Giant Cell Lesions of the Jaws Involving RASopathy Syndromes

Gigantocelularne lezije čeljusti uključene u sindrom RAZopatije

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 pojavljaju ili u mandibuli ili maksili, a obično se pojavljuju u prva tri desetljeća života s nešto malo većom zastupljenosti među ženama i smatra se da je češći u prednjem dijelu, obično donje čeljusti (2). Otporljive polovine slučajeva rezultira perforacijom kortikalne kosti, a agresivniji slučajevi pokazuju brzi rast s pomakom zuba i resorpcijom korejera na (3). Histopatološki, CGCG karakterizira nejasna lobularna proliferacija mononuklearnih vretenastih i poligonalnih stanica s mješovitim multinuklearnim gigantskim stanicama, ekstravaziranim eritrocitima i varijabilnom osteoidnom proizvodi.
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 maxillo-mandibular 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).
Gigantocellularne lezije u RAZopatijama

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, oculo-ectodermal, 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 or 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 (15-37), neurofibromatosis type I (38-47), oculo-ectodermal syndrome (48, 49), Schimmelpenning syndrome (50-52), cardio-facio-cutaneous syndrome (53), and osteoglophonic dysplasia (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, okuloektodermalni, Ramon, Schimmelpenning, Costello, kardio-faciokutani, osteoglofonska displazija i RAZopatija, u kombinaciji s pojmom gigantska stanica. Kriteriji za uključivanje bili su primarno istraživanje na engleskom jeziku, odgovarajuće kliničke, radiografske, histološke ili molekulare 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, gigantocellularne lezije koje uključuju kosti, osim mandibule/maksile (neosificirajući fibromi), sekundarna istraživanja i radovi koji nisu na engleskome jeziku.

Provjeroj cjelovitih tekstova pronađen je ukupno 41 relevantni primarni istraživački članak. Izvučeni podacii sastojali su se od roditeljskoga sindroma, dobi, spola, broja CGCG-a, lokacije i, ako su bile uključene, informacije o liječenju i praćenju. Podacii 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 sveobuhvatanog pregleda literature na engleskom jeziku na PubMedu, ukupno 124 sindromna CGCG-a ustanovljena su kod 56 pacijenata u sklopu sljedećih sindroma RAZopatije (tablica 1): Noonovan sindrom (15-37), neurofibromatoza tipa I (38-47), okuloektodermalni sindrom (48, 49), Schimmelpenningov sindrom (50-52), kardiofaciokutani sindrom (53) i osteoglofonska displazija (54, 55). Nekad objavljena simptomatizirana usporedbom radu Chrcanovice i suradnika u kojemu je obrađeno 22 270 CGCG-a, sindromskih je bilo 5,1% (121/2391), iako to vjerojatno odražava znatnu prijetnju autor jokero pojavljivanja sindroma CGCG-a manje izvještaje i udio je vjerojatno mnogo manji.

Medijan dobi pacijenata s dijagnozom sindroma CGCG-a iznosi 11 godina, a širi dobnii raspon zabilježen je kod Noonanov sindroma (4 – 22 godine) i neurofibromatoze tipa I (7 – 38 godina) nego kod drugih sindrom k o 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. Zahaćenost mandibule zabilježena je kod 92/124 (74.2 %) pacijenata s CGCG-om, a samo 5 CGCG-a (5,4 %) pojavilo se anteriorno od očnjaka. Zahaćenost 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 pogrješno smatrano kao (također) kerubizam.

 Od 88 CGCG-a s naknadnim praćenjem, 38 (43,2 %)
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%) CGCGs managed by observation. One Noonan syndrome patient had continued CGCG growth in spite of radiation therapy, antiangiogenic therapy and steroid therapy while one patient je konzervativno ekskidirowan, 20 (22.7%) je resecirano, a 30 (34,1%) je promatrano (tablica 2.). Recidiv se zabilježio kod 8 (21,1%) ekskidirowanih 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 s osteoglofonskom displazijom (54) nastavio se rast CGCG-a.

