Muenke syndrome: long-term outcome of a syndrome-specific treatment protocol

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Abstract

Object: To evaluate the long-term outcome of our treatment protocol for Muenke syndrome, consisting of a single craniofacial procedure.

Methods: Prospective observational cohort study of Muenke syndrome patients who underwent surgery for craniosynostosis within the first year of life. Symptoms and determinants of intracranial hypertension were evaluated by longitudinal monitoring of the presence of papilledema (fundoscopy), obstructive sleep apnea (OSA with polysomnography), cerebellar tonsillar herniation (MR scans), ventricular size (MR and CT scans) and skull growth (occipital frontal head circumference, OFC). Other evaluated factors included hearing, speech and ophthalmologic outcome.

Results: We included 38 patients; 36 underwent fronto-supraorbital advancement. Median age at last follow-up was 13.2 years (range: 1.3-24.4). Three patients had papilledema, which was related to ophthalmologic disorders in two. Three patients had mild OSA. Three patients had a Chiari I malformation, tonsillar descent < 5mm was present in 6 patients. Tonsillar position was unrelated to papilledema, ventricular size or restricted skull growth. Ten patients had ventriculomegaly, OFC growth curve deflected in 3. Twenty-two patients had hearing loss. Refraction anomalies were diagnosed in 14/ 15 patients measured at ≥8 years old.

Conclusions: Patients with Muenke syndrome treated with a single fronto-supraorbital advancement in their first year of life rarely develop signs of intracranial hypertension, matching with a very low prevalence of its causative factors, i.e. OSA, hydrocephalus and restricted skull growth. This illustrates that there is no need for a routine second craniofacial procedure. Their follow-up should focus on visual assessment, speech and hearing outcome.

Introduction

Muenke syndrome is a type of syndromic craniosynostosis, with a prevalence of 0.1 per 10.000 live births [5]. It is defined by the presence of the P250R mutation in the *FGFR 3*-gene, one of the most common mutations described in the human genome.[1,21] Clinical features include sensorineural hearing loss, developmental delay, uni- or bicoronal synostosis or macrocephaly in absence of craniosynostosis, hypertelorism, mild deformities of the hand and behavioral disturbances.[9,10,15,16,18] However, due to incomplete penetrance and variable expressivity, it has a wide spectrum of disease severity, and up to 20% of the patients have a mild presentation.[13]

Treatment of Muenke syndrome is, as in other craniosynostosis syndromes, focused particularly on preventing intracranial hypertension (ICH). However, the reported risk of ICH, detected through fundoscopy and invasive measurements, appears to be relatively low (0-21%) [7,14,30,34]. In the other craniosynostosis syndromes, the prevalence varies between 21-83%.[7,19,25,30] For Muenke syndrome, fronto-supraorbital advancement (FOA) is our preferred surgical procedure, because it restores their facial profile. Some centers however routinely perform a two-stage procedure, with posterior vault expansion as the first craniofacial intervention, followed by a FOA.[23]

This prospective study gives an overview of children with Muenke syndrome treated at our hospital, the only national referral center for syndromic craniosynostosis. We determined the long-term outcomes after routine single FOA.

Methods

We included ~~all children~~ all consecutive cases with Muenke syndrome born between Jan. 1990-June 2016, treated at Erasmus MC – Sophia Children's Hospital, the Netherlands. Children born after 2005 were prospectively included. IRB approval was obtained (MEC-2005-273, 2016-312). The *FGFR3* P250R mutation was confirmed in all patients. ~~According to protocol, FOA is performed at 6-12 months of age, with remodellation and advancement of the forehead and supra-orbital bar.~~

According to protocol, the routine vault expansion is FOA between 6-12 months of age. The orbital rim is approximately 1.5 cm advanced, thereby taken into consideration that the facial profile should not be significantly disturbed.

