurofibromatosis types 1 and 2 and schwannomatosis), (66). It is has been referred to historically as von Recklinghausen's disease as it was described by German pathologist Frederick von Recklinghausen in 1882 (66). The most recognizable features of NF1 are neurofibromas and café-au-lait macules, and diagnosis can be made clinically with two or more of the following findings: 6+ café-au-lait macules, 2+ neurofibromas or 1 plexiform neurofibroma, axillary/inguinal freckling, optic glioma, 2+ Lisch nodules (iris hamartomas), bony dysplasia, and a first degree relative with NF1(9207339). Café-au-lait macules and axillary/inguinal freckling are usually the first clinical features to present, followed by Lisch nodules and neurofibromas (66). Osseous lesions are often identified within the first year of life and optic gliomas, when symptomatic, are diagnosed by age 3.

These clinical criteria allow for a diagnosis of all NF1 patients by age 20 and 97% by age 8, but only 54% of cases by age 1 (66). Genetic testing for *NF1* mutations, which results in a truncated version of the neurofibromin protein, can be performed in questionable cases or in young patients, as well as in the screening of family members (67). NF1 occurs in approximately 1:3000 live births and exhibits an autosomal dominant pattern of inheritance, but de novo mutation characterizes approximately 50% of affected individuals (68). Rarely (1:40,000) post-zygotic *NF1* mutations can result in segmental mosaicism, known as segmental NF1 (68).

Complications more frequent in NF1 include macrocephaly, seizures, congenital heart disease, hypertension, and bone abnormalities (68). Plexiform neurofibromas are present in approximately 50% of NF1 patients and 8-13% of these may transform into malignant peripheral nerve sheath tumors, which have a 5-year survival rate of approximately 50% (69,70). The median life expectancy of 59 years is somewhat lower than of the general population (67).

First reported in 1982, rare patients have presented with a characteristic triad of café-au-lait macules, non-ossifying fibromas of the long bones, and CGCG, termed Jaffe-Campanacci syndrome (47). The relationship between this presentation and NF1 has been uncertain due to overlapping features with NF1 but a uniform absence of neurofibromas, though

te, manje česte RAZopatije sa značajnim kliničkim preklapanjem (61 – 64).

Značajne kraniofacijalne značajke uočene u NS-u uključuju dominaciju čela, nisko postavljene posteriorno rotirane uši, ptozu, hipertelorizam, epikantalne nabore, palpebralne pukotine nagnute prema dolje i duboko udubljeni filtrum (59, 60). Dodatna su obilježja nisko položen stražnji rub kose, svijetle boje šarenice i kovrčava gruba kosa (64). Oralni fenotip očituje se visokim lučnim nepcem (55 % – 100 %), temporomandibularnim poremećajima (72 %), klasom II malokluzije, otvorenim /stražnjim križnim zagrizom (50 % – 67 %) i mikrognatijom. Višestruki CGCG-i u NS-u povezani su s *mutacijama* PTPN11 *ili* SOS1 (65).

Nerofibromatoza tipa 1 i Jaffe-Campanaccijev sindrom

Neurofibromatoza tipa 1 (NF1) najčešći je od triju neurofibromatoznih sindroma (neurofibromatoza tipa 1 i 2 i švanomatoza), (66). Povijesno se spominje kao von Recklinghausenova bolest jer ju je 1882. godine opisao njemački patolog Frederick von Recklinghausen (66). Najprepoznatljivije značajke NF1 su neurofibromi i café-au-lait makule, a dijagnoza se može postaviti klinički s dvama ili više sljedećih nalaza: 6+ café-au-lait makula, 2+ neurofibroma ili 1 pleksiformni neurofibrom, aksilarni/ingvinalni pjegavi, optički gliom, 2+ Lischovi čvorići (iris hamartomi), koštana displazija i prvi stupanj u relaciji s NF1 (9207339). Café-au-lait makule i aksilarna/ingvinalna pjegica obično su prvi klinički znakovi poslije kojih slijede Lischovi čvorići i neurofibromi (66). Osovinske lezije često se identificiraju tijekom prve godine života, a optički gliomi, kada su simptomatski, dijagnosticiraju se u dobi od 3 godine.