### Table 1. Clinical features of RASopathy patients with CGCG

| Patients | NS | NFI/JC | OES | SS | CFC | OGD | Total |
|----------|----|--------|-----|----|-----|-----|-------|
| 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 | Female |
| Number of CGCG per patient | 1 | 2+ |
| Patients with: | Bilateral mandibular (cherubism-like) presentation | Additional CGCGs following initial CGCG diagnosis |
| Total CGCG reported | 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 | 1 | 0 | 1 | 2 | 0 | 1 | 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 | 1 | 5 |
| Posterior | 56 | 13 | 4 | 1 | 4 | 1 | 79 |
| Unknown | 3 | 0 | 4 | 0 | 1 | 0 | 8 |

NS denotes Noonan syndrome; NFI/JC denotes neurofibromatosis type 1/Jaffe-Campanacci syndrome; OES denotes oculoectodermal syndrome; SS denotes Schimmelpenning syndrome; CFC denotes cardiofaciocutaneous syndrome; OGD denotes osteoglophonic dysplasia

*Patients described as having ‘multiple’ lesions were quantified as having 3 CGCG for tabulation purposes

**Makis, et al reported continued CGCG growth in setting of vinblastine and methotrexate therapy but with response to IV bisphosphonate

NS – Noonanov sindrom; NFI/JC – neurofibromatozu tip 1/Jaffe-Campanaccijev sindrom; OES – okuloektodermalni sindrom; SS – Schimmelpenningov sindrom; CFC – kardiofaciokutani sindrom; OGD – osteoglofonska displazija

* 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

| Patients | NS | NFI/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 | 0 | 0 | 0 | 1 | 14 (46.7%) |

NS denotes Noonan syndrome; NFI/JC denotes neurofibromatosis type 1/Jaffe-Campanacci syndrome; OES denotes oculoectodermal syndrome; SS denotes Schimmelpenning syndrome; CFC denotes cardiofaciocutaneous syndrome; OGD denotes osteoglophonic dysplasia

* Makis, et al reported continued CGCG growth in setting of radiation therapy, antiangiogenic therapy, and steroid therapy

* White, et al reported continued CGCG growth in setting of vinblastine and methotrexate therapy but with response to IV bisphosphonate

NS – Noonanov sindrom; NFI/JC – neurofibromatozu tip 1/Jaffe-Campanaccijev sindrom; OES – okuloektodermalni sindrom; SS – Schimmelpenningov sindrom; CFC – kardiofaciokutani sindrom; OGD – osteoglofonska displazija

**Makis i suradnici izvijestili su o kontinuiranom rastu CGCG-a u uvjetima terapije zračenjem, te antiangiogenoj i steroidnoj terapiji

b White i suradnici izvijestili su o kontinuiranom rastu CGCG-a u postavljanju terapije vinblastinom i metotreksatom, ali s odgovorom na IV. bisfosfonat
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 evaluation (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), dok je primao vinblastin i metotreksat, ali je pokazao odgovor na intravenski administrirani bisfosfonat.

Broj prijavljenih slučajeva sindroma malen je i je 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 se vrijedno napomenuti da se velika većina (91,7%) sindromnih CGCG-a pojavljuje posle gornjih ili donjih očnjaka. Suprotno tome, čini se da izolirani CGCG ne pokazuje jasnu sklonost za pojavljivanje u prednjemu ili stražnjem segmentu čelićusti i samo manji broj slučajeva prelazi srednju liniju čelićusti, 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 priblizno 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 čelićusti, 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 sindromski CGCG može imati biološko ponašanje sličnije

### 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 | 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               |                |              |         |
| Male                 | 30/56 (53.6%)  | 876/2233 (39.2%) | 0.030  |
| Female               | 26/56 (46.4%)  | 1357/2233 (60.8%) |        |
| Location             |                |              |         |
| Mandible             | 92/124 (74.2%) | 1503/2171 (69.2%) | 0.243  |
| Maxilla              | 32/124 (25.8%) | 668/2171 (30.8%) |        |
| Recurrence following surgical treatment |                |              |         |
| Yes                  | 13/58 (22.4%)  | 232/1316 (17.6%) | 0.885  |
| No                   | 45/58 (77.6%)  | 1084/1316 (82.4%) |        |

1 Data derived from Chrcanovic BR, et al. J Oral Pathol Med. 2018;47:731 (reference 2). •
2 Cases with unknown gender or location were excluded, as in primary analysis by Chrcanovic, et al.

3 Among cases with follow-up •
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 dysmorphism, 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: PTEN11 (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 Costello syndrome is requisite for diagnosis and patient management.

Noonan syndrome

Sindromski CGCG najčešće se susreće u slučaju Noonanove sindrome (NS), česte RAZopatije koju je prvi opisao Jaqueline Noonan 1968. godine (56). NS se manifestira promjenjivim stupnjem karakterističnih značajki, uključujući cranioliko dismorfije, nizak rast, mrežaste poremećaje i kriptorhidizam (60 – 80% dječaka). Nižak 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 srca (10 – 25 %) i limfne abnor malnosti (manje od 20 %) (57,59). Inteligencija je općenito unutar normalnoga raspona, ali u 20 % slučajeva prijavljeno je i takvo oštećenje (59).