Intracranial hypertension

Patients were screened for signs of ICH, including evaluation of [30]:

- Bulging of the fontanel in babies
- Skull growth: occipital frontal head circumference (OFC) was measured pre-operatively, every three months until the age of 2, every 6 months until the age of 4, and from then yearly until 18. Growth curve deflection was defined as ≥0.5 SD fall from baseline over 2 years. As OFC reliably predicts intracranial volume in syndromic craniosynostosis,[26] OFC curve deflection is a risk factor for ICH.[30]
- Fundoscopy: to screen for papilledema and primarily used to indicate ICH . Patients are screened once pre-operatively and at the age of 2, 4 and 6 years.
- Optical Coherence Tomography (OCT): in children ≥ 4 years old, using the Spectralis OCT scanner (Heidelberg Engineering). This examination was added to the protocol in 2014. The total retinal thickness (TRT) was analyzed using our normative references, which were derived from OCT data of 67 healthy children (aged 4-12 years). Abnormal values included TRT < 276 µm and TRT > 503 µm (*van de Beeten et al., 2018, submitted*), indicating either atrophy or papilledema.

When ICH was suspected based on clinical symptoms such as daily headaches, but papilledema was absent, also during repeated fundoscopy after 6 weeks, invasive intracranial pressure (ICP) monitoring was performed. This 24-hour examination was evaluated according to the following criteria[33]

- Baseline ICP during the day and overnight: <10mmHg, normal; 10-15mmHg, borderline abnormal depending on the height and duration of abnormal plateaus; >15mmHg, abnormal. Additionally, the trend of ICP values was evaluated, to check for any increase overnight.

- Number of abnormal plateau waves: based on height (<25mmHg, normal; 25-35mmHg, borderline; >35mmHg, abnormal) and duration (<10 minutes, normal; 10-20 minutes, borderline; >20 minutes, abnormal).

Patients with papilledema and/or abnormal ICP measurement were all considered to have ICH.

Sleep study

OSA was diagnosed with clinical and ambulant sleep studies. The obstructive apnea-hypopnea index (oAHI) was calculated: the number of obstructive- and mixed apneas and obstructive hypopneas with desaturation/arousal, divided by the total sleep time. Patients were divided in either no (oAHI <1), mild (oAHI ≥1-5), moderate (oAHI ≥5-10) or severe OSA (oAHI ≥10).

Neuroimaging

Tonsillar position was reviewed on MR scans, ventricular size on MR and CT scans. All scans were reviewed in a 3D reformatting platform (AquariusNET; TeraRecon, Inc., Melbourne, Australia) to align scans in all planes. The presence and extent of tonsillar herniation (TH) was evaluated on midsagittal and adjacent slices and was classified as: 1) no ~~TH~~ tonsillar descent; 2) ~~herniation <5 mm, i.e. TH;~~ tonsillar descent <5 mm; 3) herniation >5 mm, i.e. Chiari I malformation. For these measurements, the position of the lowest tonsil was evaluated with respect to the foramen magnum.

The size of the lateral ventricles was evaluated on axial planes using the frontal occipital horn ratio (FOHR), ventricles were considered enlarged when the FOHR was > 0.34.[28] Hydrocephalus was present when ventricles were progressively enlarged on ≥ 2 MR or CT scans.

The correlation between FOHR and tonsil position was evaluated using a linear mixed model. R statistical programming was used (v3.4.4). Statistical significance was set at $P < 0.05$.

Audiometry

Hearing capacity in children ≥ 4 years was assessed by pure-tone audiometry and was classified into: 1) no hearing loss: an average pure-tone loss < 20 dB; 2) mild hearing loss: an average pure-tone loss of 20-40 dB; 3) moderate hearing loss: an average pure-tone loss of 41-70 dB; or 4) severe hearing loss: an average pure-tone loss ≥ 70 dB. Both ears were analyzed separately.

Patients < 4 years old underwent oto-acoustic emission (OAE) testing, which is considered deviant when emissions are absent in 3/5 frequencies (e.g. 1.0, 1.4, 2.0, 2.8 and 4.0 kHz). Data on the standard newborn hearing screening in the Netherlands, performed by OAE testing within 1 week post-partum, were collected. The use of hearing aids was reported, as well as the placement of tympanostomy tubes in patients with chronic serous otitis media with effusion. Speech and language development was routinely monitored.

Ophthalmologic evaluation

Visual acuity was established by an orthoptist and was evaluated at latest available follow-up, since the possible effect of papilledema on vision is a long-term effect.[25] The eye with the best visual acuity was used in the analysis, to prevent confounding caused by strabismus and/or amblyopia. Visual acuity was expressed using the logMAR scale.