Ti klinički kriteriji omogućuju dijagnozu svih bolesnika s NF1 do dobi od 20 godina i 97 % do dobi od 8 godina, ali samo 54 % slučajeva do dobi od jedne godine (66). Genetsko testiranje na mutacije NF1, koje rezultira skraćenom verzijom proteina neurofibromina, može se obaviti u dvojbenim slučajevima ili ako je pacijent mlad, te u probiru članova obitelji (67). NF1 pojavljuje se kod približno 1 : 3000 živorođenih i pokazuje autosomno dominantan obrazac nasljeđivanja, a *de novo* mutacija karakterizira oko 50 % pogođenih osoba 868??). Postzigotske NF1 mutacije (1 : 40 000) mogu rezultirati segmentnim mozaicizmom, poznatim kao segmentni NF1 868).

Češće komplikacije kod oboljelih od sindroma NF1 uključuju makrocefaliju, napadaje, prirođene bolesti srca, hipertenziju i abnormalnosti kostiju 868??). Pleksiformne neurofibromem oma približno 50 % pacijenata s NF1, a 8 do 13 % njih može se pretvoriti u zloćudne tumore perifernih živčanih ovojnica kojima je petogodišnja stopa preživljenja približno 50 % (69, 70). Medijan očekivanoga životnoga vijeka od 59 godina nešto je niži od prosjeka opće populacije (67).

Prvi put je 1982. godine objavljeno da rijetki pacijenti imaju karakterističnu trijadu makula café-au-lait, fibroma dugih kostiju koji se ne povećavaju i CGCG, što je nazvano Jaffe-Campanaccijevim sindromom (47). Veza između te manifestacije i NF1 bila je nesigurna zbog preklapanja značajki s NF1, ali i izostanka neurofibroma, iako se većina prijavljenih slučajeva pojavila kod mladih osoba, a neurofibromi obično

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most reported cases have been in young individuals and neurofibromas typically appear in early adolescence (71). Recently, *NF1* mutations have been described near universally in patients with so-called Jaffe-Campanacci syndrome, allowing for confident recognition of this pediatric presentation as within the spectrum of NF1 and arguing against its classification as a separate syndrome (72).

Bony dysplasia most frequently affects the tibia but less commonly affects craniofacial bones and, in this setting, often presents as deformation or absence of the greater wing of the sphenoid bone, known as sphenoid wing dysplasia (41). Mucosal pigmentation and neurofibromas can occasionally involve the mucosal surfaces of the head and neck, such as the oral cavity. Neurofibromas may also involve the inferior alveolar nerve, presenting as sharply demarcated enlargement of the inferior alveolar canal (73).

Schimmelpenning syndrome

Schimmelpenning syndrome, also known as Schimmelpenning-Feuerstein-Mims syndrome and (linear) nevus sebaceous syndrome, is a rare condition originally described by Gustav Schimmelpenning in 1957 and subsequently by Feuerestein and Mims in 1962 as a classic triad of sebaceous nevi, seizures, and mental retardation (74,75). The term epidermal nevus syndrome has often been used interchangeably with Schimmelpenning syndrome but is actually a parent term referring to a group of interrelated disorders characterized by various epidermal nevi (such as sebaceous nevi) with extra-cutaneous abnormalities, and does not refer to Schimmelpenning syndrome specifically (75,76).

The sebaceous nevi in Schimmelpenning syndrome typically involve the scalp and face and may present at birth or become more prominent after puberty. Sporadically occurring sebaceous nevi are characterized by somatic *HRAS* and *KRAS* mutations, and Schimmelpenning syndrome is itself characterized by post-zygotic *HRAS* and *KRAS* mutations (77). The prevalence of the syndrome is less than 1 in 200,000 people, while linear sebaceous nevi are reported in roughly 1 in 1000 live births (76,78). Other frequently reported findings in Schimmelpenning syndrome include corneal opacities, coloboma, brain abnormalities such as Dandy-Walker malformation or agenesis of the corpus callosum, and developmental delay (75).

