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Management of Acute Severe Asthma

Dhaval Darji

MBBS DNB PEDIATRICS, FPICC (Pediatric Intensive care) Consultant Pediatric Intensivist Mumbai

RASopathies are resulting from germline mutations of the protooncogene HRAS. Many of these mutations affect SHP2, SOS1, RAS, RAF and MEK proteins. Dr. White says. a group of related disorders including Costello syndrome, Noonan syndrome (NS), cardiofaciocutaneous (CFC) syndrome, and neurofibromatosis 1 (NF1), caused by abnormal functioning of the Ras-mitogen-activated protein kinase (RAS/MapK) pathway. Ras/MAPK pathway is an essential signaling pathway that controls cell proliferation, differentiation, survival and its dysregulation causes clinically overlapping genetic disorders, called as 'Rasopathies'. In this pathway, Ras, a GTPase, transmits extracellular signaling from receptor tyrosine kinases to two serine/threonine kinases (Raf and MEK) and, finally, to the activation of MAPKs. She has led the implementation of exome sequencing (a genomic technique for sequencing all of the protein-coding regions of genes in a genome known as the exome) at The Royal Children's Hospital and The Murdoch Children's Research Institute (Melbourne, Australia). Aoki et al. discovered that these germline mutations altered residues Gly12 and Gly13 in HRAS's P-loop and had been identified previously as somatic defects in various tumors. Rasopathies are developmental disorders characterised by postnatal growth retardation with delayed skeletal maturation, psychomotor retardation, cutis laxa, and acanthosis nigricans. Excessive mucopolysaccharides, which accumulate in cultured fibroblasts of patients with Costello syndrome (CS). Intracellular accumulation of chondroitin non-sulphate, as a cause of functional deficiency of the 67 kDa elastin binding protein, has been described in fibroblasts of patients with Costello syndrome. This gives support to the previous hypothesis of a defect in lysosomal degradation. In 2009, gain-of-function missence mutation in SHOC2, C4a> G(Ps2g), identified in NS-like syndrome with loose anagen hair, severe intellectual disability, hypernasal voice and skin abnormalities. Some mutations that can lead to cancer are inherited, but that's not the case with these HRAS mutations. They are known as somatic mutations because, instead of coming from a parent and being present in every cell (hereditary), they are acquired during the course of a person's life and are found only in cells that become cancerous. Somatic HRAS mutations have been associated with some cases of bladder, thyroid and kidney cancers. HRAS consists of six exons. Five exons code for a protein of 189 amino acids with a molecular weight of 21 kd. Alternative splicing, excluding residues 152–165, gives rise to a protein of 170 amino acids. The nucleotide substitution c.34G>A, resulting in p.Gly12Ser amino acid change is the most common (65/81 or 80%). The c.35G>C nucleotide resulting in p.Gly12Ala was seen in seven individuals (9%). Recently, 12 individuals with p.Gly13Cys change were identified, making this the most common amino acid change affecting the glycine in Position 13. Somatic mutation hotspots are bases encoding the glycines in Positions 12 and 13 and the glutamine in Position 61. Missense mutations at these positions lead to increased activity of the gene product. Germline mutations affect similar codons, it can be inferred that they have a similar effect on the gene product. The splicing efficiency of activating HRAS mutations can determine the rasopathy phenotype and frequency in Cancer. This unravels a potential for development of new anti-cancer therapies based on SSO-mediated HRAS exon 2 skipping. Gene correction of these germline mutations to restore normal protein functions is anticipated as a new therapeutic option. MEK is a dual specificity threonine/tyrosine kinase, so called from the term MAPK/ERK kinase. MEK is a downstream protein kinase which can be targeted to prevent reactivation of the MAPK pathway in the presence of BRAF or RAS mutations. It is a key effector of the three-layered RAS/RAF/MEK/ERK signaling cascade, expressed by seven genes from MAPK1 to MAPK7. MEK inhibitors (e.g., refametinib, selumetinib, trametinib, cobimetinib) have been tested in clinical trials. They inhibit the kinase function of this protein by inducing conformational changes that limit the movement of the activation loop by which the kinase is activated. This reduces the rate of Raf-mediated MEK phosphorylation, leaving the enzyme locked in a catalytically inactive state arrests the signaling pathway. Neurocognitive involement is a common feature of rasopathies. Isoprenylation involves the enzyme farnesyl transferase(FTase) transferring a farnesyl group from farnesyl pyrophosphate (FPP) to the pre-Ras protein. Pathway modulators or small molecule inhibitors such as statins causes significant improvement in verbal and nonverbal memory, visual attention & efficacy by inhibiting the posttranscriptional lipid modification of RAS. RAF-1 inhibition by C-type Natriuretic Peptide (CNP) improved bone growth in preclinical animal models and it is a potential targeted therapeutic drug to improve the stature of patients affected with disruption of the RAS/MEK/ERK pathway. Oxidative stress-play a role in cancer development and free radicals- determine non-neoplastic clinical features such as elastin anomalies, alteration of skin and appendages, developmental retardation and cardiac defects. PAR therapy (potassium ascorbate with ribose) a reduction in oxidative stress biomarkers in parallel with improvement of clinical features. It combines the antioxidant action of vitamin C with the stabilizing intracellular effects of potassium and causes improvement of skin and appendage lesions, better evolution of psychomotor development, no Progression of heart hypertrophy, nor tumor development. It is low cost, no side-effects, orally administered and useful for all genetic syndromes with cancer risk

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