Cycloplegic refraction was classified into [22]:

- Myopic: ≤ -0.50D, highly myopic: ≤ - 6.00D
- Emmetropic: > -0.50D to ≤ 0.50D
- Mildly hyperopic: >+0.50D to +2.00D, hyperopic: +2.00 to +6.00D, highly hyperopic: >+6.00D

Refraction was analyzed at 2 time points:

- In children aged < 6 years, when they are at risk of developing ICH [30]. Hyperopia ≥3.00D is associated with a crowded optic disk appearance, which can mimic papilledema [3,35]. Consequently, we used refraction data to interpret fundoscopy results.
- At the age of ≥ 8 years, since visual development continues up to 7-8 years [36].

Neuropsychological functioning

The educational level was monitored at visits to the outpatient clinic.

Results

Patient characteristics

We included 38 patients, 22 were female. Thirty-five patients primarily underwent FOA in our treatment center. Two patients were referred to our center after endoscopic strip craniectomy elsewhere, they subsequently underwent FOA in our treatment center. One patient primarily underwent occipital expansion (OE) because of papilledema. A second vault expansion was indicated in 3 patients, two patients had a severe phenotype, one had recurring papilledema.

The median age at first surgery was 8.5 months for the whole group (range: 2.3-18.3), while it was 9.0 months (3.4-18.3) for patients primarily referred to our center. The mean estimated blood loss was 490cc (range: 100-900). The median age at last follow-up was 13.2 years (range: 2.0-24.44).

Intracranial hypertension

See table 1 for an overview of factors involving ICH

Bulging fontanel: There were no babies with bulging of the fontanel.

Skull growth: Two patients had a deflecting OFC growth curve. OFC deflection occurred 3 years after first surgery in one patient, while it was diagnosed 1.8 years after second skull surgery in the other (patient nr. 1, table 1),

Fundoscopy: Twenty-eight patients underwent repeated fundoscopies. Three had bilateral papilledema before vault expansion, which recurred in 1 post-operatively.

The first patient (Nr. 6 table 1) had mild papilledema before vault expansion, which disappeared post-operatively. Hyperopia 3.00D was diagnosed at the age of 12 months.

The second patient (Nr. 7 table 1) had mild papilledema pre-operatively, which disappeared after occipital expansion.

The third patient (Nr. 1 table 1) had papilledema pre-operatively. Papilledema initially disappeared after surgery, but reoccurred 6 months later. At this time, OFC growth curve and ventricle size were normal. Subsequently, she underwent invasive ICP monitoring: mean ICP overnight was 10 mmHg with an increase to 13 mmHg. There were 5 plateau waves during REM sleep, with a maximal peak of 27 mmHg, although peaks were rarely >20 mmHg. Considering the patients' young age (1.5 years) this was evaluated as borderline abnormal, the patient was re-operated by occipital decompression, after which papilledema resolved. Hyperopia ≥3.00D was diagnosed at the age of 2 years.

Optical coherence tomography (OCT)

Seven patients underwent OCT scanning, none had abnormal TRT. The patient with papilledema at the age of 6.9 and 18 months (Nr. 1 table 1) showed a sloping optical disk on the OCT-scan performed at the age of 12 years, which mimics blurring of the optical disk. This anomaly was congenital, and probably influenced the fundoscopy evaluation.

Obstructive sleep apnea

Twenty-nine patients underwent a routine sleep study, the 9 patients who did not undergo a polysomnography were asymptomatic. Four patients had mild OSA (table 1).

Neuroimaging

Thirty patients underwent MR scanning (median age 4.9 years, range 0.3-24.13). Three patients had a Chiari I malformation, whereas tonsillar descent < 5mm was present in 6 patients. The first tonsillar descent < 5 mm was diagnosed at the age of 4 years. Three patients with tonsillar descent through the foramen magnum had repetitive scans, the tonsillar position progressively lowered in 2 patients, and was stable in the other one.

The lateral ventricles were evaluated on 68 scans in 36 patients (MR scan n = 41, CT scan n = 27). The mean age at evaluation was 6.0 years (range: 0.03-24.13). Mean FOHR was 0.33 (range 0.19 – 0.42). FOHR was > 0.34 in 10 patients, see table 1 for detailed information. Tonsil position and FOHR were not significantly correlated (P= 0.37).