Associated craniofacial defects are common and include frontal bossing, maxillofacial hypoplasia and macrocephaly (76). Sebaceous nevi can rarely present intraorally, where they can be mistakenly considered as squamous papillomas on account of their rough surface texture (53,76). Patients may present with hypoplastic, misshapen or hyperpigmented dentition (52). Of note, a variety of odontogenic neoplasms, in addition to CGCG, have been reported including adenomatoid odontogenic tumor, ameloblastoma and ameloblastic fibro-odontoma (50-52, 79,80). These rare neoplasms, interestingly, have also been shown to harbor *KRAS* or *BRAF* mutations when occurring sporadically and therefore could be expected to occur more frequently in the setting of germline MAPK signaling dysregulation (81,82).

nastaju u ranoj adolescenciji (71). Nedavno su mutacije NF1 opisane gotovo univerzalno kod pacijenata s takozvanim Jaffe-Campanaccijevim sindromom, što omogućuje pouzdano prepoznavanje toga oblika unutar spektra NF1 i argumentiranje te klasifikacije kao zasebnoga sindroma (72).

Koštana displazija najčešće zahvaća potkoljenicu, a rjeđe kraniofacijalne kosti i, u tom okruženju, često se manifestira kao deformacija ili odsutnost većega krila sfenoidne kosti i poznata je kao sfenoidna displazija krila (41). Pigmentacija sluznice i neurofibromi mogu povremeno zahvatiti sluznične površine glave i vrata, kao što je usna šupljina. Neurofibromi također mogu zahvatiti alveolarni živac, što se manifestira kao oštro razgraničeno proširenje donjega alveolarnoga kanala (73).

Schimmelpenningov sindrom

Schimmelpenningov sindrom, poznat i kao Schimmelpenning-Feuerstein-Mimsov sindrom i (linearni) nevusni lojni sindrom, rijetko je stanje koje je 1957. godine izvorno opisao Gustav Schimmelpenning, a 1962. godine Feuerestein i Mims kao klasičnu trijada lojnih nevusa, napadaja i mentalne retardacije (74, 75). Pojam epidermalni nevusni sindrom često se upotrebljava naizmjenično sa Schimmelpenningovim sindromom, ali je zapravo roditeljski pojam koji se odnosi na skupinu uzajamno povezanih poremećaja koje karakteriziraju različiti epidermalni nevusi (kao što su lojni nevusi) s izvankožnim abnormalnostima, a ne odnose se na Schimmelpenningov sindrom (75 – 76).

Lojni nevusi u Schimmelpenningovu sindromu obično uključuju vlasište i lice i mogu biti prisutni pri rođenju ili postati istaknutiji nakon puberteta. Sporadično nastali lojni nevusi karakteriziraju somatske mutacije *HRAS-a* i *KRAS-a*, a sam Schimmelpenningov sindrom obilježavaju postzigotske mutacije *HRAS-a* i *KRAS-a* (77). Prevalencija sindroma manja je od 1 : 200 000 osoba, a linearni lojni nevusi prijavljeni su otprilike kod 1 : 1000 živorođenih (76, 78). Ostali često prijavljeni nalazi u Schimmelpenningovu sindromu su zamućenost rožnice, kolobom, abnormalnosti mozga kao što su Dandy-Walkerova malformacija ili agenza *corpus callosum* i kašnjenje u razvoju 875??).

Povezane kraniofacijalne mane česte su i uključuju dominaciju čela, maksilofacijalnu hipoplaziju i makrocefaliju (76). Lojni nevusi rijetko se mogu pojaviti intraoralno gdje se mogu pogrešno smatrati skvamoznim papilomima zbog njihove grube površinske teksture (53, 76). Pacijenti mogu imati hipoplastičnu, pogrešno oblikovanu ili hiperpigmentiranu denticiju (52). Napominjemo, prijavljene su različite odontogene neoplazme uz CGCG, uključujući adenomatoidni odontogeni tumor, ameloblastom i ameloblastični fibroodontom (50 – 52, 79, 80). Te rijetke novotvorine također sadržavaju *KRAS* ili *BRAF* mutacije kada se pojavljuju sporadično i zato se može očekivati da će se češće pojavljivati u postavki disregulacije signalizacijskoga MAPK-a (81, 82).