Incidenca NS-a procenjuje 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 germlinea u nekoliko gena signalizacijskoga puta MAPK-a: PTEN11 (50 %), SOS1, RAF1 i RIT1 kao odgovorni za 93 % slučaja (61,62). Mutacije su rjeđe pronađene na KRAS, N RAS, BRAF, MAP2K1 i SOS2 (63). Pretpostavka genetskoga testiranja postavlja se zanimljivo pitanje o tomu što može li osnovna predispozicija značajne linije utjecati na brži rast. Konačne zaključke, kad je riječ o optimalnoj skrbi za pacijente, onemogućuju mali broj slučajeva s informacijama o praćenju, ali ti naliži upućuju na primarnu ulogu ekscizije/resekcije sindromnih CGCG-a, za razliku od pomnogom proračuna u kojemu je približno polovina slučajeva (46,7 %) pokazala kontinuirani rast. Dugoročno praćenje razvoja dodatnih CGCG-a rješeno je zabilježeno (12,5 pacijenata), ali se čini razboritnim.

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 cranioliko značajki u kojima mogu biti prisutni.
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-posterioretelyrotated ears, ptosis, hypertelorism, epicantal 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 PTEN11 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 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 (920739). 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 there is no clear diagnosis in the cases described.

Nerofibromatoza tipa I i Jaffe-Campanaccijev sindrom

Nerofibromatoza tipa 1 (NF1) najčešći je od triju nerofibromatoznih sindroma (nerofibromatoza tipa 1 i 2 i švammatoza), (66). Povećana se spominje kao von Recklinghausenova bolest jer je u 1882. godine opisao njemački patolog Frederick von Recklinghausen (66). Najprepoznavljivije znacajke NF1 su nerofibromi i café-au-lait makule, a dijagnoza se može postaviti klinički s dvama ili više sljedećih nalaza: 6+ café-au-lait makula, 2+ nerofibroma ili 1 pleskiformni nerofibrom, aksilarni/inginalni piegavi, optički gliom, 2+ Lischovi čvorići (iris hamartomi), košta dispazija i prvi stupanj u relaciji s NF1 (920739). Café-au-lait makule i aksilarni/inginalni piegavi obično su prvi klinički znakovi pošlije kojih slijede Lischovi čvorići i nerofibromi (66). Osoinske 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 nerofibromina, može se obaviti u dvobežnim slučajevima ili ako je pacijent mlad te u promiju članova obitelji (67). NF1 pojavljuje se kod približno 1 : 3000 živih rođenja i pokazuje autosomno dominantan obrazac nasljedivanja, a de novo mutacija karakterizira oko 50 % pogođenih osoba (868??). Postziotske NF1 mutacije (1 : 40 000) mogu rezultirati segmentnim mozaicismom, poznatim kao segmentni NF1 (868).

Češće komplikacije kod oboljelih od sindroma NF1 uključuju makrocefaliju, napadaje, prirodene bolesti srca, hipertenziju i abnormalnosti kostiju (868??). Pleksiformne nerofibromoina približno 50 % pacijenata s NF1, a 8 do 13 % njih može se pretvoriti u zločude tumore perifernih živčanih ovojica kojima je petogodišnja stopa preživljavanja približno 50 % (69,70). Medijan očekivanog životnog vijeka od 59 godina nešto je niži od prošljeg opće populacije (67).

Prvi put je 1982. godine objavljeno da rijetki pacijenti imaju karakterističnu triadu 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 znacajki s NF1, ali i izostanka nerofibromina, iako se većina prijavljenih slučajeva pojavila kod mladih osoba, a nerofibromi obično

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Luna i sur.
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 Feuerstein 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 germ-line MAPK signaling dysregulation (81,82).

nastaju u ranoj adolescenciji (71). Nedavno su mutacije NF1 opisane gotovo univerzalno kod pacijenata s tako zvanim Ja -ffe-Campanaccijevim sindromom, što omogućuje pouzdan prepoznavanje toga oblika unutar spektra NF1 i argumenti -ranje te klasifikacije kao zasebnoga sindroma (72).

Koštana displazija najčešće zahvaća potkoljenicu, a rjeđe kraniofacialne kosti i, u tom okruženju, često se manifesti -ra 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. Neurofibro -mi također mogu zahvatiti alveolarni živac, što se manifesti -ra kao oštro razgrančeno proširenje donjega alveolarnoga ka -nala (73).

Schimmelpenningov sindrom

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

Lojni nevusi u Schimmelpenningovom sindromu obično uključuju vlasite i lice i mogu biti prisutni pri rođenju ili postati istaknutiji nakon puberteta. Sporadično nastali lojni nevusi karakteriziraju samotske mutacije HRAS-a i KRAS-a, a sam Schimmelpenningov sindrom obilježavaju postzigot -ske mutacije HRAS-a i KRAS-a (77). Prevalencija sindroma manja je od 1 : 200 000 osoba, a linearni lojni nevusi prijav -ljeni 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 agena corpus callosum i kašnjenje u razvoju 8752).