Hearing capacity and speech development

Twenty-eight patients underwent audiological evaluation (21 pure-tone audiometry, 7 OAE testing). Twenty-one patients had hearing loss, see table 2 for detailed information on the results and figure 1 for typical audiogram and OAE. Thirteen patients required hearing aids.

Twenty-two patients were referred for speech therapy because of delayed speech and language development. Ten patients had no delay, two patients were too young for evaluation, and data regarding referral was lacking in 4 patients.

Ophthalmologic evaluation

Twenty-three patients underwent visual acuity testing (median age at testing 8.7 years, range 3.4-16.63), see table 2 for the results. Cycloplegic refraction was measured in 15 patients aged ≥ 8 years. One patient was emmetropic, 6 were mildly hyperopic, 4 had hyperopia and 4 patients were myopic.

Educational level

Twenty-eight patients were in a regular school curriculum. Five patients followed an individualized curriculum at a special school (3 because of speech- and language delay, 2 because of behavioral problems). The educational level was missing in one patient, whereas 4 children were in nursery school

.

Discussion

Following our standard protocol of a single fronto-supraorbital advancement, signs of ICH occurred in only 8% of patients, which is a small fraction in comparison with other craniosynostosis syndromes.[14,19,25,30] Considering the ophthalmologic anomalies in 2 of the patients with papilledema (hyperopia ≥ 3.00D, hyperopia with sloping of the optic disk) without the presence of any other signs of ICH, the percentage might be even as low as 3%. The striking difference with ICH prevalence of 33.3% in Saethre-Chotzen syndrome patients treated at our center is particularly interesting, because these patients underwent an identical surgical procedure at the same age [30]. Following our results, we have a number of recommendations, see table 3.

The causative factors for ICH - craniocerebral disproportion, OSA, hydrocephalus and venous outflow obstruction – are all rare in Muenke syndrome, as shown in this study and previous ones [12]. Craniocerebral disproportion is unusual: OFC deflection occurred in 2 patients and the mean SD before first surgery was -0.40, while brain volumes are normal in Muenke syndrome [8]. OSA was detected in only 8% of the patients and was of mild severity, which does not increase the risk of ICH in craniosynostosis [30,31]. No patients had hydrocephalus.

~~TH occurred in 30%, but was unrelated to papilledema or increased ventricular size, as is common in other craniosynostosis syndromes. [8,32] Additionally, factors influencing the development of TH, such as a reduced posterior fossa volume, venous hypertension, and lambdoid suture synostosis are absent or arise infrequently in Muenke syndrome.[4,12,27,28] This implicates that the etiology of TH in Muenke syndrome might be different. In previous research we found an increased volume of both the cerebellum and posterior fossa in Muenke patients, indicating an anatomical anomaly.[27] This may be associated with the abnormal position of cerebellar tonsils that we found, which mimics TH on imaging, without being related to ICH. Another explanation can be the altered osseous configuration of the skull base, which can result in false-positive measurements of tonsil position. Research has shown that patients with a reduced clivus length are more prone to a lower tonsil position.[11] Furthermore, the spheno-occipital synchondrosis closes earlier in approximately 30% of Muenke patients.[29] This structure is known to facilitate growth of the clivus.[6] A final explanation might be that mild TH (< 5 mm) also occurs in healthy children. [29] Consequently, mild tonsillar descent (< 5 mm) might be explained in a fraction of these patients. To further elucidate the etiology of TH in Muenke syndrome, and MRI-scan at the age of 4 and 10 years would be required.~~

CM-I and mild tonsillar descent occurred in 30%, but was unrelated to papilledema or increased ventricular size, as is common in other craniosynostosis syndromes. [8,32] Additionally, factors influencing the development of tonsillar descent, such as a reduced posterior fossa volume, venous hypertension, and lambdoid suture synostosis are absent or arise infrequently in Muenke syndrome.[4,12,27,28] This implicates that the etiology of tonsillar descent in Muenke syndrome might be different compared to the other craniosynostosis syndromes. Primarily, tonsillar descent (< 5mm) also occurs in healthy children, in at least 25% of the cases.[29] Consequently, the tonsillar position might be normal in the majority of the Muenke patients. Another explanation

can be the altered osseous configuration of the skull base, which can result in false-positive measurements of tonsillar position. Research has shown that patients with a reduced clivus length are more prone to a lower tonsillar position.[11] Likewise, the spheno-occipital synchondrosis closes earlier in approximately 30% of Muenke patients.[20] This structure is known to facilitate growth of the clivus.[6] A final explanation might be that the volume of both the cerebellum and posterior fossa in Muenke patients is increased. [27] This may be associated with the position of cerebellar tonsils that we found, which mimics tonsillar descent on imaging, without being related to ICH. To further elucidate the evolution of tonsillar position in Muenke syndrome, repetitive MRI-scans would be valuable, e.g. pre-operatively and at the age of 4 and 10 years. This would be for research purposes only.