Cardio-facio-cutaneous syndrome

Cardio-facio-cutaneous syndrome (CFC) derives its name from the characteristic findings of congenital heart disease (commonly pulmonary stenosis, atrial septal defect or hypertrophic cardiomyopathy), distinctive facial features, and skin abnormalities (including rough/dry skin, melanocytic nevi, wrinkled palms/soles, keratosis pilaris and sparse hair), which occur in most people (83). Infants typically exhibit with hypotonia and failure to thrive; other notable features include moderate to severe growth retardation and intellectual disability (84). In adulthood, individuals may suffer from vision problems and seizures but usually lead a normal lifespan. CFC shares clinical overlap with Noonan syndrome and Costello syndrome (53,83-85).

CFC is very rare condition that affects an estimated 200-300 people worldwide (53,85,86). Most mutations occur de novo in the absence of family history, though in rare cases familial inheritance has been documented (53,87). *BRAF* mutations account for 75-80% of all cases and *MAP2K1*, *MAP2K2* or *KRAS* account for remaining published cases (87-91).

The most commonly seen craniofacial features of individuals with CFC are telencanthic appearance, macrocephaly, high forehead with bitemporal narrowing, hypertelorism, convex facial profile, short nose and low set/posteriorly rotated ears (92-95). Intraoral findings include constricted and high-arched palate with anterior open bite and posterior crossbite (92,93).

Oculo-ectodermal syndrome

Oculo-ectodermal syndrome (OES) is a somatic RASopathy primarily characterized by a combination of two distinctive features: focal areas of scalp lesions (aplasia cutis congenita) and unilateral or bilateral ocular lesions (epibulbar dermoids), (96). Other common findings include macrocephaly (50% of affected individuals), upper eyelid anomalies, skin hyperpigmentation, Blaschko's lines and epidermal nevi. In addition, all described cases of OES have shown some level of multi-organ involvement that include cardiovascular (coarctation of the aorta, atrial/septal defect), CNS (arachnoid cyst, seizures) and genitourinary system abnormalities (bladder exstrophy, epispadias), (97-99). Generally, individuals present with normal growth and neurocognitive development, but intellectual disability has been reported (98,99).

OES was first described by Toriello et al. in 1993 and is a very rare neurodevelopmental syndrome with less than 25 reported cases in the literature. All cases have occurred sporadically, and most patients have been diagnosed within the first few years of life (48,49,96-102). Recent studies have shown that postzygotic *KRAS* mutations cause OES (49-103). Two other syndromes, encephalocraniocutaneous lipomatosis (ECCL) and Schimmelpenning syndrome, share clinical features with OES, and are also classified as mosaic RASopathies. Some authors consider OES as a mild version of ECCL due to their overlapping phenotype, with the only difference being the presence of intracranial lipomas, which is characteristic of ECCL (100-102).

Kardiofaciokutani sindrom

Naziv kardiofaciokutani sindrom (CFC) potječe od karakterističnih nalaza prirođene srčane bolesti (obično plućna stenoza, atrijski septalni defekt ili hipertrofična kardiomiopatija), karakterističnih crta lica i abnormalnosti na koži (uključujući grubu/suhu kožu, melanocitne nevuse, naborane dlanove/tabane, keratozu pilarisa i rijetku kosu) koji se pojavljuju kod većine ljudi (83). Dojenčad obično pokazuje hipotoniju i zaostajanje u napredovanju, a druge značajke su umjereno do teško zaostajanje u rastu i intelektualni deficiti (84). U odrasloj dobi pojedinci mogu patiti od problema s vidom i napadaja, ali obično imaju normalan životni vijek. CFC se klinička preklapa s Noonanovim i Costellovim sindromom (53, 83 – 85).

CFC je vrlo rijetko stanje koje pogađa oko 200 do 300 ljudi diljem svijeta (53, 85, 88). Većina mutacija nastaje *de novo* bez obiteljske anamneze, iako je u rijetkim slučajevima zabilježeno obiteljsko nasljeđivanje (53, 87), mutacija *BRAF-a* čini 75 do 80 % svih slučajeva, a *MAP2K1*, *MAP2K2* ili *Kras* čine preostale objavljene slučajeve 887 – 91).

Najčešća kraniofacijalna obilježja osoba s CFC-om su telenkantni izgled, makrocefalija, visoko čelo s bitemporalnim suženjem, hipertelorizam, konveksni profil lica, kratak nos i nisko postavljene/posteriorno rotirane uši (92 – 95). Intraoralni nalazi obuhvaćaju stisnuto i visoko lučno nepce s prednjim otvorenim ugrizom i stražnjim križnim ugrizom (92, 93).