Povezane kraniofacialne mane česte su i uključuju domi -naciju čela, maksilo-facialnu hipoplaziju i makrocefali (76). Lojni nevusi rijetko se mogu pojaviti intraoralno gdje se mo -gu pogrešno smatrati skvamoznim papilomima zbog njihove grube površinske teksure (53, 76). Pacijenti mogu imati hi -poplastičnu, pogrešno oblikovanu ili hiperpigmentiranu dis -ticiju (52). Napominjemo, prijavljene su različite odontogene neoplazme uz CGCG, uključujući adenomatoidni odontoge -ni tumor, ameloblastom i ameloblastični fibroodontom (50 – 52, 79, 80). Te rijetke novotvorine također sadržavaju KRAS ili BRAF mutacije kada se pojavljaju sporadično i zato se mo -že 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, keratoses 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 telencephalic appearance, macrocephaly, high forehead with bitemporal narrowing, hypertelorism, convex facial profile, short nose and low set/posterioy 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 hypopigmentation, 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 Schimelenpenning 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 prirodene srčane bolesti (obično plućna stenoza, atrijski septalni defekt ili hipertrofni kardiomioptij), karakterističnih crta lica i anomalija na koži (uključujući grubu/suho kožu, melanocitne nevuse, naborane dlanove/tabanke, keratouzu pilarisu i rijeketu kosu) koji se pojavljaju kod većine ljudi (83). Dojenčad obično pokazuje hipotoniju i zaostajanje u napredovanju, a druge značajke su umjereno do teško zaostajanje u rastu i intelektualnim deficiti (84). U odrasloj dobi pojavljuju se probleme 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 pogada 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 nasljedivanje (53, 87), mutacija BRAF-a čini 75 do 80 % svih slučajeva, a MAP2K1, MAP2K2 ili Kras čine preostale objavljene slučajevne (88 – 91).

Najčešća kraniofakto nalazi obuhvaćaju stiznutu i visoko lučno nepcem i rijetku kosu 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 vlasista (aplasia cutis congenita) i jednostranih ili bilateralnih očnih lezija (epibulbar dermo id) (96). Postoji čestih nalazi su makrocefalija (50 % pogode njih osoba), anomalija gornjih vjeda, hiperpigmentacije kože, Blaschkove linije i epidermalni nevusi. Uz to su svi opisani slučajevi OES-a pokazali određenu razinu multiorganne za -hvaćenosti koja uključuje kardiovaskularne abnonormalnosti (koarktacija aorte, atrijski/septalni defekt), CNS (arahnoi dna cista, napadaji) i abnonormalnosti genituirannog sustava (epistrofija niskih modificiranoga mjejura, epizadije) (97 – 99). Općenito, osobe su normalnoga rasta i neurokognitivnog razvoja, ali su intelektualno invaliditete (98, 99).

OES su prvi opisali Toriello i suradnici 1993. godine i vr lo je rijekad neurorazvojni sindrom s manje od 25 prijavljenih slučajeva u literaturi. Svi slučajevi pojavljivali su se sporadično, a većinu pacijenata dijagnosticiran je tijekom prvih nekoliko godina života (48, 49, 96 – 102). Nedavna istraživanja pokazala su da OES uzrokuju postizgotske Kras mutaci je (49, 103). Druga dva sindromna – encefalokraniokutana lipomatosa (ECCL) i Schimelenpenningov sindrom – dij ele kliničke značajke s OES-om, a također su klasificirani kao mozaične RAZopatije. Neki autori smatraju OES blagom postizgotskom sindromom (ECCL-a zbog njihova preklapajućeg fenotipa, a jedina razlika je prisutnost intrakranijalnih lipoma, što je karakteristično za ECCL (100 – 102).
Osteoglofonijska displazija

Osteoglofonijska displazija (OGD) je autosomal dominantni poremećaj povezan sa mutacijama FGFR1. Glavni klinički nalazi u toj RAZopatiji uključuju patuljaste i prepoznatljive kraniofacijalne značajke (103). Pojam osteoglofoničan potječe od grčkog 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 poremećaj nepoznate prevladljivosti – u literaturi je zabilježeno manje od 20 slučajeva, većina s mutacijama de novo (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).

Zaključak

Zaključno, CGCG i- su dobroćudne novotvorine s vjerojatno manje od 5% incidenca 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 neobičnoj povezanosti i identifikaciji drugih karakterističnih 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.
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