Hearing loss was mostly sensorineural, and was impaired in 75%, which is similar to previously reported percentages.[17] However, neonatal hearing screening was deviant in only one patient and is thus an unreliable screening method for Muenke patients. An explanation for the lower diagnostic accuracy of this screening in our patients, is that the newborn hearing screening is found to be abnormal when OAEs are absent in 3 out of the 5 tested frequencies. Our patients typically had no emissions in the lower 2 frequencies, which resulted in normal testing outcomes according to the screening. Earlier detection of hearing loss would be favorable, because mild hearing loss influences behavior and school performance [2] and can have an additional effect on the intrinsic intellectual and behavioral problems in children with Muenke syndrome. [17,18]

The most common refractive error was mild hyperopia (40%), which is similar to proportions in healthy children [22]. In contrast, high hyperopia occurred more frequently than in healthy children (32% in Muenke patients versus 16% in healthy controls aged < 6 years old) [24]. An explanation for this higher prevalence might be that the orbitae of these patients are deformed as a consequence of the coronal synostosis. This deformation can result in an altered axis length of the eye, which is associated with axial ametropia [37].

A limitation of our study included incomplete data in some patients. For example, repeated MR scans were missing, which limits follow-up of the development and possible consequences of ventriculomegaly and cerebellar tonsillar herniation. For future research, it would be valuable to

compare follow-up of our patients to subjects treated according to a different protocol at other craniofacial centers.

Conclusion

The outcomes of treating Muenke syndrome with a single fronto-supraorbital advancement within first year of life demonstrate a low risk of developing symptoms of ICH (3-8%), but a rather high prevalence of (mild) tonsillar descent ~~tonsillar herniation~~ of 33%, which is unrelated to ICH or ventricular size. A routine single-stage procedure appears to be sufficient treatment. The follow-up should particularly focus on visual assessment, hearing irrespective of neonatal screening outcome, and speech.

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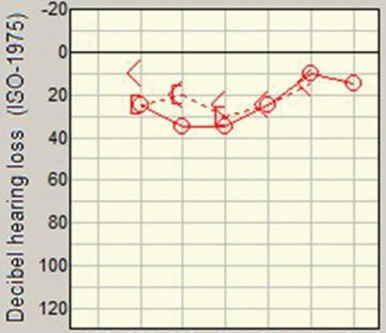
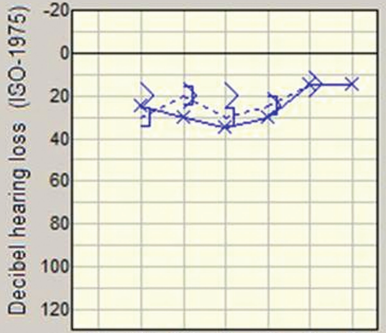
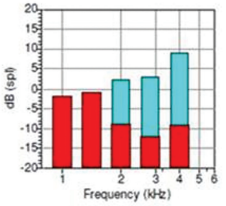
Figure legends

Figure 1: Typical features of Muenke syndrome. Above: classic audiogram. Below: oto-acoustic emission.



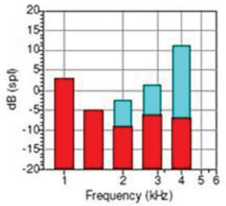


Half octave band OAE power — Right ear



Freq (kHz)	Signal (dB spl)	Noise (dBspl)	SNR (dB)
1.0	-7.5	-1.9	-5.6
1.4	-5.3	-1.0	-4.3
2.0	2.3	-9.0	11.3
2.8	2.8	-12.1	14.9
4.0	9.1	-9.2	18.2