Okuloektodermalni sindrom

Okuloektodermalni sindrom (OES) somatska je RAZopatija koju uglavnom karakterizira kombinacija dviju značajki – žarišnih područja lezija vlasišta (*aplasia cutis congenita*) i jednostranih ili bilateralnih očnih lezija (*epibulbarni dermoid*) (96). Ostali česti nalazi su makrocefalija (50 % pogođenih osoba), anomalija gornjih vjeđa, hiperpigmentacija kože, Blaschkove linije i epidermalni nevusi. Uz to su svi opisani slučajevi OES-a pokazali određenu razinu multiorganske zahvaćenosti koja uključuje kardiovaskularne abnonormalnosti (koarktacija aorte, atrijski/septalni defekt), CNS (arahnoidna cista, napadaji) i abnormalnosti genitourinarnoga sustava (ekstrofija mokraćnoga mjehura, epizpadije) (97 – 99). Općenito, osobe su normalnoga rasta i neurokognitivnog razvoja, ali su intelektualno invaliditetne (98, 99).

OES su prvi opisali Toriello i suradnici 1993. godine i vrlo je rijedak neurorazvojni sindrom s manje od 25 prijavljenih slučajeva u literaturi. Svi slučajevi pojavljivali su se sporadično, a većini pacijenata dijagnosticiran je tijekom prvih nekoliko godina života (48, 49, 96 – 102). Nedavna istraživanja pokazala su da OES uzrokuju postzigotske *Kras* mutacije (49, 103). Druga dva sindroma – encefalokraniokutana lipomatoza (ECCL) i Schimmelpenningov sindrom – dijele kliničke značajke s OES-om, a također su klasificirani kao mozaične RAZopatije. Neki autori smatraju OES blagom verzijom ECCL-a zbog njihova preklapajućeg fenotipa, a jedina razlika je prisutnost intrakranijalnih lipoma, što je karakteristično za ECCL (100 – 102).

Osteoglophonic Dysplasia

Osteoglophonic Dysplasia (OGD) is an autosomal dominant disorder associated with *FGFR1* mutations. Major clinical findings in this RASopathy include dwarfism and distinctive craniofacial features (103). The term osteoglophonic derives from the Greek word meaning "hollowed out" and refers to the characteristic occurrence of multiple non-ossifying fibromas affecting the metaphysis of long bones, resulting in radiolucent defects (104-106). OGD is a very rare skeletal disorder of unknown prevalence; less than 20 cases have been reported in the literature, the majority with de novo mutations (55,107).

Craniosynostosis is a frequent clinical finding and typically presents as acrocephaly or mild cloverleaf skull (kleeblattschädel deformity). Other notable craniofacial features are: frontal bossing, proptosis, hypertelorism, midface hypoplasia, mandibular prognathism, and macroglossia. Hypertrophic gingiva with delayed or arrested tooth eruption, presenting clinically as anodontia, is also common (104-109).

Some individuals might present with psychomotor delay and inability to speak. However, intelligence is generally normal (106). Early features commonly seen are feeding difficulties, failure to thrive, nasal obstruction, and serious respiratory complications (54,106,107). Life expectancy is variable and depends on severity of the craniofacial abnormalities at birth (54,106,107).

Conclusion

in conclusion, CGCG are benign neoplasms with likely far less than 5% occurring in the setting of RASopathy syndromes. Syndromic CGCG has a predilection for the posterior mandible and may occur bilaterally or even multifocally and can be confused with cherubism in this context, particularly if the possibility of an underlying syndromic predisposition is not considered. Considering the rarity of syndromic CGCG, recognition of the underlying syndrome in previously undiagnosed individuals rests on awareness of this uncommon association and identification of other more characteristic syndromic features. It is possible that increased awareness of the association between CGCG and RASopathy syndromes may lead to early diagnosis in patients for whom an underlying syndromic disorder has not yet been diagnosed.