Half octave band OAE power — Left ear



Freq (kHz)	Signal (dB spl)	Noise (dBspl)	SNR (dB)
1.0	-2,1	2,9	-5,0
1.4	-6,0	-5,1	-0,9
2.0	-2,7	-9,1	6,4
2.8	1,2	-6,3	7,4
4.0	11,2	-7,1	18,4

Study subject	Involved suture(s)	Type of surgery (age in years)	OFC in SD before first surgery	Deflecting OFC growth curve postoperatively	OSA	Neuro-imaging: cerebellar tonsillar herniation (tonsil position in mm, age in years)	Neuro-imaging: Highest FOHR[1] (age in years)	Papilledema pre-operatively/during follow-up	Hyperopia ≥ 3.00D
1	Bicoronal	FOA (0.6), OE (1.6)	0.08	+[2]	-	Mild tonsillar descent (4.2, 5.5)[2]	0.32 (11.0)	+/+	+
2	Bicoronal	FOA (0.5)	-5.82	-	-	-	0.40 (6.3)	-/-	-
3	Bicoronal	FOA (0.6)	-1.46	-	Mild[3]	Chiari I malformation (7.7, 4.6)	0.33 (3.1)	-/-	-
4	Unicoronal	FOA (1.0)	Missing	-	Missing	Mild tonsillar descent (2.6, 6.0)	0.30 (6.0)	-/-	-
5	Unicoronal	FOA (1.0)	0.21	-	-	-	0.39 (0.4)	-/-	-
6	Bicoronal	FOA (0.6)	-1.06	+	-	-	0.42 (0.3)	+/-	+
7	Bicoronal	OE [3] (0.7)	-1.05	-	-	-	0.28 (0.3)	+/-	-
8	Bicoronal	FOA (0.9)	-0.55	-	Missing	-	0.34 (6.3)	-/-	-
9	Unicoronal	FOA (0.9)	-0.06	-	-	Missing	Missing	-/-	+
10	Unicoronal	FOA (0.5)	Missing	-	Mild[4]	-	0.40 (7.4)	-/-	-
11	Bicoronal	FOA (0.7)	1.64	-	Mild[5]	-	0.36 (4.4)	-/-	Missing
12	Bicoronal	FOA (0.6)	-1.54	-	Missing	-	0.42 (0.3)	-/-	-
13	Unicoronal	Endoscopic strip craniectomy[5] (0.4) , FOA (1.3)	0.84	-	Missing	-	0.37 (1.1)	-/-	Missing
14	Bicoronal	FOA (0.9)	Missing	-	-	Missing	0.31 (0.9)	-/-	-
15	Unicoronal	FOA (1.5)	-0.89	-	-	Missing	0.29 (1.5)	-/-	Missing
16	Unicoronal	FOA (0.9)	0.14	-	-	Mild tonsillar descent (1.2, 6.7)	0.34 (0.8)	-/-	-
17	Bicoronal	FOA (0.7)	Missing	-	-	Mild tonsillar descent (1.8, 8.1)	0.32 (8.1)	-/-	-
18	Unicoronal	FOA (0.9)	-0.95	-	-	Mild tonsillar descent (1.2, 6.5)	0.30 (6.5)	-/-	Missing
19	Bicoronal	FOA (0.8)	-1.21	-	-	Mild tonsillar descent (2.7, 4.0)	0.32 (4.0)	-/-	Missing
20	Bicoronal	FOA (0.6)	0.73	-	-	-	0.32 (5.9)	-/-	-
21	Bicoronal	FOA (0.9)	-0.43	-	-	-	0.34 (0.5)	-/-	-
22	Bicoronal	FOA (1.0)	1.67	-	-	-	0.30 (0.4)	-/-	-
23	Unicoronal	FOA (0.9)	0.54	-	-	-	0.33 (0.4)	-/-	-
24	Bicoronal	Endoscopic strip craniectomy[6]	0.99	-	-	-	0.30 (1.3)	-/-	Missing

		(0.2), FOA (1.2)							
25	Bicoronal	FOA (0.7)	2.53	-	Missing	Missing	0.34 (0.3)	-/-	-
26	Bicoronal	FOA (1.3)	0.63	-	Missing	Missing	0.19 (0.9)	-/-	+
27	Bicoronal	FOA (0.8)	-1.64	-	Missing	Missing	0.31 (0.3)	-/-	Missing
28	Metopic	FOA (1.1)	-1.05	-	Missing	Missing	0.31 (0.8)	-/-	Missing
29	Unicoronal	FOA (0.9)	1.38	-	-	Chiari I malformation (5.6, 13.9)	0.33 (13.9)	Missing[7]	-
30	Bicoronal partially	FOA (0.9)	0.80	-	-	Chiari I malformation (6.3, 11.8)	0.41 (7.8)	Missing[7]	Missing
31	Bicoronal partially	FOA (0.3)	Missing	-	Mild[3]	Missing	Missing	Missing[7]	-
32	Unicoronal	FOA (0.7)	0.68	-	-	-	0.36 (8.9)	Missing[7]	+
33	Bicoronal	FOA (0.8)	-0.41	-	Missing	-	0.34 (0.03)	Missing[7]	-
34	Bicoronal	FOA (0.4)	-1.75	-	-	-	0.33 (19.9)	Missing[7]	-
35	Both lambdoids + sagittal	FOA (0.6)	-2.41	-	-	-	0.36 (12.2)	Missing[7]	-
36	Bicoronal	FOA (0.7)	-1.73	-	-	-	0.34 (19.2)	Missing[7]	-
37	Unicoronal + both lambdoids	FOA (0.7)	-0.27	-	-	-	0.28 (10.6)	Missing[7]	-
38	Bicoronal	FOA (0.5)	-1.25	-	-	-	0.32 (7.3)	Missing[7]	Missing

Table 1: Overview of risk factors and intracranial hypertension

[1] Ventricle size remained stable in all patients, none developed hydrocephalus

[2] OFC deflection occurred after second cranial vault expansion. Tonsillar herniation was diagnosed 4 years after occipital expansion.

[3] Indicated because of papilledema

[4] OSA resolved after a wait-and-see policy.

[5] OSA resolved after adenotonsillectomy

[6] These patients underwent endoscopic strip craniectomy elsewhere before referral to our center

[7] Fundoscopy results were excluded in these patients due to insufficient follow-up with fundoscopy

Abbrevations: FOA – fronto orbital advancement, FOHR – fronto-occipital horn ratio, OE – occipital expansion, SD – standard deviation, TH – tonsillar herniation

Hearing capacity		
Pure tone audiometry, N =21	N	
No hearing loss	2	
Unilateral moderate sensorineural hearing loss[1] (no hearing loss in the other ear)	2	
Bilateral sensorineural hearing loss[1] - Mild - Mild in one ear, moderate in the other - Moderate - Severe	 11 4 2 0	
Oto-acoustic emission testing, N = 7		
Normal	4	
Abnormal	3	
	N	%
Neonatal hearing screening normal	37/38	97.4
Tympanostomy tubes	22/38	57.9
Ophthalmologic evaluation		
	Unicoronal subjects	Bicoronal subjects
Mean visual acuity of the better eye (logMAR)	0.02 (range: 0.08 – 0.2)	0.07 (-0.08 – 0.5[2])
Strabismus (N)	7	11
Amblyopia (N)	4	6

Table 2: Overview of hearing capacity and ophthalmologic results in Muenke syndrome

[1] Deficits were typically present at low and mid frequencies, e.g. 250/500 and 1000 Hz in 12 patients and 250/500/1000 and 2000 Hz in 7 patients. Thirteen patients required hearing aids.

[2] The patient with 0.5 logMAR visual acuity did not have papilledema, strabismus or amblyopia. However, hyperopia + 1.00D and astigmatism were diagnosed.

Genetic research	P250R FGFR3
(3D-) CT scan	Prior to surgery in all patients to confirm craniosynostosis
MRI	Pre-operatively and post-operatively at the age of 4 and 10 years for research purposes (monitoring of TH/ventriculomegaly)
Cranial vault remodeling	Single fronto-orbital advancement at the age of 12 months
Polysomnography	If anamnestic breathing difficulties are present
Fundoscopy	When patients have a deflecting OFC growth curve/symptoms suggestive of intracranial hypertension
Sight	Screening for refractive disorders from first visit, further ophthalmic work-up if present. Visual acuity testing from the age of 3.
Hearing	OAE till 4 years, pure tone audiometry in patients ≥ 4 years old
Evaluation of speech	Referral at the age of 2

Table 3: Muenke syndrome treatment protocol recommendations