Osteoglofonijska displazija

Osteoglofonijska displazija (OGD) je autosomno dominantni poremećaj povezan s *mutacijama* FGFR1. Glavni klinički nalazi u toj RAZopatiji uključuju patuljaste i prepoznatljive kraniofacijalne značajke (103). Pojam osteoglofoničan potječe od grčke riječi koja znači „izdubljen" i odnosi se na karakterističnu pojavu višestrukih neosificirajućih fibroma koji utječu na metafizu dugih kostiju, što rezultira radiolucentnim defektima (104 – 106). OGD je vrlo rijedak skeletni poremećaj nepoznate prevalencije – u literaturi je zabilježeno manje od 20 slučajeva, većina s mutacijama *de novo* (55, 107).

Kraniosinostoza je čest klinički nalaz i obično je to akrocefalija ili lubanja u obliku djeteline (kleeblattschädel deformitet). Ostale značajne kraniofacijalne značajke su dominacija čela, propoza, hipertelorizam, hipoplazija srednjega lica, mandibularni prognatizam i makroglosija. Također je česta hipertrofična gingiva s odgođenom ili zaustavljenom erupcijom zuba koja se klinički manifestira kao anodoncija (104 – 109).

Neki pojedinci mogu psihomotorički kasniti i ne mogu govoriti. Međutim, inteligencija je općenito normalna (106). Česte rane značajke su poteškoće s hranjenjem, zaostajanje u napredovanju, opstrukcija nosa i ozbiljne respiratorne komplikacije (54, 106, 107). Očekivani životni vijek je promjenjiv i ovisi o težini kraniofacijalnih abnormalnosti pri rođenju (54, 106,107).

Zaključak

Zaključno, CGCG-i su dobroćudne novotvorine s vjerojatno manje od 5 % incidencije u sklopu sindroma RAZopatije. Sindromski CGCG obično se pojavljuje u stražnjem dijelu mandibule i može nastati bilateralno ili čak multifokalno te se može zamijeniti s kerubizmom u tom kontekstu, osobito ako se ne razmatra mogućnost osnovne sindromske predispozicije. S obzirom na rijetkost sindromskoga CGCG-a, prepoznavanje temeljnoga sindroma kod prethodno nedijagnosticiranih osoba temelji se na svijesti o toj neuobičajenoj povezanosti i identifikaciji drugih karakterističnijih sindromskih značajki. Moguće je da povećana svijest o povezanosti sindromskoga CGCG-a i RAZopatije može dovesti do rane dijagnoze kod pacijenata kod kojih osnovni sindromski poremećaj još nije dijagnosticiran.

Sažetak

Cilj: Gigantocelularne lezije čeljusti (GCLJ) rijetko se mogu pojaviti u sklopu sindroma RAZopatije poput Noonanova sindroma ili neurofibromatoze I. Nedavno su centralni gigantocelularni granulomi (CGCG), najčešći među GCLJ-ovima, prepoznati kao benigne neoplazme koje karakteriziraju mutacije signalnih puteva Ras/MAPK. To daje racionalnu osnovu za razumijevanje GCLJ-a u sindromima RAZopatije kao sindromski nastaloga CGCG-a. Cilj ovoga preglednoga rada jest sažeti kliničko-patološke značajke sindromskoga CGCG-a i dati pregled kliničkih i kraniofacijalnih značajki sindroma u kojima se rijetko mogu pojaviti. **Materijal i metode:** Obavljena je elektronička pretraga u trima bazama podataka, a tražili su se GCLJ/CGCG-i u sindromima RAZopatije. **Rezultati:** U sklopu šest sindroma RAZopatije identificirano je 124 CGCG-a kod 56 pacijenata. Medijan dobi u dijagnozama sindromskoga CGCG-a bio je 11 godina, 69,6 % (39/56) pacijenata razvilo je dva ili više CGCG-a, a 58,9 % (33/56) imalo je bilateralne posteriorne mandibularne CGCG-e koji oponašaju kerubizam. Od 88 CGCG-a s praćenjem ponovilo se 22,4 % (13/58) izrezanih/reseciranih CGCG-a, a 46,7 % (14/30) praćenih pokazalo je kontinuirani rast. **Zaključak:** Sindromski CGCG obuhvaća nekoliko sindroma RAZopatije i može oponašati kerubizam ili se pojavljuje izolirano. Bitno je poznavati i druge kliničke nalaze sindroma RAZopatije jer je to ključno za odgovarajuću dijagnozu i zbrinjavanje pacijenata.

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